Murat Beyzadeoglu
Gokhan Ozyigit
Cuneyt Ebruli

Basic Radiation Oncology

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Murat Beyzadeoglu MD
Professor and Chairman of Radiation Oncology
Gulhane Military Medical School
Department of Radiation Oncology
Ankara
Etlik
Turkey
mbeyzadeoglu@yahoo.com

Gokhan Ozyigit MD
Associate Professor of Radiation Oncology
Hacettepe University, Faculty of Medicine
Department of Radiation Oncology
06100 Ankara
Turkey
gozyigit@hacettepe.edu.tr

Cuneyt Ebruli MD
Instructor of Radiation Oncology
Gulhane Miltary Medical School
Department of Radiation Oncology
Currently affiliated to:
Kocaeli State Hospital
Department of Radiation Oncology
Kocaeli, Turkey
cuneytebruli@hotmail.com

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Dedication

Dedicated to the memory of Professor Ibtisam Lale Atahan, MD (1945–2007)

Foreword

Revolutionary advances have been taking place in radiation oncology as our world has entered a new millennium. Developments in radiological and functional imaging techniques over the last two decades have enabled us to delineate tumors more accurately in the three spatial and the fourth (temporal) dimensions. More powerful computerized planning systems are facilitating accurate three-dimensional dose calculations as well as inverse planning processes. We have even started to use robotic technology to track our targets in real time for more precise delivery of radiotherapy.

All of those high-tech machines sometimes cause us to spend many hours in front of detailed displays of serial computerized tomography (CT) slices. However, we are still treating our patients with the same types of ionizing radiation discovered more than a century ago. Therefore, every member of a radiation oncology team should know the interactions of ionizing radiation with matter at the atomic level, and be familiar with its effects in biological systems. In addition, every radiation oncologist should have an essential knowledge of evidence-based clinical oncology in relation to the indications and technical aspects of radiotherapy at major cancer sites.

Basic Radiation Oncology is an up-to-date, bedside-oriented textbook that integrates radiation physics, radiobiology and clinical radiation oncology. The book includes the essentials of all aspects of radiation oncology, with more than 300 practical illustrations and color figures. The layout and presentation is very practical and enriched with many eye-catching conceptual highlights. The first three chapters review crucial ideas in radiation physics and radiobiology as well as the terminology of clinical radiation oncology. Basic descriptions of all high-tech radiotherapy machines are also given. The remaining eleven clinical chapters describe anatomy, pathology, general presentation, treatment algorithms and the technical aspects of radiotherapy for major cancer sites. The 2010 (seventh) edition of the AJCC Staging System is provided for each tumor type. Practical details about key studies, particularly randomized ones, and available RTOG consensus guidelines for the determination and delineation of targets are also included at the end of each clinical chapter.

Basic Radiation Oncology meets the need for a practical and bedside-oriented radiation oncology textbook for residents, fellows, and clinicians of radiation, medical and surgical oncology, as well as for medical students, physicians and medical physicists interested in clinical radiation oncology.

K.S. Clifford Chao, MD

Preface

The aim of writing *Basic Radiation Oncology* was to provide a structured overview of the theory and practice of radiation oncology, including the principles of radiation physics, radiation biology and clinical radiation oncology. We have encompassed the fundamental aspects of radiation physics, radiobiology, and clinical radiation oncology. In the last two decades, there have been many technical and conceptual advances in both treatment planning systems and radiation delivery systems. However, there are no changes in the basic interactions of radiation with atoms or cells. Therefore, basic concepts that are crucial to understanding radiation physics and radiobiology are reviewed in depth in the first two sections. The third section describes radiation treatment regimens appropriate for the main cancer sites and tumor types according to the seventh edition of the American Joint Committee on Cancer Staging System. Many 'pearl boxes' are used to summarize important information, and there are more than 350 helpful illustrations. *Basic Radiation Oncology* meets the need for a practical radiation oncology book. It will be extremely useful for residents, fellows, and clinicians in the fields of radiation, medical, and surgical oncology, as well as for medical students, physicians, and medical physicists with an interest in clinical oncology.

Evidence-based data are also available at the end of the section on each clinical subsite. However, every clinician should be aware of the fact that there is a very fine line between evidence-based and probability-based medicine. Cancer is a highly complex subject, and it is impossible to fit it into a simple mathematical formula or "p" value. Therefore, we must not throw away experience-based data during our clinical decision-making procedures. We extend our most sincere gratitude to Zeki Bayraktar, the Dean of Gulhane Military Medical School, as well as to our families for their understanding as we worked to meet our publication deadlines.

Ankara, Turkey — Dr. M. Beyzadeoglu
Ankara, Turkey — Dr. Gokhan Ozyigit
Kocaeli, Turkey — Dr. Cuneyt Ebruli

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Contents

Introduction and History

Roentgen was working on Crook's Vacuum tube on November 8th 1895. He suddenly realized that shadows of his wife's finger bones and ring in her finger appeared on the palette. This was the discovery of X-rays and the beginning of radiation history (Fig. 1).

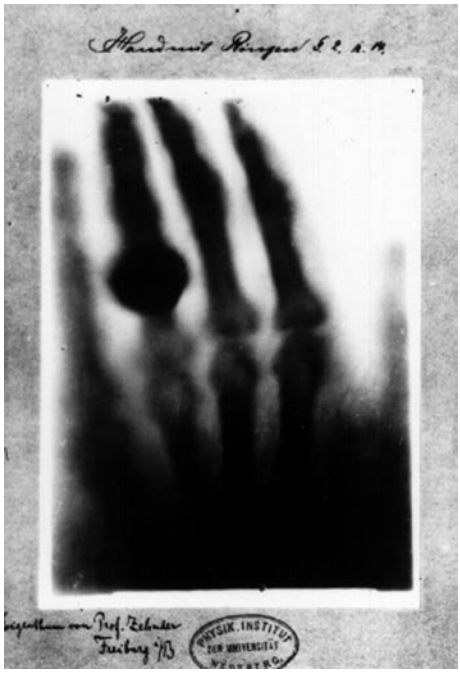

Fig. 1 The first X-ray (X-ray of the hand of Anna Bertha Roentgen)

Henri Becquerel opened his drawer in his laboratory on March 1896. He was greatly surprised when he saw blackened photo glasses despite their being kept in a totally dark medium. This was the discovery of natural radioactivity (Fig. 2).

It has been more than a century since the discovery of X-rays by Roentgen and that of natural radioactivity by Becquerel, and in that time the field of radiation oncology has seen enormous changes due to the now-standard use of extraordinarily complex systems and

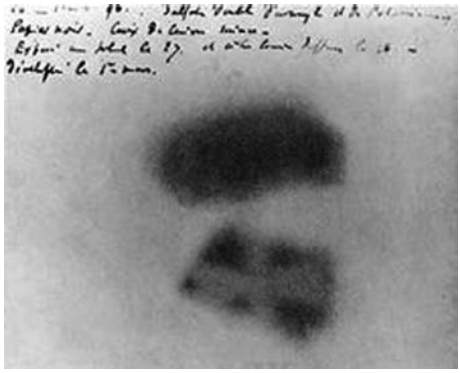

Fig. 2 The blurred photo glasses of Becquerel

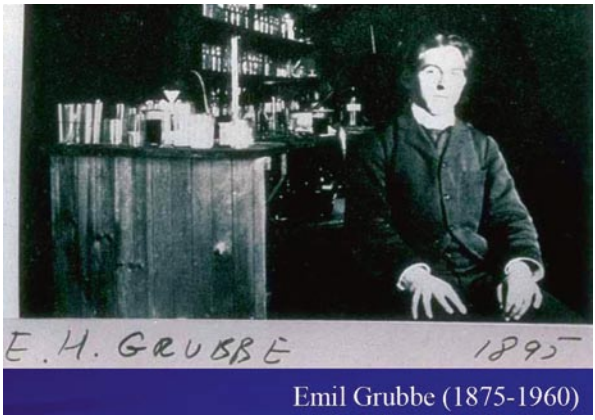

Fig. 3 The first radiation oncologist, Emil Grubbe

high-technology products to treat cancers. Indeed, just two months after the discovery of X-rays (i.e., on 1 Jan 1896), a medical student named Emil Grubbe (Fig. 3) used X-rays to treat a 65 year old female patient named Rosa Lee with recurrent breast carcinoma at a lamp factory in Chicago.

We can summarize the most important developmental steps in the field of radiation oncology chronologically as follows:

1895: Discovery of X-rays by Wilhelm Conrad Roentgen (Germany)
1895: Use of X-rays in breast cancer by Emil Grubbe (Chicago, USA)
1896: Use of X-rays in nasopharyngeal cancer and in pain palliation by Voigt J. Ärztlicher Verein (Germany)
1896: Discovery of natural radioactivity by Henri Becquerel (Paris, France)
1896: Use of X-rays in the treatment of gastric cancer by Despeignes (France)
1896: Use of X-rays in the treatment of skin cancer by Léopold Freund (Austria)
1897: Discovery of electrons (Thompson)
1898: Discovery of radium by Pierre and Marie Curie (France)
1899: Definition of the alpha particle (E. Rutherford)

1901: The first use of radium in skin brachytherapy (Dr. Danlos, France)
1903: Publications showing the efficacy of radiotherapy in lymphoma (Senn & Pusey)
1905: Discovery of the sensitivity of seminoma to radiation (A. Béclère, France)
1905: Discovery of the photoelectric effect by A. Einstein (Germany)
1906: Discovery of characteristic X-rays (G. Barkla)
1922: Demonstration of the Compton effect (Arthur H. Compton)
1931: First cyclotron (Ernest O. Lawrence, USA)
1932: Discovery of neutrons (Sir James Chadwick, UK)
1934: Discovery of artificial radioelements (Irène and Frédéric Joliot-Curie, France)
1934: 23% cure rate in head and neck cancer (Henri Coutard)
1934: Death of Mrs. Marie Curie due to pernicious anemia (myelodysplasia)
1940: The first betatron (Donald W. Kerst)
1951: The first cobalt-60 teletherapy machine (Harold E. Johns, Canada)
1952: The first linear accelerator (linac) machine (Henry S. Kaplan, USA)
1968: Discovery of the gamma knife (Lars Leksell)
1971: The first computerized tomography (CT) (G.N. Hounsfield, UK)
1973: The first MRI machine (Paul C. Lauterbur, Peter Mansfield)
1990: The first use of computers and CT in radiotherapy (USA)
1994: The first clinical IMRT treatment (USA)
1996: FDA approval of the first IMRT software
2001: FDA approval of robotic radiosurgery
2002: FDA clearance of spiral (helical) tomotherapy
2003: The first use of image-guided radiation therapy (IGRT) technology

Radiation Physics

1

Murat Beyzadeoglu, Gokhan Ozyigit, and Cuneyt Ebruli

1.1 Atom

The word "atom" derives from the Greek word "atomos," which means indivisible; an atom was the smallest indivisible component of matter according to some philosophers in Ancient Greece [1]. However, we now know that atoms are actually composed of subatomic particles: protons and neutrons in the nucleus of the atom, and electrons orbiting that nucleus (Fig. 1.1).

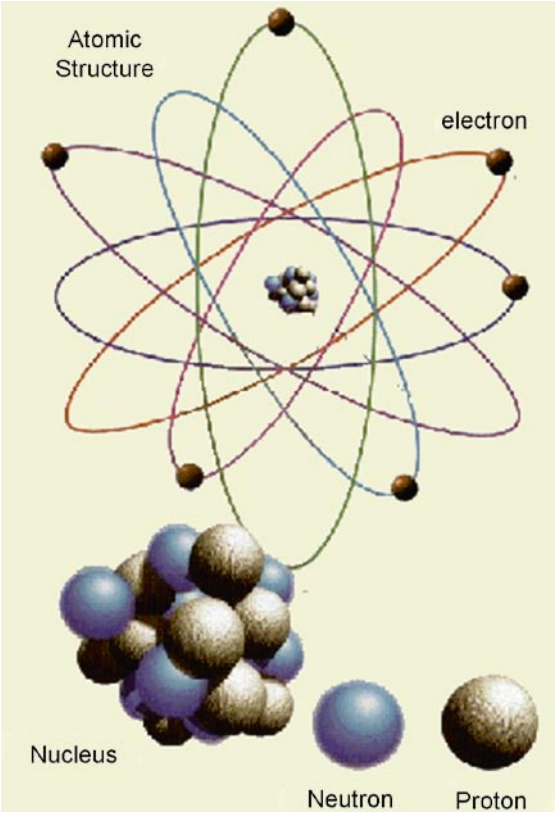

Fig. 1.1 The structure of an atom

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Electrons are negatively charged particles.

Protons are positively charged particles. The mass of a proton is about 1,839 times greater than that of an electron.

Neutrons are uncharged (neutral) particles. The mass of a neutron is very slightly larger than that of a proton.

Protons and neutrons form the nucleus of an atom, and so these particles are also called nucleons.

The diameter of an atom is about 10^{-8} cm, whereas the diameter of the atomic nucleus is 10^{-13} cm.

The total number of protons and neutrons in a nucleus (p + n) (i.e., the total number of "nucleons") is termed the mass number of that atom, symbolized by A [1]. The total number of protons is called the atomic number and is symbolized by Z. The atomic number and the mass number of an element X are usually presented in the form ${}^{A}_{Z}\mathrm{X}$ (Fig. 1.2).

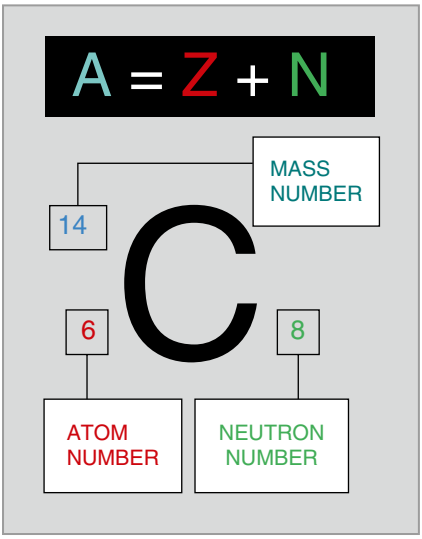

Fig. 1.2 Writing a element in nuclide format (carbon-14 is used as an example)

Nuclide → if an atom is expressed in the form ${}^{A}_{Z}X$, it is called a nuclide (e.g., ${}^{4}_{2}\mathrm{He}$).

Radionuclide → if the atom is expressed in the form ${}^{A}_{Z}\mathrm{X}$ and is radioactive, it is called a radionuclide.

1.2 Radiation

The propagation of energy from a radiative source to another medium is termed radiation. This transmission of energy can take the form of particulate radiation or electromagnetic radiation (i.e., electromagnetic waves). The various forms of radiation originating from atoms, which include (among others) visible light, X-rays and γ-rays, are grouped together under the terms "electromagnetic radiation" [1] or "the electromagnetic spectrum" [1, 2]. Radio waves, which have the longest wavelengths and thus the lowest frequencies and energies of the various types of electromagnetic radiation, are located at tone end of the electromagnetic spectrum, whereas X-rays and γ-rays, which have the highest frequencies and energies, are situated at the other end of this spectrum.

Photon

- If the smallest unit of an element is considered to be its atoms, the photon is the smallest unit of electromagnetic radiation [3].
- Photons have no mass.

Common features of electromagnetic radiation [4, 5]:

- It propagates in a straight line.
- It travels at the speed of light (nearly 300,000 km/s).
- It transfers energy to the medium through which it passes, and the amount of energy transferred correlates positively with the frequency and negatively with the wavelength of the radiation.
- The energy of the radiation decreases as it passes through a material, due to absorption and scattering, and this decrease in energy is negatively correlated with the square of the distance traveled through the material.

Electromagnetic radiation can also be subdivided into ionizing and nonionizing radiations. Nonionizing radiations have wavelengths of $\geq 10^{-7}$ m. Nonionizing radiations have energies of <12 electron volts (eV); 12 eV is considered to be the lowest energy that an ionizing radiation can possess [4].

Types of nonionizing electromagnetic radiation [5]:

- Radio waves
- Microwaves
- Infrared light
- Visible light
- Ultraviolet light

1.3 Ionizing Radiation

Ionizing (high-energy) radiation has the ability to remove electrons from atoms; i.e., to ionize the atoms. Ionizing radiation can be electromagnetic or particulate radiation (Fig. 1.3). Clinical radiation oncology uses photons (electromagnetic) and electrons or (rarely) protons or neutrons (all three of which are particulate) as radiation in the treatment of malignancies and some benign conditions [6].

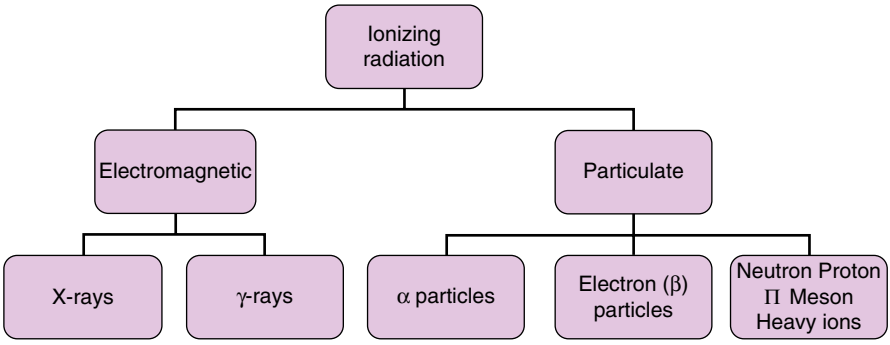

Fig. 1.3 Ionizing radiations

1.3.1 Ionizing Electromagnetic Radiation

The electromagnetic spectrum comprises all types of electromagnetic radiation, ranging from radio waves (low energy, long wavelength, low frequency) to ionizing radiations (high energy, short wavelength, high frequency) (Fig. 1.4) [7].

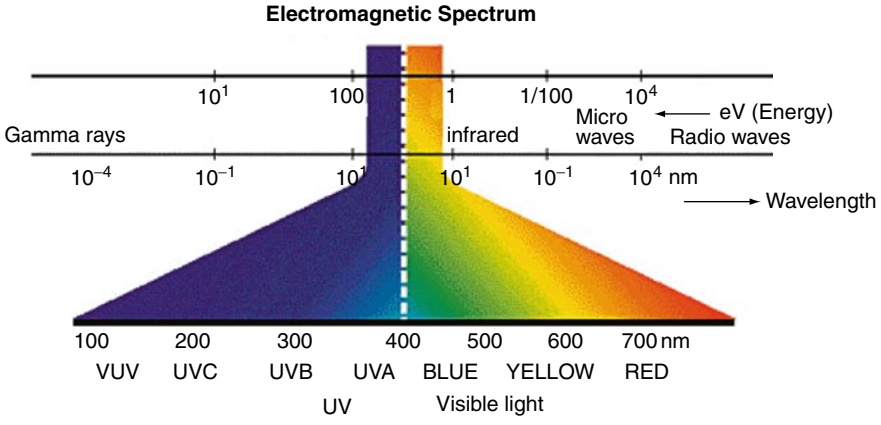

Fig. 1.4 Electromagnetic spectrum

Electrons are knocked out of their atomic and molecular orbits (a process known as ionization) when high-energy radiation interacts with matter [8]. Those electrons produce secondary electrons during their passage through the material. A mean of energy of 33.85 eV is transferred during the ionization process, which in atomic and molecular terms is a highly significant amount of energy. When high-energy photons are used clinically, the resulting secondary electrons, which have an average energy of 60 eV per destructive event, are transferred to cellular molecules.

1.3.1.1 X-Rays

X-rays were discovered by the German physicist Wilhelm Conrad Roentgen in \95 [9]. The hot cathode Roentgen tube, which was developed by William David Coolidge in 1913, is a pressured (to 10^{-3} mmHg) glass tube consisting of anode and cathode layers between which a high-energy (10^{6} –10^{8} V) potential is applied (Fig. 1.5a, b). Electrons produced by thermionic emission in the cathode are accelerated towards the anode by the potential. They thus hit the anode, which is a metal with high melting temperature. X-rays are produced by the sudden deceleration of these electrons due to Coulomb interactions with nuclei in the anode (this sudden deceleration of fast-moving electrons is known as bremsstrahlung; Fig. 1.6). The energy and the wavelength of the X-rays depend on the atomic number of the target (anode) metal, as well as the velocity and the kinetic energy of the electrons. This process is used to produce medical radiation in diagnostic X-ray units, linear accelerators (linacs), and betatrons.

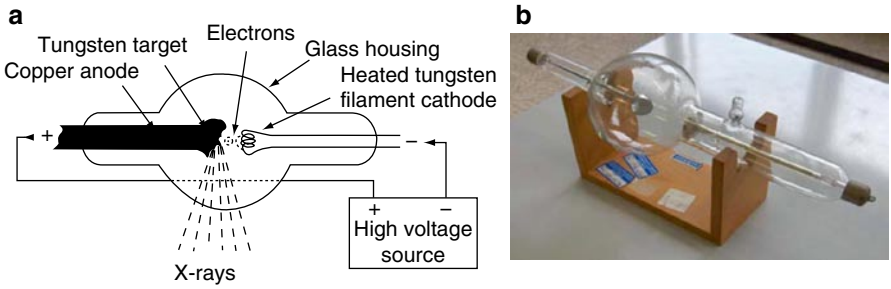

Fig. 1.5 (**a**) Schematic representation of an X-ray tube; (**b**) photograph of an X-ray tube

X-rays are produced by extranuclear procedures. Two kinds of X-rays are created by X-ray tubes [10, 11]. The first type corresponds to the bremsstrahlung X-rays mentioned above. The second type occurs because an electron in an inner atomic orbital is knocked out by an incoming electron, and the resulting space in the orbital is filled by other electron that moves from an outer atomic orbital (Fig. 1.7). This electron must shed energy to move in this manner, and the energy released is radiated as characteristic X-rays [12]. They are characteristic due to the fact that their energy depends on the target metal onto which the electrons are accelerated.

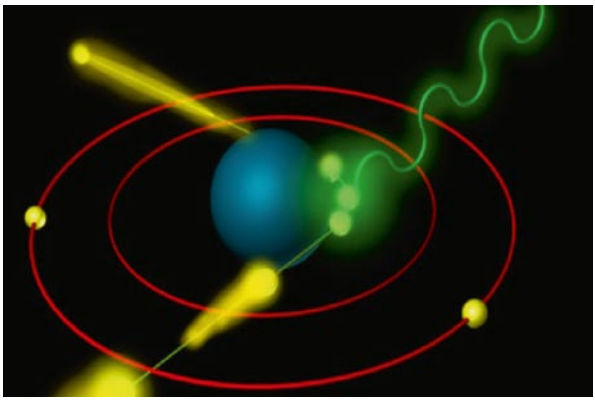

Fig. 1.6 Bremsstrahlung process

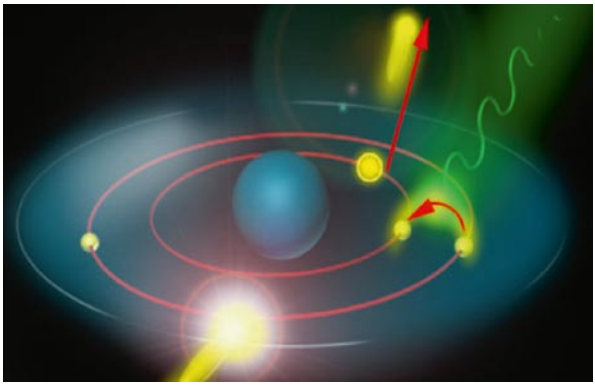

Fig. 1.7 Characteristic X-ray generation

X-rays produced by bremsstrahlung have a broad energy spectrum (→ heterogeneous), while characteristic X-rays are monoenergetic beams.

1.3.1.2 Gamma (γ) Rays

Gamma rays are physically identical to X-rays, but they are emitted from atomic nuclei (intranuclearly). An unstable atomic nucleus sheds its excess energy in the form of either an intranuclear electron (e^-) (beta particle) or a helium nucleus (an "alpha particle") (Fig. 1.8). If it still possesses excess energy after that, gamma rays are emitted in order to reach its steady state (Fig. 1.9).

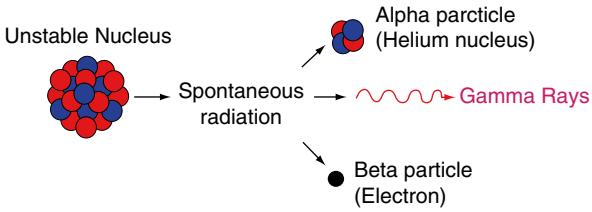

Fig. 1.8 Alpha particle generation

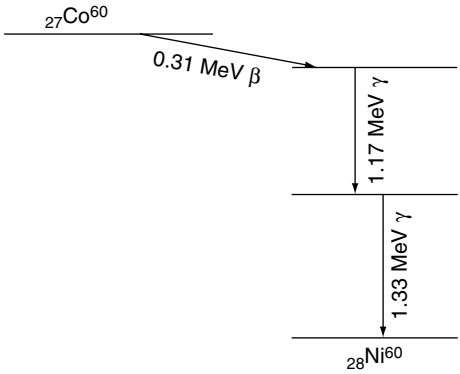

Fig. 1.9 Co-60 decay

Gamma rays have well-defined energies. For instance, two monoenergetic gamma rays with a mean energy of 1.25 MV (1.17 and 1.33 MV) are emitted after beta rays of 0.31 MV energy have been emitted during the decay of ^{60}Co (cobalt-60; Co-60). Through this process, ^{60}Co transforms into a final, stable decay product, ^{60}Ni (nickel-60; Ni-60). There is actually a stable naturally occurring form of cobalt: ^{59}Co. ^{60}Co is created through neutron bombardment in nuclear reactors, and has a half-life of 5.26 years. One gram of ^{60}Co has an activity of 50 Ci (1.85 terabecquerels) [13, 14].

The half-life of a radioisotope is the time required for its activity to half [15].

The activity of a radioisotope is the number of decays per second, and is defined in becquerels or curies.

- Becquerel (Bq): the standard unit of (radio)activity; it is defined as one disintegration (decay) per second.
- Curie (Ci): an older unit of (radio)activity, corresponding to 3.7×10^{10} disintegrations per second.

The decay of a radioactive nucleus is a spontaneous process. There are three forms of radioactive decay. Alpha or beta particles are emitted during the alpha and beta decays of an unstable nucleus in order to reach a stable nucleus. A gamma decay occurs without any change in the form of the nucleus.

Alpha Decay [16]. An alpha particle consisting of two protons and two neutrons is emitted if a nucleus is unstable because it has an excessive number of both protons and neutrons (Fig. 1.10).

After alpha decay, the alpha particle possesses most of the energy, due to the conservation of momentum and the fact that the alpha particle is much less massive than the residual nucleus. Although the ${}^{4}_{2}\mathrm{He}$ nucleus is very energetic, does not travel very far compared to most forms of radiation, due to its relatively heavy mass. Alpha decay is usually observed in nuclei with mass numbers of more than 190. The energy spectrum of alpha decay is not continuous, and varies between 4 and 10 MeV. Alpha particles strongly interact with the electrons of the matter through which they pass, since they are charged particles.

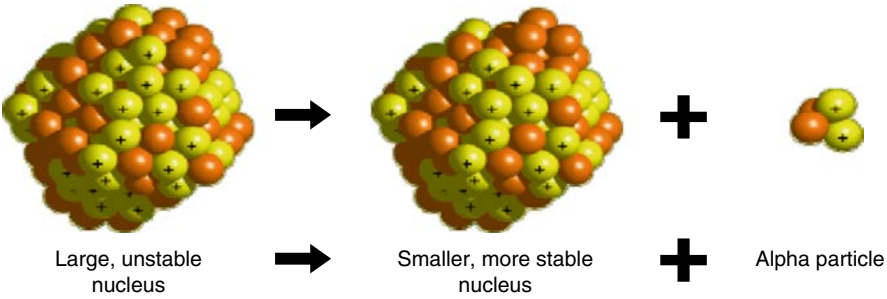

Fig. 1.10 Alpha decay

Beta Decay [17]. There are three types of beta decay.

If a radionuclide is unstable because it has an excess number of neutrons in its nucleus, it transforms one of the neutrons into a proton and an electron in order to reduce the amount of energy in its nucleus (Fig. 1.11). The electron is rapidly propelled out of the nucleus, while the proton remains. This high-speed electron called a β^- particle or negatron, and the process is termed *β^- decay*. The atomic number of the radionuclide increases by one, and thus it changes into the next element in the periodic table. Note that the mass number does not change (it is an "isobaric" decay) [16, 17].

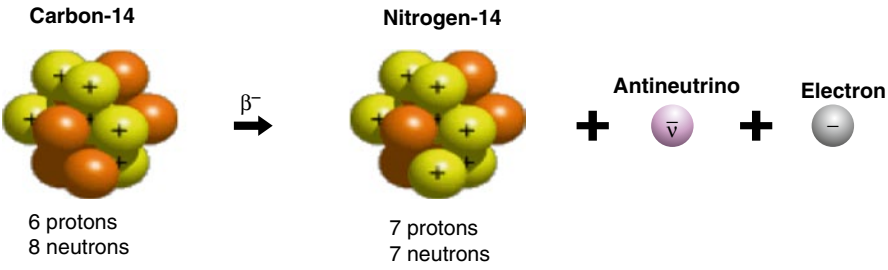

Fig. 1.11 β^- decay

If a radionuclide is unstable due to an excess amount of protons or a lack of neutrons, one of the protons transforms into a neutron and a small positively charged particle called a positron in a process termed β^+ *decay* [17]. The neutron stays in the nucleus while the positron is propelled out of it (Fig. 1.12). The atomic number of the radionuclide that emits the positron decreases by one, and thus it changes into the preceding element in the periodic table. Again, note that the mass number does not change.

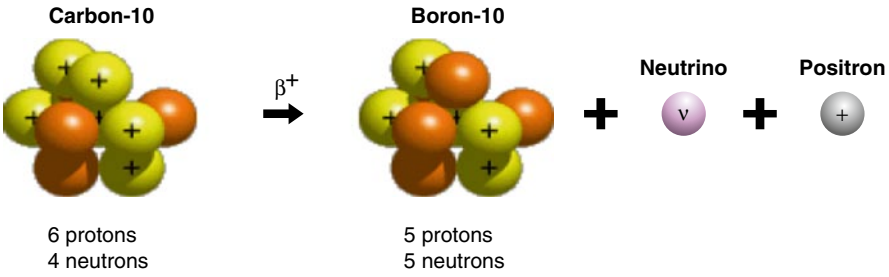

Fig. 1.12 β^+ decay

If the nucleus is unstable due an excess amount of protons, one of the electrons close to the atomic nucleus, such as an electron in a K and L orbital, is captured by the nucleus (Fig. 1.13). This electron then combines with a proton, yielding a neutron and a neutrino. This process is called *electron capture* [16]. Note that no particle is emitted from the nucleus, but the atomic number decreases by one, as in positron decay. Yet again, the mass number does not change. The space in the inner orbital is filled by an electron from an outer orbital, resulting in the emission of characteristic X-rays.

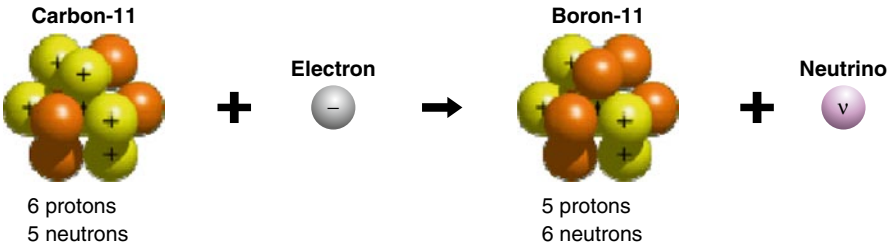

Fig. 1.13 Electron capture phenomenon

There are also three types of beta decay. In all of them, the mass number of the nucleus remains constant during the decay, while the numbers of protons and neutrons change by one unit. Furthermore, the emission of some massless, uncharged particles called neutrinos and antineutrinos is observed during each beta decay process. The existence of these particles was first suggested by Pauli in 1930, although it was Fermi that provided the name "neutrino" [16].

Gamma Emission [13, 14, 16]. A nucleus is not always fully stable (i.e., at its basal energy level) just after it decays; sometimes, the nucleus will be in a semi-stable state instead (Fig. 1.14). The excess energy carried by the nucleus is then emitted as gamma radiation. There is no change in the atomic or mass number of the nucleus after this decay, so it is termed an "isomeric" decay.

The half-lives of gamma radiation sources are much shorter than sources of other types of decay, and are generally less than 10^{-9} s. However, there are some gamma radiation sources with half-lives of hours or even years. Gamma energy spectra are not continuous.

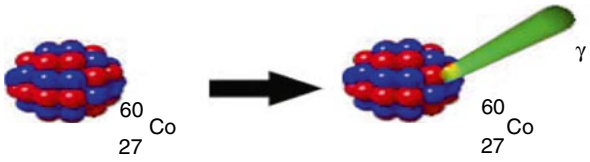

Fig. 1.14 Gamma emission

Isotope [18]. Atoms with the same atomic number but different mass numbers are called isotopes (e.g., ${}^{11}_{6}\mathrm{C}$, ${}^{12}_{6}\mathrm{C}$, ${}^{13}_{6}\mathrm{C}$).
Isotone. Atoms with the same number of neutrons, but different numbers of protons are called isotones (e.g., ${}^{9}_{3}\mathrm{Li}$, ${}^{10}_{4}\mathrm{Be}$, ${}^{11}_{5}B$, ${}^{12}_{6}\mathrm{C}$).
Isobar. Atoms with the same number of nucleons but different numbers of protons are called isobars (e.g., ${}^{12}_{5}\mathrm{B}$, ${}^{12}_{6}C$, ${}^{12}_{7}\mathrm{N}$).
Isomer. Atoms with the same atomic and mass numbers but which are in different energy states are called nuclear isomers ($\mathrm{Tc}^{99\mathrm{m}}$)

1.3.2 Ionizing Particulate Radiation

Electrons, protons, alpha particles, neutrons, pi mesons and heavy ions are all forms of ionizing particulate radiation [19]. Electrons are the particles that are generally used in routine clinics. Other particles are only used in specific clinics worldwide.

Electrons, due to their negative charge and low mass, can be accelerated to high energies in linacs or betatrons.

The mass of an electron is $9.109\,3826(16) \times 10^{-31}$ kg.
The electrical charge of an electron is $-1.602\,176\,53(14) \times 10^{-19}$ C.

Electrons are normally bound to a (positively charged) nucleus. The number of electrons is equal to the number of protons in a neutral atom. However, an atom can contain more or less electrons than protons, in which case it is known as a negatively or positively charged ion,

respectively. Electrons that are not bound to an atom are called free electrons; free electrons can be produced during nuclear decay processes, in which case they are called beta particles.

Electrons have much smaller ranges (i.e., they travel smaller distances) in matter than gamma and X-rays, and can be absorbed by plastics, glass or metal layers (Fig. 1.15).

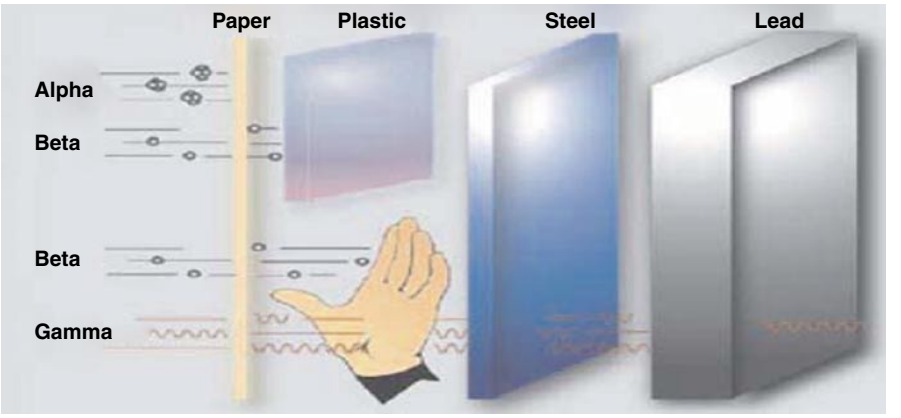

Fig. 1.15 Penetration ranges of various ionizing radiations

Neutrons are the neutrally charged particles that enable the formation of stable large atomic nuclei (Fig. 1.16) by decreasing the repulsion between the protons in the nucleus. However, neutrons, like protons, actually consist of particles called quarks; a neutron is one up quark and two down quarks, while a proton (Fig. 1.17) is two up quarks and one down quark.

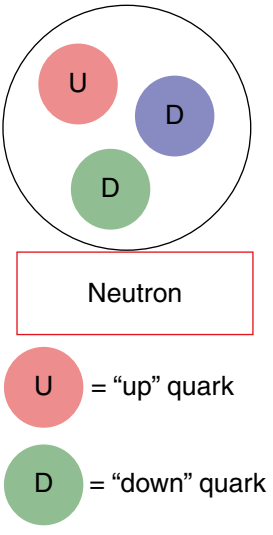

Fig. 1.16 Neutron

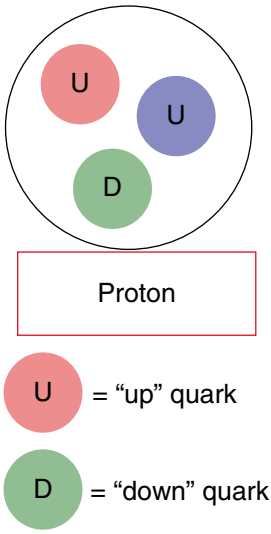

Fig. 1.17 Proton

1.4 The Interaction of Radiation with Matter

Radiation is scattered and absorbed when it passes through tissue [19, 20]. The intensities of monoenergetic X-rays or gamma rays attenuate exponentially within tissues. In other words, the intensity of radiation constantly decreases as it propagates within tissues. This decrease depends on the type of tissue and its thickness. If the wavelength stays constant, the intensity of the radiation passing through a tissue can be calculated by the following formula:

$$I = I_0 . e^{-\mu t} \tag{1.1}$$

I = intensity of outgoing radiation beam
I_0 = intensity of incoming radiation beam
μ = absorption coefficient (which is positively correlated with the fourth power of the atomic number of the penetrated tissue, and the third power of the wavelength of the radiation)
t = tissue thickness

As seen in the above formula, the intensity of the radiation decreases exponentially with the absorbent thickness, and the intensity of the outgoing radiation depends on the tissue absorption coefficient and its thickness.

Three of the five types of interaction of radiation with matter determine the absorption coefficient → photoelectric effect, Compton effect, and pair production.

1.4.1 Photoelectric Effect

This phenomenon, which was theorized by Albert Einstein in 1905, was actually first observed by Heinrich Rudolf Hertz in 1887, and was therefore also known as the Hertz effect [21]. To define it simply, when any electromagnetic radiation reaches a surface (generally a metallic surface), it transfers its energy to the electrons of that surface, which are then scattered. At the atomic level, the incoming radiation knocks an electron from an inner atomic orbital, propelling it from the atom (Fig. 1.18).

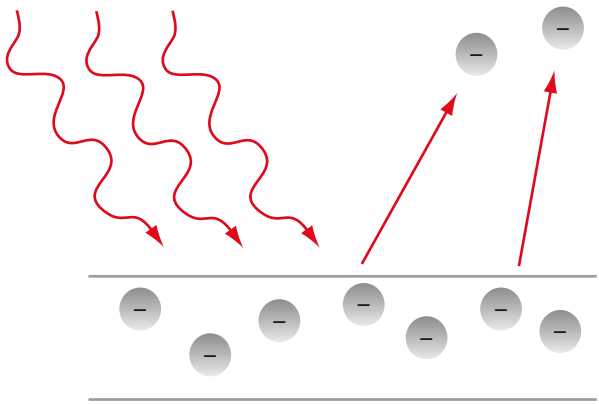

Fig. 1.18 Photoelectric effect

Photoelectric Effect (Fig. 1.19)

This is the basic interaction in diagnostic radiology.

It is dominant at energies of less than 35 kV, and in atoms with high atomic numbers (Z).

Since the atomic number of bone is higher than that of soft tissue, bone absorbs more radiation than soft tissue. This absorption difference is the basis of diagnostic radiology.

This effect also explains why metals with high atomic numbers (e.g., lead) are used to absorb low-energy X-rays and gamma rays.

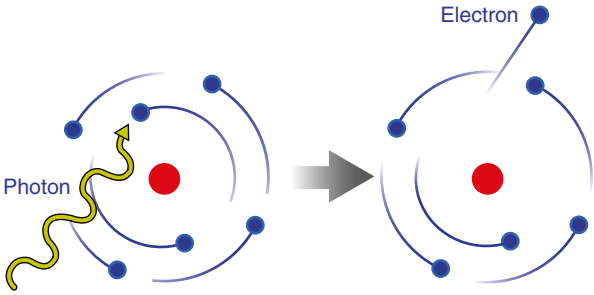

Fig. 1.19 The illustration of photoelectric effect

1.4.2 Compton Effect

In the Compton effect, a photon collides with an electron in an outer orbital, and the photon and electron are scattered in different directions (where θ is the angle between the directions) [21]. The energy of the incoming photon is transferred to the electron in the form of kinetic energy. The scattered electron also interacts with the outer orbital electrons of other atoms. After the interaction, the photon has a lower energy than it did beforehand (Fig. 1.20).

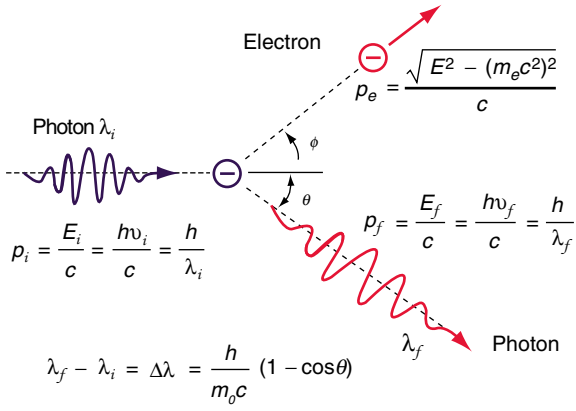

Fig. 1.20 Math associated with the Compton effect

Compton Effect (Fig. 1.21)

This is the main mechanism for the absorption of ionizing radiation in radiotherapy.

It is the dominant effect across a wide spectrum of energies, such as 35 kV–50 MV.

It has no dependency on the atomic number (Z) of the absorbent material, but it does depend on the electron density of the material.

The absorption of incoming radiation is the same for bone and soft tissues.

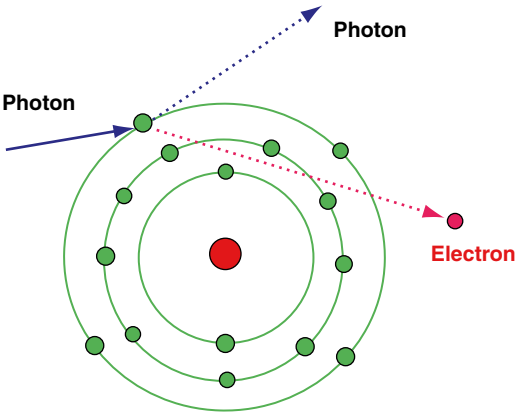

Fig. 1.21 Illustration of the Compton effect

1.4.3 Pair Production

This is a relatively rare effect. In it, a photon transforms into an electron and a positron near a nucleus (Fig. 1.22) [21]. The electron sheds all of its energy by the absorption processes explained above. On the other hand, the positron propagates through the medium ionizing atoms until its energy has dropped to such a low level that it pulls a free electron close enough to combine with it, in a process called annihilation. This annihilation causes the appearance of a pair of photon moving in opposite directions, and each with 0.511 MeV of energy. These annihilation photons are absorbed through either photoelectric or Compton events.

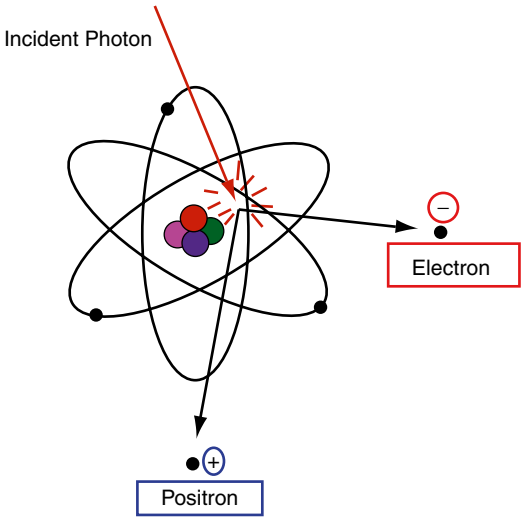

Fig. 1.22 Pair production

Pair Production

The threshold photon energy level for pair production is 1.02 MeV; below this, pair production will not occur.

The probability of pair production occurring increases as Z increases.

Pair production is more frequently observed than the Compton effect at energies of more than 10 MeV (Fig. 1.23).

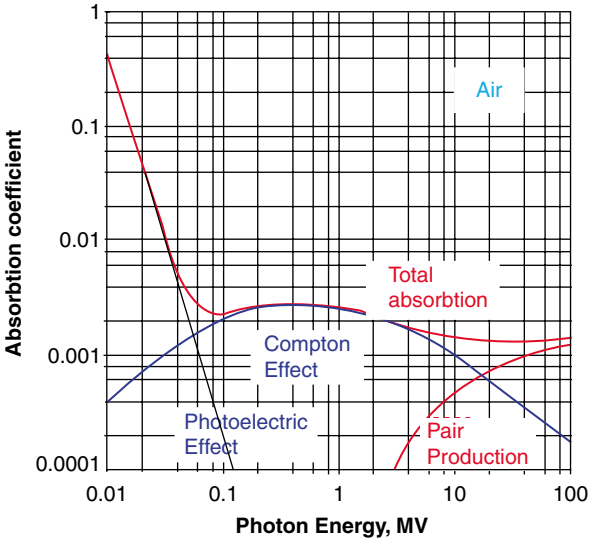

Fig. 1.23 Relationship between photon energy and absorption coefficient for various types of interaction with matter (in air)

1.4.4 Coherent Effect (= Rayleigh Scattering, = Thomson Scattering)

Here, an electron is scattered when an electromagnetic wave or photon passes close to it [21]. This type of scattering is explained by the waveform of the electromagnetic radiation. There are two types of coherent scattering: Thomson scattering and Rayleigh scattering (Fig. 1.24). The wave/photon only interacts with one electron in Thomson scattering, while it interacts with all of the electrons of the atom in Rayleigh scattering. In Rayleigh scattering, low-energy radiation interacts with an electron, causing it to vibrate at its own frequency. Since the vibrating electron accelerates, the atom emits radiation and returns to its steady state. Thus, there is no overall transfer of energy to the atom in this event, so ionization does not occur. The probability of coherent scattering is high in heavy (i.e., high-Z) matter and for low-energy photons.

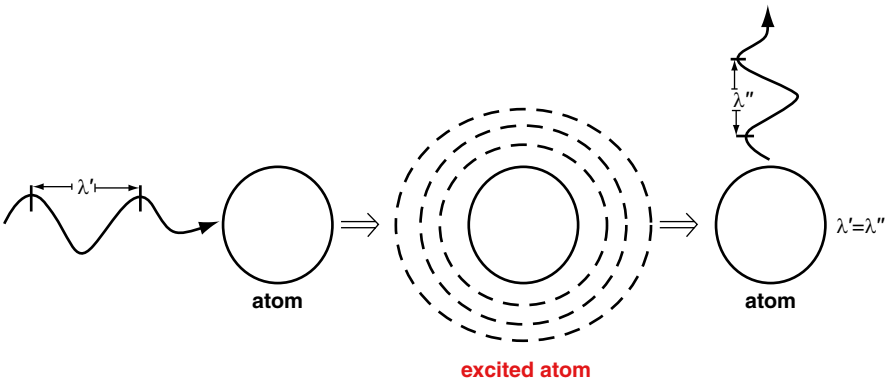

Fig. 1.24 Rayleigh scattering

- The coherent effect is the reason that the sky is blue during the day and reddish at sunset (Fig. 1.25)
- X-rays and γ-rays show the same intrinsic effects, but are produced in different ways (X-rays are generated extranuclearly, and gamma rays intranuclearly)
- Low-energy (nonionizing) radiation cannot ionize atoms because it does not have sufficient energy to do so, and thus it only causes excitation
- The target in mammography tubes is molybdenum, which produces characteristic X-rays of 17 keV

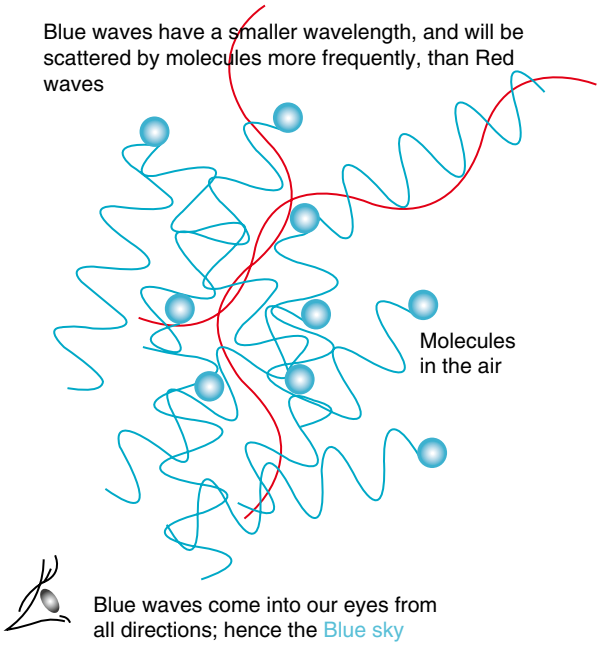

Fig. 1.25 Why the sky is blue

The probabilities of the various photon–matter interactions are summarized in Table 1.1.

Table 1.1 Interaction probabilities for various photon energies in the photoelectric effect, the Compton effect, and pair production in water

Photon energy (MeV)	Interaction probability (%)		
	Photoelectric effect	Compton effect	Pair production
0.01	95	5	0
0.026	50	50	0
0.060	7	93	0
0.150	0	100	0
4.00	0	94	6
10.00	0	77	23
24.00	0	50	50
100.00	0	16	84

Modified from [44]

The differences between bremsstrahlung X-rays and characteristic X-rays are described in Table 1.2.

Table 1.2 The differences between bremsstrahlung X-rays and characteristic X-rays

Bremsstrahlung	Characteristic X-rays
Also known as white radiation or braking radiation	Since it is produced by the movement of an outer orbital electron to an inner orbital, the energy of the X-ray is equal to the difference in the binding energies of the two orbits
Photon energy spectrum is equal to the initial electron energy	Produced X-rays are monoenergetic (constant energy)
Occurrence probability increases with the square of the target's atomic number	Characteristic X-rays comprise 30% of the X-rays used in diagnostic radiology, but only 3% of those used in radiotherapy
Used to create most X-rays >100 keV	
For <100 keV, the angle between the photon produced by brehmsstrahlung and the outgoing electron is 90°; this angle shortens when the beam energy is >100 keV	Occurrence probability increases with the square of the target's atomic number
Produced X-rays are heterogeneous in energy	

Electron volt (eV): this is the amount of kinetic energy gained by an electron when it is accelerated by a potential difference of 1 V ($1\ eV = 1.60217646 \times 10^{-17}\ erg = 1.60217646 \times 10^{-19}\ J$).

1.5 Specific Features of X-Rays

X-rays are a type of electromagnetic radiation with wavelengths of 10–0.01 nm, frequencies of 30–30,000 pHz (10^{15} Hz), and typical photon energies of 100 eV–100 keV (Table 1.3).

Table 1.3 Features of X-rays of various energies

Photon energy		Frequency (Hz)	Wavelength (pm, = 10^{-12} m)	Half-value layer (HVL)			
(keV)	(J)			Cement	Lead	Human body	Aluminum
1	1.602×10^{-16}	2.418×10^{17}	1,240	0.87 µm	0.117 µm	1.76 µm	2.17 µm
10	1.602×10^{-15}	2.418×10^{18}	124	147 µm	4.68 µm	1,220 µm	97.9 µm
100	1.602×10^{-14}	2.418×10^{19}	12.4	17.3 mm	0.110 mm	38.6 mm	15.1 mm
1000	1.602×10^{-13}	2.418×10^{20}	1.24	46.4 mm	8.60 mm	93.3 mm	41.8 mm
10,000	1.602×10^{-12}	2.418×10^{21}	0.124	132 mm	12.3 mm	298 mm	111 mm

The energy of an X-ray photon depends on its wavelength:

$$E = h\frac{c}{\lambda} \tag{1.2}$$

- Here, h is the Planck constant (6.626×10^{34} J/s), c is the speed of light, and λ is the wavelength.

X-rays are generally produced in either X-ray tubes or linacs. X-ray tubes are the main source of X-rays in laboratory instruments. In such a tube, a focused electron beam is accelerated under high voltage within a glass vacuum tube impacts a fixed or rotating target. When the electrons approach target atoms, Coulomb interactions with the nuclei cause the electrons to be suddenly deflected from their previous paths and slowed. During this braking process, energy in the form of X-rays is produced in a continuous spectrum (→ bremsstrahlung X-rays). High-energy electrons hit inner orbital electrons and knock them out of the atom during the ionization process. Free electrons from outer orbits then fill the empty spaces in the inner orbitals, and X-rays with energies that are characteristic of the target are produced (→ characteristic X-rays) (Fig. 1.26).

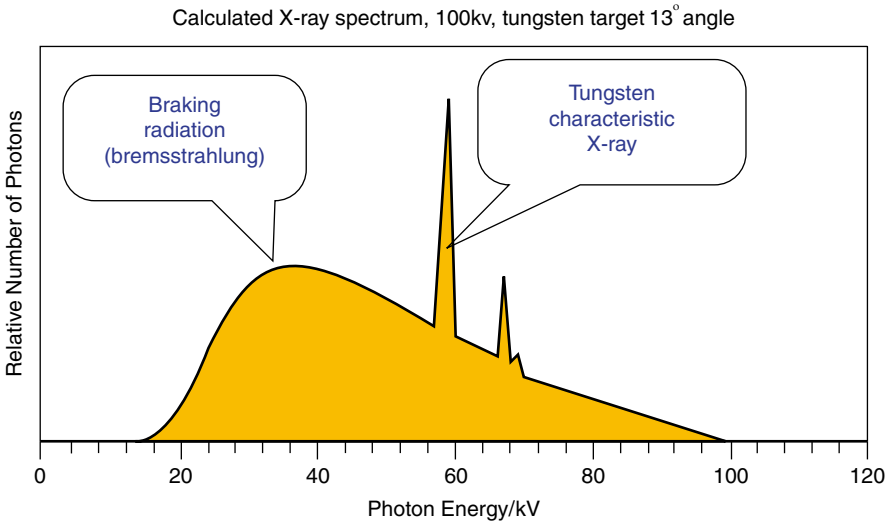

Fig. 1.26 X-ray spectrum

Early in the history of radiotherapy, the X-ray beams used had energies of only between 250 and 400 kV. The penetrative abilities of those X-rays were rather poor. Most of the energy of the X-rays produced can be explained by the X-ray energy spectrum. Unfiltered low-energy X-rays can easily be absorbed by superficial tissues in the human body, and so excessive dose accumulation can occur in these areas, and causing serious dermal reactions during the treatment of deeply seated tumors.

X-rays are used in various applications in industry and medicine (Table 1.4).

Table 1.4 The various uses of X-rays and their features

Usage		Acceleration potential	Target	Source type	Mean photon energy
X-ray crystallography		40 kV 60 kV	Cooper Molybdenum	Tube	8–17 keV
Diagnostic radiology	Mammography	26–30 kV	Rhodium Molybdenum	Tube	20 keV
	Dentistry	60 kV	Tungsten	Tube	30 keV
	Roentgen	50–140 kV	Tungsten	Tube	40 keV
	CT	80–140 kV	Tungsten	Tube	60 keV
Airport, customs	Airport	80–160 kV	Tungsten	Tube	80 keV
	Customs	450 kV– 20 MV	Tungsten	Tube/linear Accelerator	150 keV– 9 MeV
Structural analysis		150–450 kV	Tungsten	Tube	100 keV
Radiotherapy		10–25 MV	Tungsten/high atomic number matter	Linear accelerator	3–10 MeV

1.6 Specific Features of Electron Energies

Electrons with energies of 2–10 MeV are low-energy electrons, whereas electrons with energies of 10–42 MeV are high-energy electrons. Low-energy electrons can also be produced by some radioactive isotopes such as yttrium-90. Medium- to high-energy electrons are produced in linacs or betatrons. They are used in superficial treatments due to their limited penetration ability.

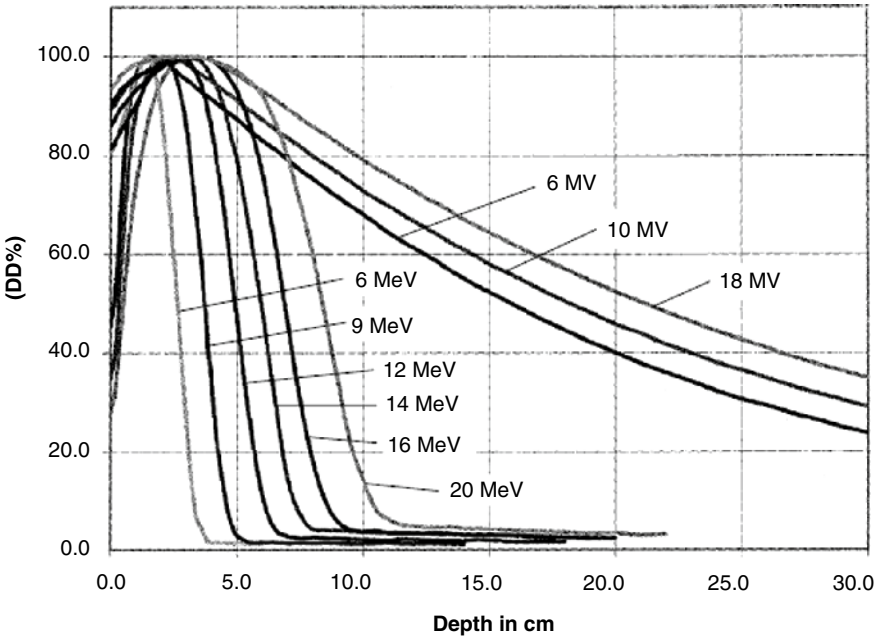

Fig. 1.27 Relative depth dose distributions of photons and electrons

Energy is selected according to target depth and field size in radiotherapy (Fig. 1.27). Co-60 can be selected for thin regions such as the head and neck and extremities, whereas high-energy X-rays are preferred for thicker regions such as the abdomen, pelvis, and thorax. Electrons are generally used to treat skin cancers and superficially located tumors.

1.7 Ionizing Radiation Units

The amount of radiation delivered needs to be known in order to determine possible harmful biological effects and to reach definite conclusions in studies that use ionizing radiation. Specific units are required for radiation measurement.

Units of radiation measurement have changed dramatically over the years, and some units have been completely abandoned (e.g., the pastille), while other units have been introduced (Fig. 1.28).

Fig. 1.28 Scientists whose names are used as the units in which radiation-associated quantities are measured

The measured quantities associated with ionizing radiation can be briefly summarized as follows (Fig. 1.29):

Source → activity units
The first interaction point → kinetic energy released in matter (kerma)
Matter → absorbed dose

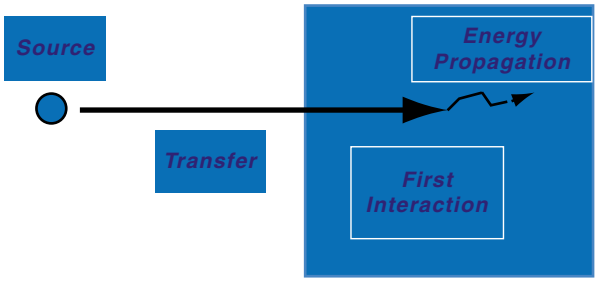

Fig. 1.29 Three points associated with ionizing radiation measurement

Activity unit. This is the number of spontaneous nuclear disintegrations (N) per unit time (t) ($A = N/t$), as measured in becquerels (Bq). Note that an older system of units, the curie (Ci), is also often encountered.

Radioactivity. This is the transition of an unstable nucleus to a steady state through the emission of particulate or electromagnetic radiation from the nucleus.
Curie (Ci). This is an activity of 3.7×10^{10} disintegrations per second.
Becquerel (Bq). This is an activity of one disintegration per second.

$1\ \text{Ci} = 33.7 \times 10^{10}\ \text{Bq}$
$1\ \text{Bq} = 2.7 \times 10^{-11}\ \text{Ci}$

Kerma (kinetic energy released in the medium). This is the sum of the initial kinetic energies of all of the charged particles liberated by uncharged ionizing radiation (neutrons, protons) in a sample of matter divided by the mass of the sample. The kerma is measured in the same units as absorbed dose (Gy).

The *reference air kerma* is used to define the visible activity. It is the dose delivered in one hour to air one meter away from a source with an activity of 1 MBq. Its units are $1\ \mu Gy^{-1}.\ m^2 = 1\ cGy.\ h^{-1}.\ cm^2$.

Absorbed dose. The basic quantity associated with radiation measurement in radiotherapy is the absorbed dose. This defines the amount of energy absorbed from a radiation beam per unit mass of absorbent material. It is measured in grays (Gy), although an older unit, the rad, is also still used.

Rad. This is the amount of radiation that causes one erg (of energy) to be absorbed per gram of irradiated material (rad = radiation absorbed dose).

1 rad = 100 erg/g.

Gray (Gy). This is the amount of radiation amount that cause one joule to be absorbed per kilogram of irradiated material.

1 Gy = 1 J/kg.

1 Gy = 100 cGy = 100 Rad.

Exposure. This is the amount of ionization produced by photons in air. Since it is impossible to directly measure the absorbed dose in tissue, the measurement of radiation is performed in air. The exposure is the amount of radiation required to liberate a positive or negative charge of one electrostatic unit of charge (esu) in 1 cm^3 of dry air at standard temperature and pressure (this corresponds to the generation of approximately 2.08×10^9 ion pairs). It is measured in coulombs per kilogram (C/kg), although the old unit of the roentgen (R) is also commonly encountered.

Roentgen (R). In normal air conditions (0°C and 760 mmHg pressure), this is the amount of X-radiation or gamma radiation that produces 2.58×10^{-4} coulombs of electrical charge (in the form of ions) in one kilogram of air.

C/kg. In normal air conditions, this is the amount of radiation that produces one coulomb of electrical charge (in the form of ions) in one kilogram of air.

Integral dose. This is the total energy absorbed in the treated volume (in J = kg × Gy).

Equivalent dose. Since different radiations have different harmful effects on human tissues, the basic dosimetric unit of absorbed dose (→ Gy) is not sufficient for studies of radiation protection. Thus, the absorbed dose in tissue must be multiplied by a radiation-weighting factor that depends on the type of radiation employed. The resulting dose is called the equivalent dose, and it is measured in sieverts (Sv), although an older unit, the rem (roentgen equivalent man), is often used too.

$$H = D \times WR \tag{1.3}$$

H = equivalent dose (Sv)
WR = radiation-weighting factor (no unit)
D = dose (Gy)
1 Sv = 1 J/kg = 100 rem

The roentgen and C/kg are only used for photonic radiation (X-rays and gamma rays), not for particulate radiation.

The energies of therapeutic or diagnostic gamma rays and X-rays are in the kilovolt (kV) or megavolt (MV) range, while the energies of therapeutic electrons are in the megaelectronvolt (MeV) range.

1.8 Radiotherapy Generators

Kilovoltage X-rays are generally used in the treatment of skin cancers and superficial tumors, whereas megavoltage X-rays are used in the management of deeply seated tumors [22]. Megavoltage electrons, on the other hand, are used in the treatment of superficial tumors.

Kilovoltage Machines (<500 kV)

Contact therapy machines

40–50 kV
Filtered with 0.5–1.0 mm aluminum.
SSD = 2 cm
50% depth dose is 5 mm.

Superficial therapy machines (Fig. 1.30)

50–150 kV
Filtered with 1–4 mm aluminum.
SSD = 20 cm
50% depth dose is 1–2 cm.

Orthovoltage therapy machines (Fig. 1.31)

150–500 kV
Filtered with 1–4 mm copper
SSD = 50 cm (for a field size of 20 × 20 cm)
50% depth dose is 5–7 cm
Basic therapy machine before 1950

Supervoltage therapy machines

500–1,000 kV
Filtered with 4–6 mm copper
50% percent depth dose is 8–10

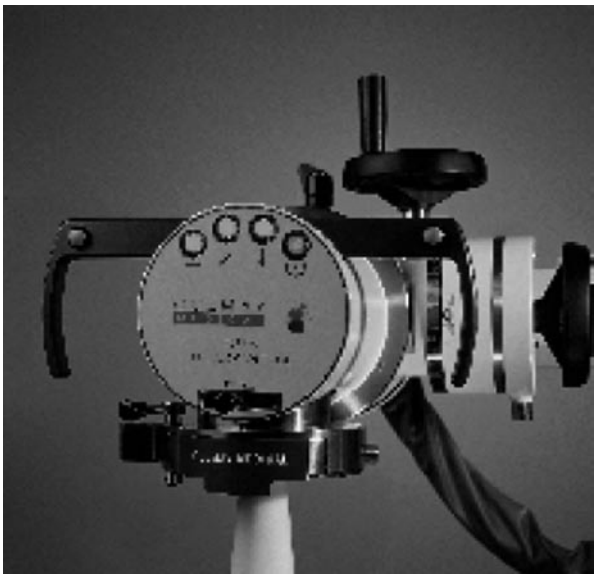

Fig. 1.30 Superficial therapy machine

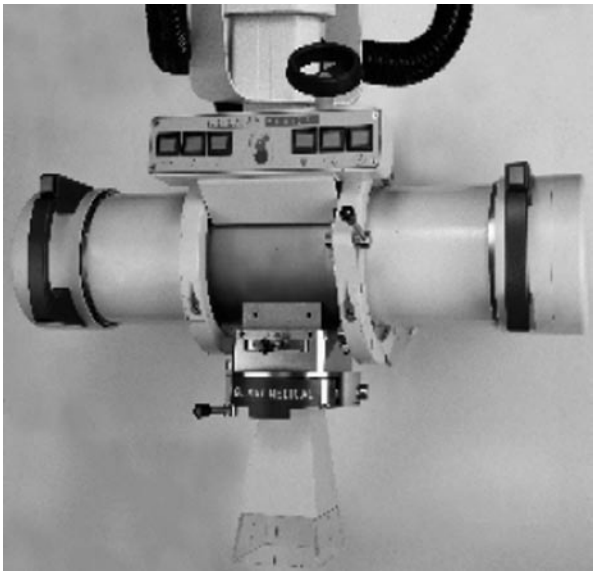

Fig. 1.31 Orthovoltage therapy machine

Megavoltage Therapy Machines (>1 MV)

Van de Graaf generator (Fig. 1.32)
Also known as an electrostatic generator
Produces energies of up to 25 MV

Cobalt-60 teletherapy unit *(Co-60)*
Manufactured in 1951

(*continued*)

(continued)

Two gamma rays with energies of 1.17 and 1.33 MV
Dose rate >150 cGy/min
SSD = 80–100 cm (for field sizes of 35 × 35 or 40 × 40 cm)
50% depth dose is 10 cm
The half-life of Co-60 is 5.27 years
Source is 2 cm in diameter, and has a large penumbra in comparison to a 4 MV linac.

Betatron (Fig. 1.32)

Developed in 1940

Developed for the circular induction acceleration of electrons and light particles. The magnetic field guide is increased over time in order to keep the particles in a constant-diameter circle

Mean energy is 45 MeV (maximum energy ~300 MV)

Not used after the advent of linacs, due to their large dimensions, high costs, and low dose rates

Linear accelerator (linac)

Entered into routine clinical service in 1953
SSD = 100 cm (for a field size of 40 × 40 cm)
Produces several photon and electron energies

Microtron (Fig. 1.32)

Entered clinics in 1972
Combination of a linac and a cyclotron
A circular particle accelerator for accelerating electrons to energies of several MeVs

Has a simple structure and it is easy to select the appropriate energy. Small compared to other linacs. Just one microtron generator can provide electrons for more than one treatment room

Produces energies of up to 50 MeV

Cyclotron

A circular particle accelerator in which charged subatomic particles generated at a central source are accelerated spirally outward in a plane perpendicular to a fixed magnetic field by an alternating electrical field. A cyclotron is capable of generating particle energies of between a few million and several tens of millions of electron volts

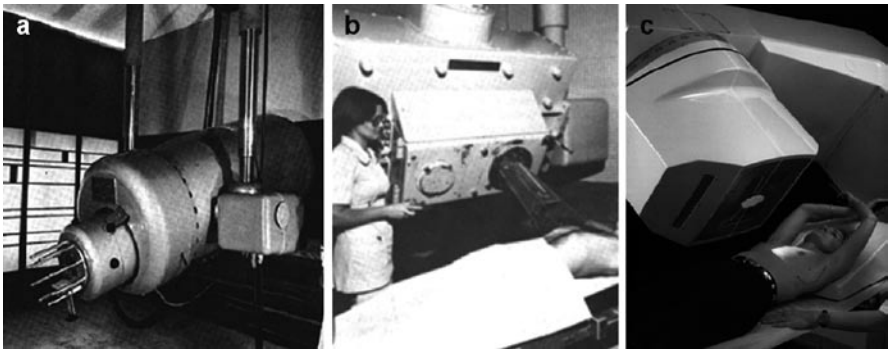

Fig. 1.32 (**a**) Van de Graaf generator; (**b**) betatron; (**c**) microtron

Orthovoltage treatment machines [22]
These machines have similarities with machines used in diagnostic radiology. X-rays are produced by accelerating electrons into tungsten. These X-rays are shaped by collimators before they reach the tumor tissue. Essentially all of the dose is directed onto the surface of the skin; the percentage depth dose (PDD) curve drops sharply. Thus, deeply seated tumors cannot be treated using these machines. Orthovoltage treatment machines are currently only found in a few centers, and are only used to treat skin cancers or some very superficial lesions in the head and neck region.

Megavoltage treatment machines [22]
Megavoltage treatment machines are the foundation of modern radiotherapy techniques. Photon beams are produced in megavoltage treatment machines. Their one difference from orthovoltage machines is the skin-sparing effect (i.e., the maximum energy is delivered in the subepidermal region). The skin-sparing effect is directly proportional to the energy of the photons. The maximum dose point distance from the skin is 0.5 cm for Co-60, 1.5 cm for 6 MV photon beams, and 2.5 cm for 10 MV photon beams. In addition, these machines have more suitable depth doses for deeply seated tumors and a sharper dose distribution at the field edge due to reduced side scattering. When electrons are used, deeper healthy tissues are well protected in the treatment of superficially located tumors by controlling the penetration depth.

1.8.1 Cobalt-60 Teletherapy Unit

Natural cobalt is a hard, stable, bluish-gray, easily breakable metal with properties similar to iron and nickel. Its atoms contain 27 protons, 32 neutrons, and 27 electrons [23]. Nonradioactive cobalt can be found mixed with various minerals in nature, and has been used to impart a blue color to glass and ceramics for thousands of years.

In 1735, a Swedish scientist, George Brandt, showed that the bluish color in colored glasses was due to a previously unknown element that he named cobalt. The melting point of cobalt is 1,495°C, its boiling point is 2,870°C, and its density is 8.9 g/cm^3.

The well-known isotope of cobalt is unstable radioactive Co-60. This isotope was discovered by Glenn Seaborg and John Livingood at California Berkeley University in 1930. Co-60 is now produced commercially in nuclear reactors.

The decay of Co-60 starts with a β^- decay, and then two gamma emissions with energies of 1.17321 and 1.33247 MV are observed (Fig. 1.33).

The half-life ($t_{1/2}$; i.e., the time required for the activity of the source to half) of Co-60 is 5.27 years. For practical purposes it is considered harmless and inactive after ten half-lives. Thus, Co-60 should be stored safely for approximately 53 years.

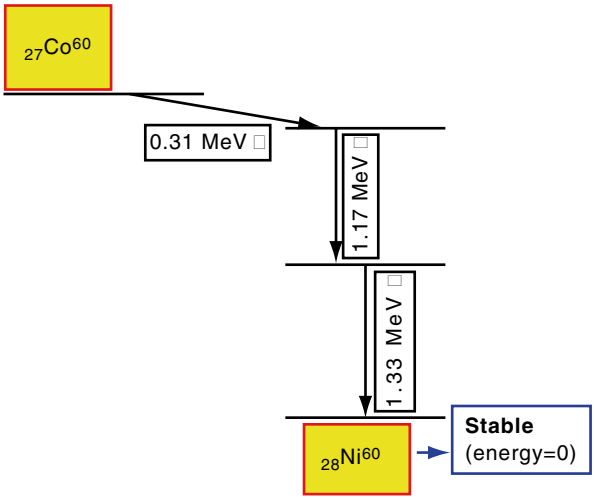

Fig. 1.33 Cobalt-60 decay scheme

Co-60 teletherapy units have a cylindrical source 2 cm in diameter. The activity of the source is generally between 5,000 and 15,000 Ci (Fig. 1.34). A source with an activity of less than 3,000 Ci is replaced with a new one; this is necessary after 5–7 years of use.

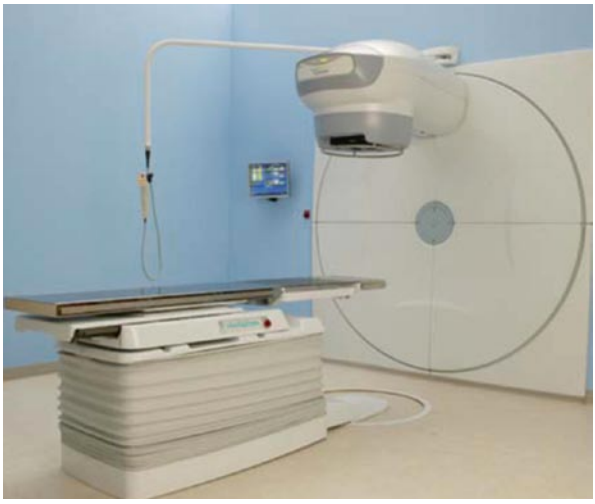

Fig. 1.34 Cobalt-60 teletherapy unit

Co-60 teletherapy units provide good performance for tumors with depths of <10 cm. Thus, the use of a linac is recommended for more deeply seated tumors.

Treatment Head and Collimator (Figs. 1.35 and 1.36)

This has the capacity to take a source with an activity of 10.000 Roentgens per hour at a meter (RHm) (165 Roentgens per minute at a meter (Rmm)).

The leakage from the treatment head is not more than 2 mR/h at 1 m.

The drive mechanism for the source within the treatment head has a very simple linear structure, and returns to its parked position spontaneously in emergencies (even during electric interruptions).

It has the property of interlocking with the source head at an angle of 0°.

The source–skin distance (SSD) is 80–100 cm.

The rotational movement of the collimator is continuous, and it can rotate 360° about its own axis.

An optical distance indicator showing the SSD is present on the treatment head of the system.

The collimator system can move to any position when the gantry is rotated.

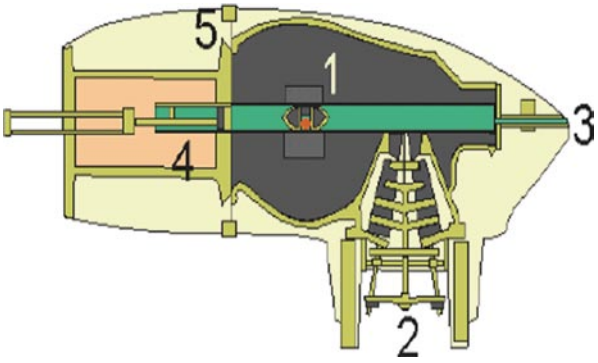

Fig. 1.35 Treatment head of a cobalt-60 teletherapy unit. The cobalt source (*orange*) is situated in a drawer, and surrounded by lead (*1*). When the device is in the resting position, the source is protected by layers of enriched uranium. The source is then pushed by a pneumatic system (*4*) to the treatment position. *2*, The collimator system; *3*, manual system that can pull the source to the resting position in case of emergency; *5*, link between the head and the rotating part of the machine that is used to change the source when its activity is no longer sufficient for treatment

Gantry

The source–isocenter distance (SAD) is 80–100 cm.

The rotational movement of the gantry is motorized and controlled in two directions continuously; its rotation speed can be adjusted.

The gantry can rotate by 360°.

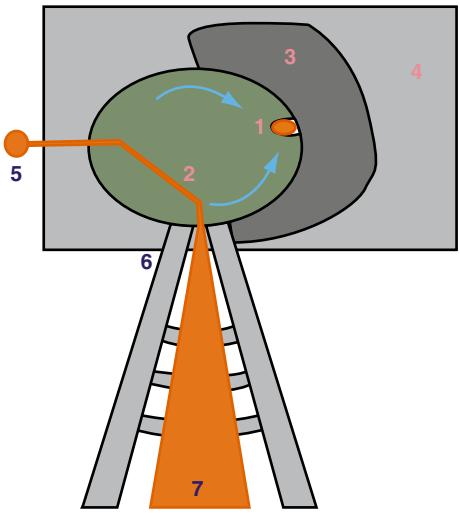

Fig. 1.36 Cobalt-60 head. *1*, Cobalt-60 source; *2*, tungsten cylinder; *3*, enriched uranium; *4*, lead; *5*, laser source; *6*, collimator; *7*, γ-rays

1.8.2 Linear Accelerator (Linac)

There are two types of accelerator that are used for radiation treatment [23]. Betatron and linac electron accelerators comprise 99% of all current accelerator machines used in radiation treatment. Cyclotrons, on the other hand, are heavy particle accelerators that are used for proton or neutron treatments.

Free electrons emitted from a metal wire via thermionic emission (as in the case of the X-ray tube) are accelerated in an electromagnetic field to increase their kinetic energies. These accelerated high-energy electrons can either be used directly for radiotherapy (generally for superficial therapy), or they are directed into a target and high-energy X-rays are produced (for deeply seated tumors). In this way, X-rays with energies of 4–25 MV are produced by electrons with energies of 4–25 MeV. It is impossible to accelerate the electrons to more than 400 kV within conventional X-ray tubes. Thus, high-frequency magnetic wave chambers are used in linac machines, and the negatively charged electrons are accelerated by the magnetic fields in such machines, thus gaining kinetic energy.

Microwave chamber. This consists of cylindrical, conductive metal chambers (8 cm in diameter), and it produces 3,000 MHz electromagnetic waves.
Electron acceleration. High-frequency electromagnetic waves occurring within the chamber move into the canal in the middle of cylinder, and electrons are accelerated linearly by passing from one chamber to other one within this canal. The velocity of an electron exiting this tube is equal to the sum of the velocities gained by the electron within each chamber.

The operational principle of electron accelerators. An electric impulse is deposited in the modulator. A specific control mechanism sends this impulse simultaneously to the electron gun and to the section responsible for microwave production (called the klystron or magnetron) at certain intervals (frequency: 50–200 Hz). The electrons liberated by the pulses are sent to the accelerator tube. An automatic frequency control module generates electromagnetic waves in the accelerator tube with the same frequency.

Electrons produced in the electron gun are sent to the accelerator tube with energies of 50 keV. The electrons ride on top of the electromagnetic waves, so they are accelerated and their energies are boosted to the MeV level. They reach their maximum energies at the end of the accelerator tube.

Electrons exiting through the accelerator tube are then diverted at an angle of 90 or 270° and guided to the head, where the beam exits.

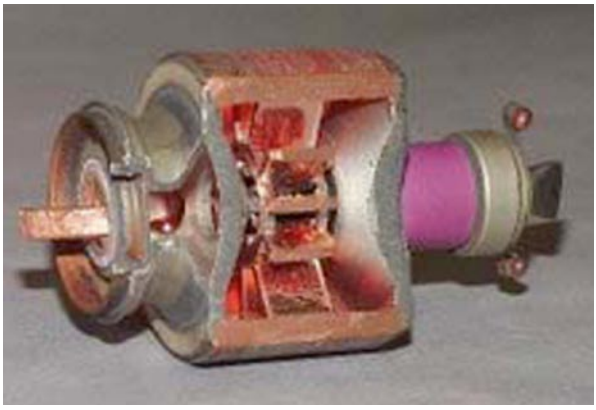

Fig. 1.37 Magnetron

Magnetron (Fig. 1.37) [24]

This is an oscillator that produces hundreds of microwaves per second. The frequency of the microwaves is 3,000 MHz.

The exit power of a low-energy linac magnetron (lower than 6 MV) is 2 MW.

Klystron (Fig. 1.38) [24]

This does not produce microwaves; it is a microwave amplifier.

Microwaves produced in low-power oscillators are sent to the klystron in order to gain power (energy).

The klystrons used in a high-energy linac can boost the energy to 25 MV, leading to an exit power of 5 MW.

The dose stabilities of klystrons are much better than those of magnetrons.

Fig. 1.38 Klystron

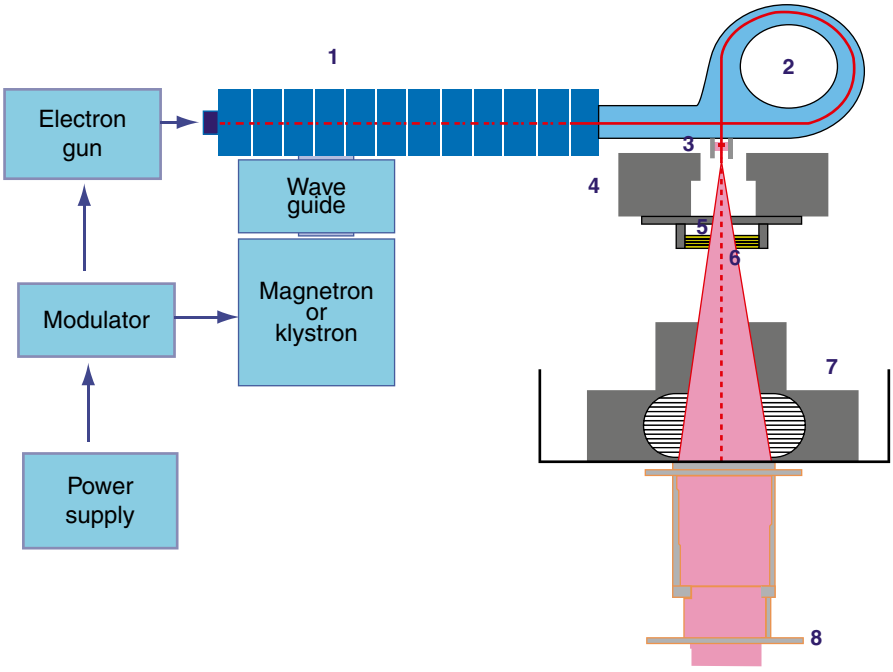

Fig. 1.39 General illustration of a linear accelerator. (1) The production and the acceleration of electrons, (2) The 270° bending of electrons, (3) Target and primary filter, (4) Primary collimators, (5) Main filter, (6) Ionizing Chamber, (7) Multileaf collimator, (8) Electron applicator

- The electron gun used in a linac is a hot-wire filament (Fig. 1.39)
- The main purpose of the flattening filter in a linac is to collect low-energy X-rays and enable the passage of high-energy X-rays (i.e., it "flattens" the beam)
- In some linacs an electromagnetic wave transmitter is used instead of a scattering foil

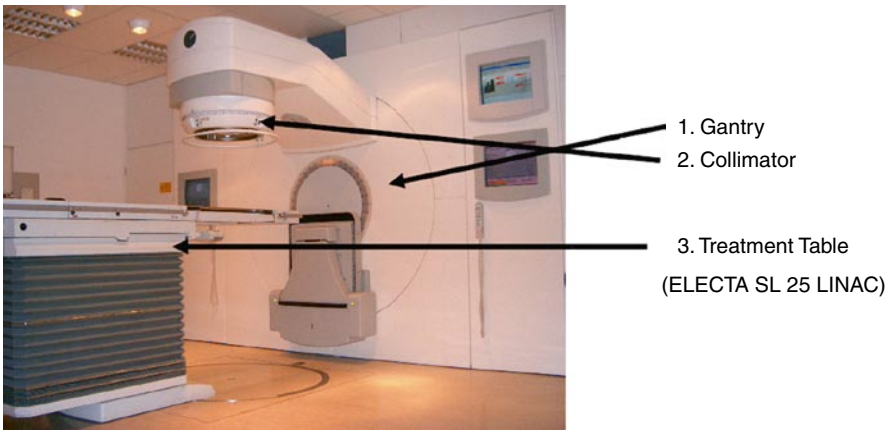

Fig. 1.40 A linear accelerator (linac)

The Electa SL 25 linac treatment head consists of (in order): a tungsten target, a primary collimator, a flattening filter (main filter) containing a mixture of tungsten and aluminum that is used to adjust the spatial modulation of the beam intensity, a scattering foil to spatially spread the electron beams, two ion chambers, a motorized 60° wedge filter and multileaf collimator (Fig. 1.40).

1.9 Measurement of Ionizing Radiation

The maximum allowable dose is limited to 20 mSv per year for people working with radiation. This limit is 1 mSv for the normal population. The effects of irradiation on an organism may change according to the dose, the type of contamination, and the features of the radiation source. It is crucial to perform measurements on the radiation generators used for diagnostic or therapeutic purposes. The measurement of radiation is called dosimetry, and the equipment used for dosimetric procedures is called a dosimeter or a detector [25].

Detector Types

1. Detectors according to the principle of operation:
   (a) Pulse type
   (b) Current type
2. Detectors according to their structures:
   (a) Gas-filled detectors:
      - Ionization chambers
      - Proportional detectors (with or without a window)
      - Geiger–Müller detectors (with or without a window)
      - Gas scintillation detectors
   (b) Solid-state detectors:
      - Crystal detectors
        – Scintillation detectors
        – Semiconductive detectors
      - Plastic detectors (solid or liquid)
      - Glass detectors
3. Film detectors
4. Dosimeters:
   (a) Electron spin resonance (ESR)/alanine
   (b) Thermoluminescence (TLD)
5. Chemical detectors
6. Neutron detectors

1.9.1 Portable Measuring Equipment

The basic principle of a portable measuring device is ionization inside a gas-filled detector. Radiation creates ion pairs, and these ion pairs are collected and converted into an electrical signal (impulse or current) when they pass through an electrical field. This signal is used to determine whether and how much radiation is present.

There are several types of detector, and they all work on the same principle. Ion chambers and Geiger–Müller counters are the two main types of measuring instrument.

Ionization Chamber [25]

This is designed to measure the dose rate of ionizing radiation in mR/h or R/h. The detector usually takes the form of a cylinder that is filled with air (Fig. 1.41). When the radiation interacts with the air in the detector, ion pairs are generated, and collecting them results in a small current. The charge occurring within the air defines the dose rate.

- Ion chambers are used for the measurement of X-rays, gamma rays, and beta particles.

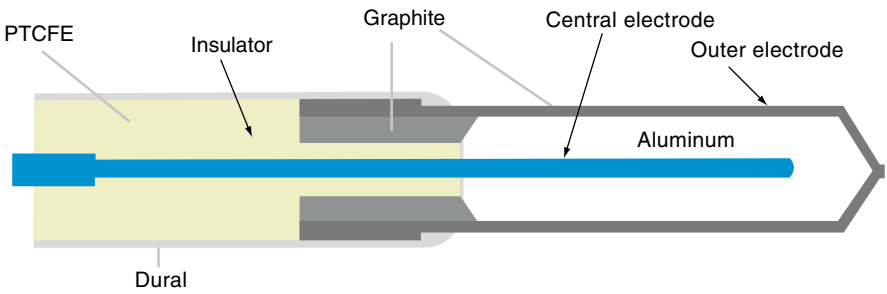

Fig. 1.41 Basic design of a Farmer-type ionization chamber

Geiger–Müller Counter (GM Counter)

A GM counter consists of a tube filled with "Q-gas" (98% helium and 1.3% butane; see Fig. 1.42). As in an ion chamber, the detector records every interaction instead of measuring the average current that occurs after several reactions. In other words, one ionizing event will produce a pulse or a count in the GM tube. This does not take into account the number of pairs that started the pulse; all pulses are the same. Thus, a GM counter does not differentiate between types of radiation or their energies. For this reason, most GM counters are calibrated to give counts per minute (CPM). GM counters are usually used to simply detect the presence of radioactive material.

- GM counters are used to detect low-energy X and gamma rays.

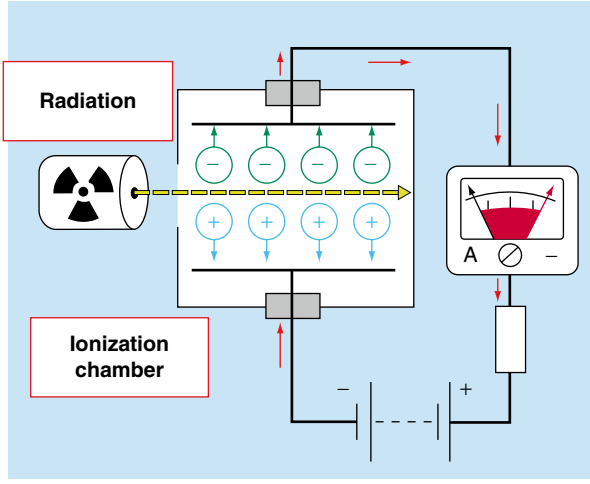

Fig. 1.42 Simple illustration of a Geiger–Müller counter

Film dosimeters [25]: A film dosimeter is the oldest and most popular system that is used to determine the dose taken a person working with radiation (Fig. 1.43). It is based on the effect of radiation on the optical density of developed photographic film. A dosimeter consists of two main parts: the film and its holder. There are filters of various thickness and types in order to have the optical density resulting from the radiation on the film to be independent from radiation type and energy. The dose calculation is done by measuring optic densities behind the filters on the film.

- The radiation doses taken from beta, gamma, and X-ray sources can be measured by film dosimeters

Fig. 1.43 Personal dosimeters

Thermoluminescence dosimeters (TLD) [25]: Thermoluminescence is the phenomenon where a material luminesces (emits significant amounts of light–glows) when it is heated. In a solid crystalline material, there is forbidden energy zone between the valance band and conduction band where no electron can exist. When the crystal is excited by radiation, traps appear, and electrons coming from the valance band or returning from the conductive band are caught in these traps (Fig. 1.44). Thus, some of

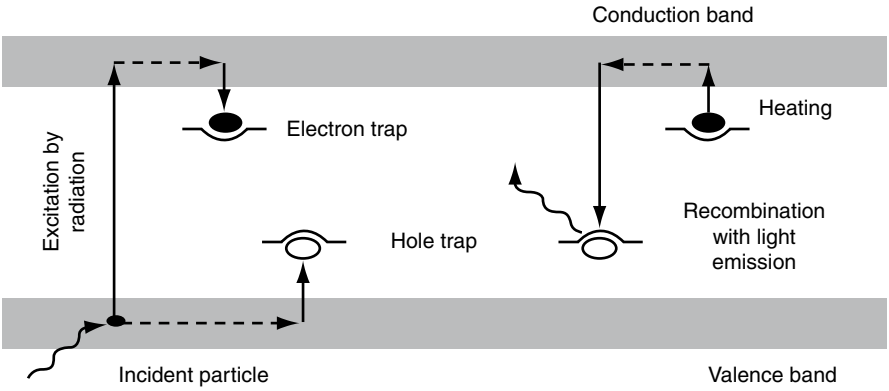

Fig. 1.44 Energy level diagram for a TLD crystal

the energy transferred from the radiation to the crystal is deposited. If this crystal is heated to a certain temperature, the electrons gain enough energy to release themselves from these traps and return to the valance band, and the energy they release when they do so is emitted as light (i.e., luminescence). This luminescence can be measured by an electrometer. Crystals that exhibit this phenomenon include LiB_4O_7, LiF, and $CaSO_4$, and these are used in TLDs.

- TLDs can separately measure gammas, X-rays, beta particles and thermal neutrons with energies of between 10 keV and 10 MeV

1.9.2 Other Measuring Equipment

Electron Spin Resonance (ESR)/Alanine Dosimeter [25]
One device that can be used to measure high doses is the ESR/alanine dosimeter. Here, powdered alanine crystals are mixed with a defined ratio of combiners. When the alanine is exposed to radiation, free radicals are generated. The number of radicals is determined by the ESR technique, and this can then be used to work out the absorbed dose is found. Alanine is a tissue-equivalent material due to its characteristics (e.g., composition, density, and effective atomic number). ESR/alanine dosimeters give sensitive, reliable and repeatable results for a wide range of doses.

Neutron Dosimeter [25]
These dosimeters are sensitive to low-energy thermal neutrons with energies of between 0.02 and 50 eV. They utilize lithium and copper TLD crystals, and can be used to measure neutron doses of between 0.005 mSv and 0.5 Sv.

1.10 Radiation Dosimetry

The quality of the radiation produced can differ between radiotherapy machines. The quality of radiation depends on the type of radiation, its energy and its penetrating ability. These characteristics should be experimentally measurable and confirmable. Several physical measurements, measuring techniques, and units help to increase radiotherapy efficacy, in accordance with the principle of *primum non nocere*. Dosimetric measurements are performed in patients, and water or tissue-equivalent phantoms and physical treatment parameters are determined.

1.10.1 Phantom

Phantoms are models constructed from tissue-equivalent material and used to determine the radiation absorption and reflection characteristics of a human body or a specific organ (Fig. 1.45) [26]. Phantom materials are equivalent to human tissues in terms of their characteristics under X-ray and electron irradiation. Soft tissue, bone and lungs are equivalent of real density. Soft tissues are mimicked by heat-hardened plastic material. The effective atomic number of soft tissue is $7.30 \pm 1.25\%$, and its density is $0.985 \pm 1.25 g/cm^3$. Although lung has the same atomic number as soft tissue (7.30), its density is 0.32 ± 0.01 g/cm^3. The bones used in a phantom are real human bones, and the same cavities exist as in the human body. The phantom is divided into slices of 2.5 cm thickness. There are drilled holes of 2.5–6 mm diameter for TLD insertion in each slice.

Fig. 1.45 An Alderson RANDO phantom

1.10.2 Definition of Beam Geometry

The accurate delivery of a radiation dose to patient depends on the precise positioning of the patient and radiation source. The geometric parameters linking the source and target (tumor at treatment) are described below (Fig. 1.46).

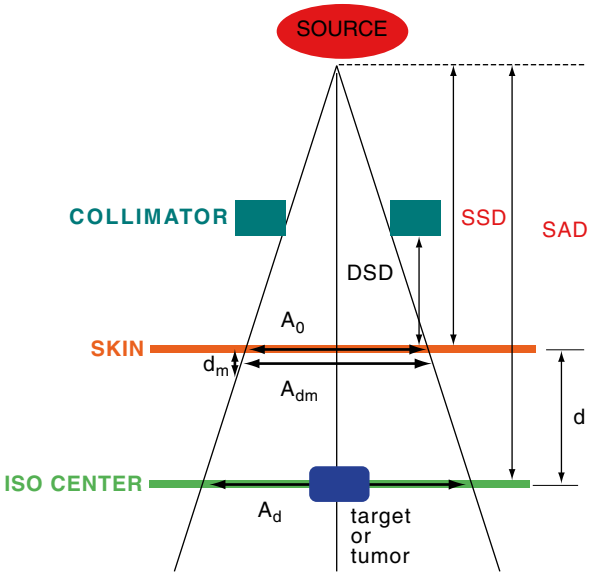

Fig. 1.46 Geometric parameters between the source and target

SSD: skin to source distance
SAD: skin to axis distance
DSD: diaphragm to skin distance
A_0: field on skin
Ad: field at D_0 depth (field at the location of the tumor)
A_{d_m} : field size at the point of dose maximum (field at build-up point)
d: depth (tumor depth)
d_m: depth at dose maximum (D_{max})

A_0 and A_{d_m} can be found mathematically using the geometric parameters between source and the target:

$$A_d = \frac{A_0 \times (\mathrm{SSD} + d)}{\mathrm{SSD}} = A_0 \times \frac{\mathrm{SAD}}{\mathrm{SSD}} \tag{1.4}$$

$$A_{d_m} = A_0 \frac{(\mathrm{SSD} + d_m)}{\mathrm{SSD}} \tag{1.5}$$

SSD and SAD are geometric parameters that can be changed, and the ability to change them leads to two different planning and treatment set-up modalities (Fig. 1.47):

- *Constant SSD technique* [27]. Here, the isocenter (the point at which all of the radiation beams cross) of the treatment machine (or simulator) is on the patient's skin (= nonisocentric technique).
  - Field and dose are defined according to A_0.
- *Constant SAD technique* [27]. Here the isocenter of the treatment machine (or simulator) is in the patient (in the tumor) (= isocentric technique; Fig. 1.48).
  - Field and dose are defined according to A_d.

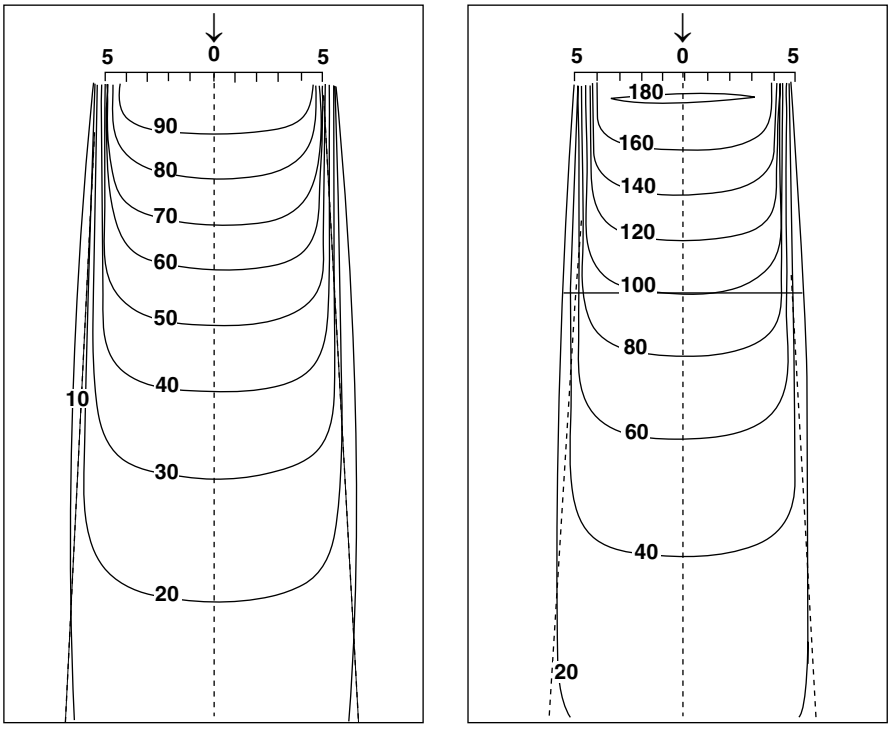

Fig. 1.47 Isodose curves in SSD and SAD techniques

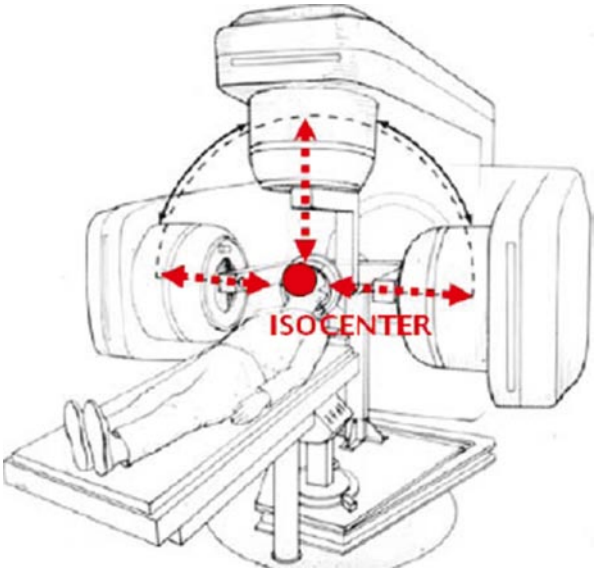

Fig. 1.48 Isocenter

1.10.3 Build-Up Region

The region between the skin and the depth at dose maximum (D_{max}) is called the build-up region (Fig. 1.49) [27, 28]. This region between the surface and depth d is referred to as the dose build-up region in megavoltage beams, and it results from the kinetic energy deposited in the patient by secondary charged particles (which have relatively long ranges) released inside the patient by photon interactions (photoelectric effect, Compton effect, pair production) (Tables 1.5 and 1.6).

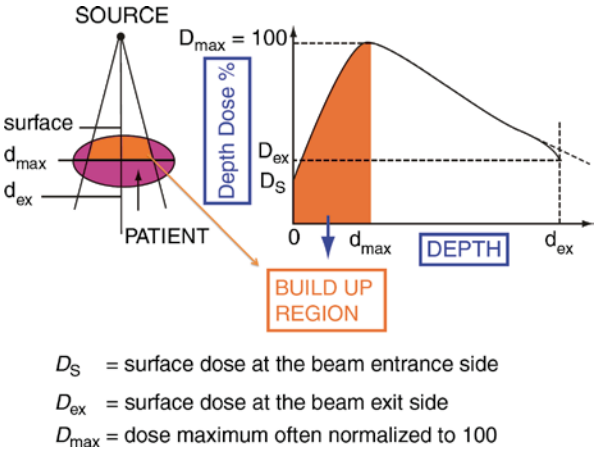

Fig. 1.49 Build-up region

Table 1.5 Build-up points (depth of D_{max}) for various photon energies

	Superficial	Orthovoltage	Co-60	4 MV	6 MV	10 MV	18 MV	25 MV
Depth of D_{max} (cm)	0	0	0.5	1	1.5	2.5	3.5	5

Field size = 5 × 5 cm

Table 1.6 Build-up points (depth of D_{max}) for various electron energies

	6 MeV	9 MeV	12 MeV	15 MeV	18 MeV	22 MeV
Depth of D_{max} (cm)	1.2	1.56	2.1	1.7	1.5	1.49

1.10.4 Half-Value Layer (HVL)

A radiotherapy machine is characterized by the penetrating ability of its radiation. The thickness of material that decreases the intensity of the incoming radiation to half of its initial value (50%) is called the half-value layer (HVL), and quoted in mm or cm of absorbent material (Fig. 1.50) [29]. The absorbent materials that are generally used in this context are aluminum, copper and lead (Table 1.7).

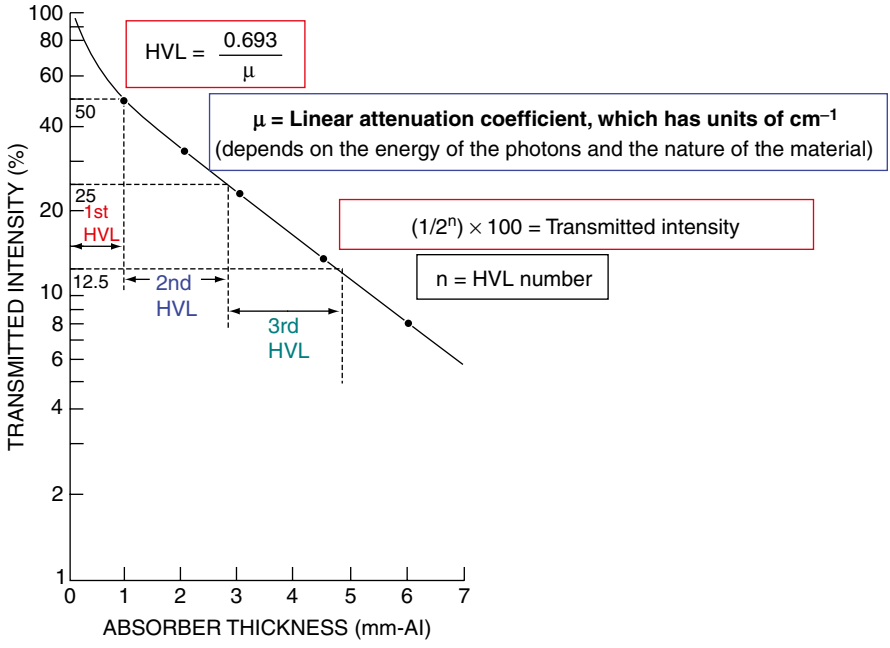

Fig. 1.50 Transmission of an X-ray beam through an aluminum absorbent

The HVL is generally used to characterize low-energy X-ray machines.

A high-energy radiation beam is characterized by its maximum energy and the depth at the 50% isodose curve.

Table 1.7 Half-value layers of various radioisotopes

Radioisotopes	Half-value layer (cm)		
	Lead	Iron	Cement
Tc-99m	0.02	–	–
I-131	0.72	–	4.7
Cs-137	0.65	1.6	4.9
Ir-192	0.55	1.3	4.3
Co-60	1.1	2.0	6.3

Blocks with thicknesses of ~4–5 HVLs are used in radiotherapy. A block five HVLs thick transmits 3.125% of the incoming radiation.

1.10.5 Percentage Depth Dose (PDD)

The ratio (in percent) of the dose absorbed at a predefined depth (D_x) to D_{max} (the dose maximum) for a predefined SSD and field size is termed the percentage depth dose (PDD or DD%) [30]:

$$DD_x\% = 100 \times \frac{D_x}{D_{max}} \tag{1.6}$$

DD% is also defined as the dose at a specific depth as a function of distance, field and energy in a water phantom.

The percentage depth dose curve provides information on the quality of the radiation and its energy.

The depth at dose maximum can be calculated.

The most probable energy at the surface of the phantom can be found by calculating the range of the electrons. This can give information on X-ray contamination.

Synonyms for D_{max}:

- Given dose
- Entrance dose

Dose: Energy transferred per unit mass of target tissue, and its unit is Gray (Gy).

- The dose in radiotherapy is normalized to the D_{max} calculated in the phantom.

PDD curves are created by plotting DD% values at different depths from the surface of the phantom (Figs. 1.51–1.53).

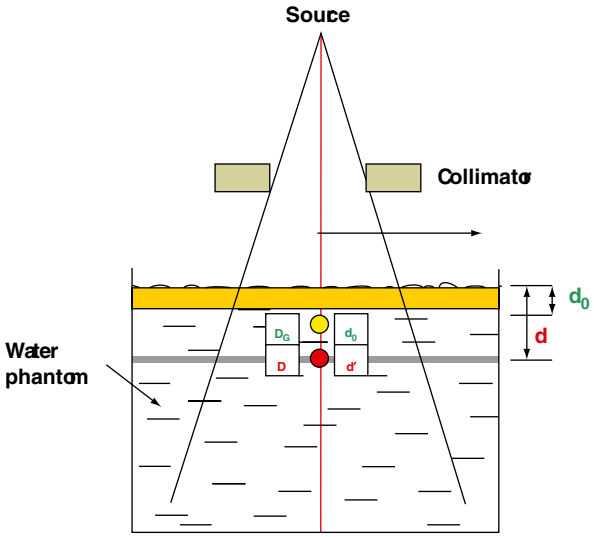

Fig. 1.51 Percentage depth dose (PDD) in a water phantom

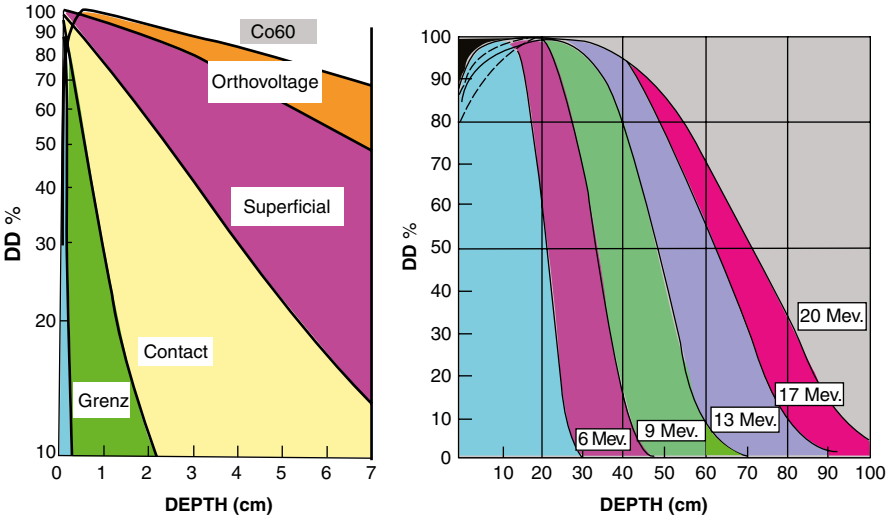

Fig. 1.52 PDDs for various X-ray and electron energies

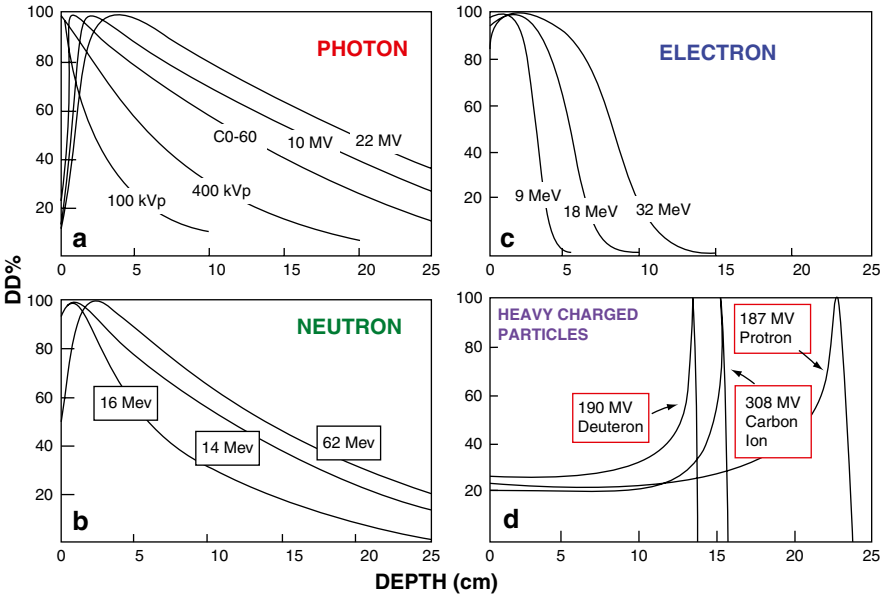

Fig. 1.53 PDD curves for photon, electron, neutron and heavy charged particles

1.10.6 Isodose Curves

Isodose curves are prepared by combining the points in the phantom or target tissue that receive the same dose (Fig. 1.54) [31]. They are calculated by various dosimetric measurements, and the highest dose is considered 100%. The curves are placed in percentage order, and then used to create the dose distribution graphics for the target tissue and the energy of interest (Fig. 1.55). By the using the isodose curves during treatment planning, the dose distribution of the radiation delivered to the target tissue and neighboring structures can be seen from different angles.

- In a plot of isodose curves, the *y*-axis shows the depth below the surface of the skin, while the *x*-axis shows the range of the field

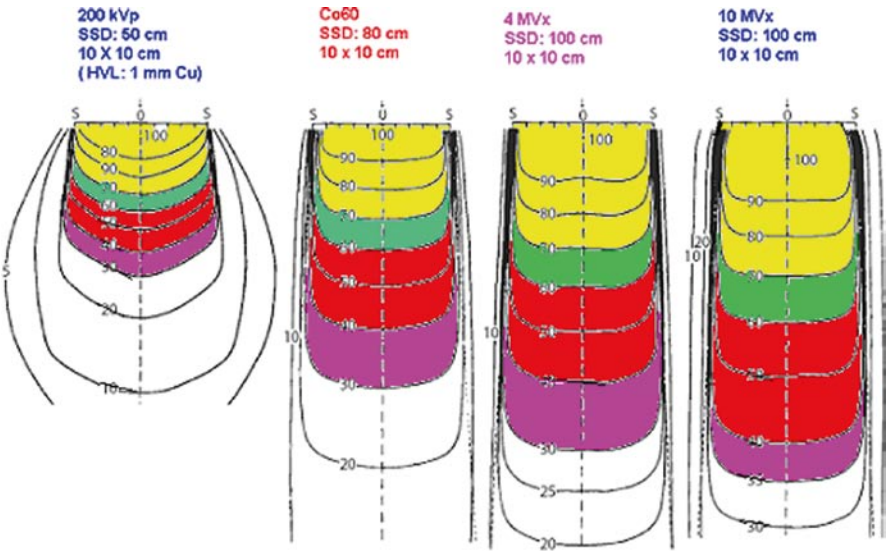

Fig. 1.54 Isodose curves for various X-ray energies

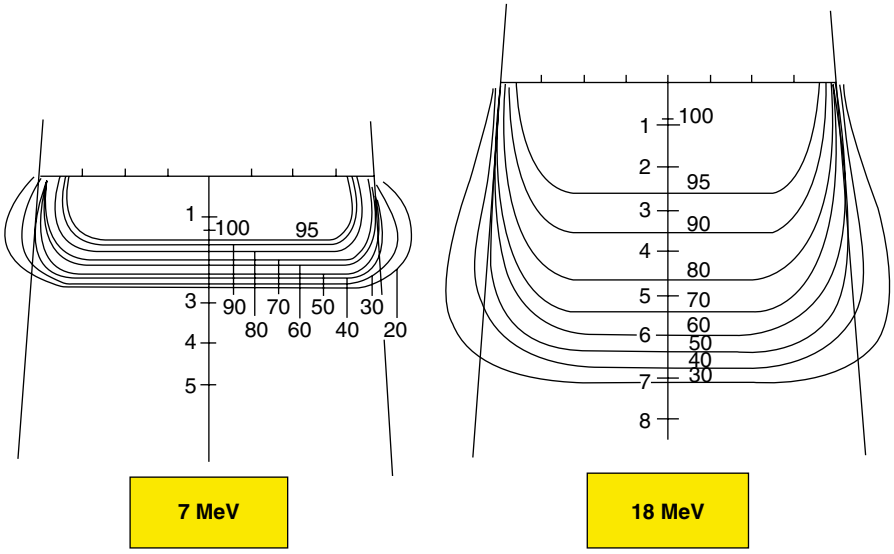

Fig. 1.55 Isodose curves for various electron energies

Ionization Chamber in a Water Phantom

- The *isodose distribution* along the central axis is determined for that energy
- The *dose profile* perpendicular to the central axis (i.e., parallel to earth) is determined for that energy

1.10.7 Dose Profile

The characteristics of the delivered radiation can be determined by performing measurements in ionization chamber within a water phantom (Fig. 1.56). These characteristics are the flatness, symmetry, and penumbra for that energy (Fig. 1.57) [32].

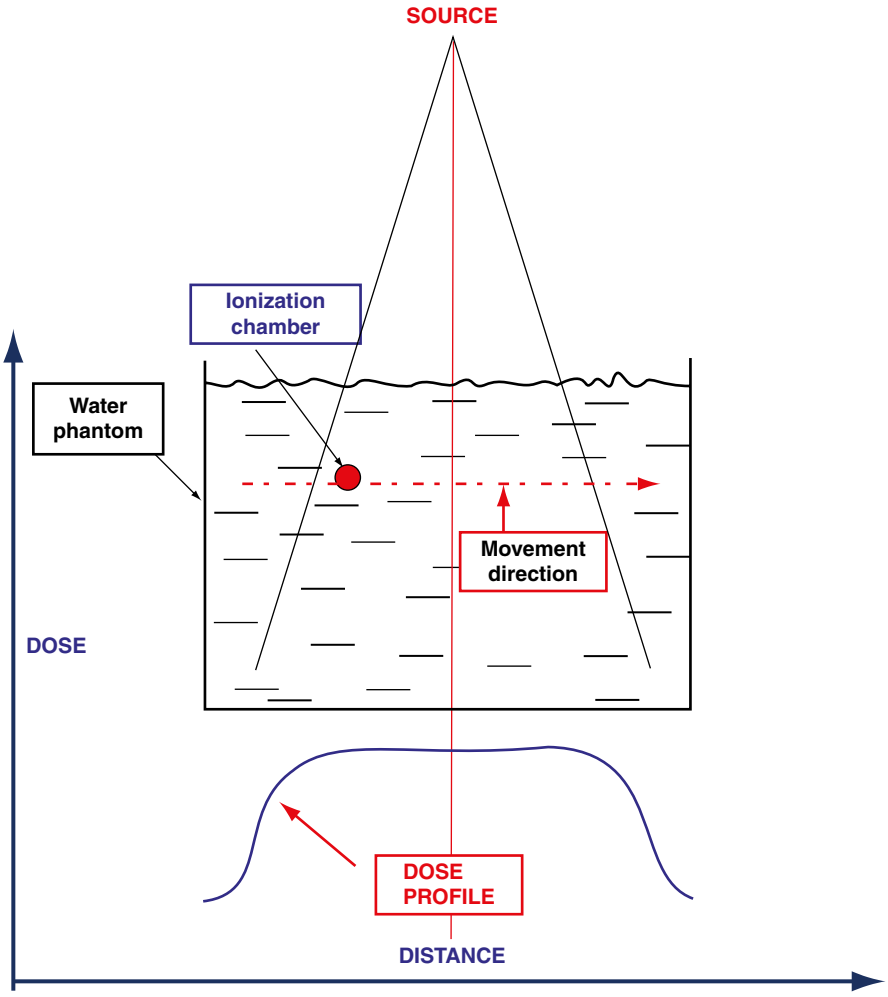

Fig. 1.56 Measurement of dose profile in a water phantom

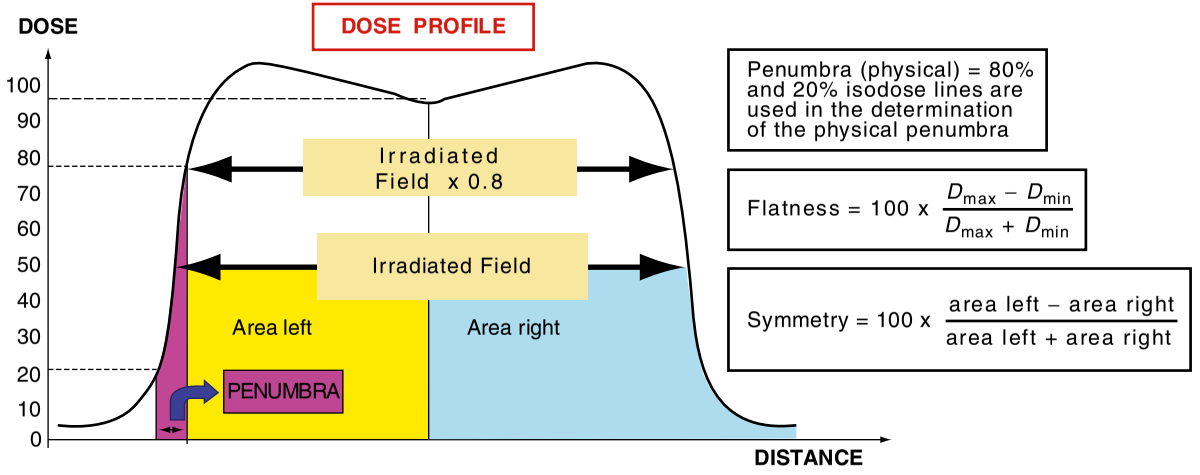

Fig. 1.57 Dose profile and its components

General Features of a Water Phantom System

The system can perform three-dimensional computerized controlled analyses of the dose, depth dose, dose ratios [TMR, TPR (measurement and calculation)] and isodose calculations.

It has an air scanner capable of making measurements in air, along with an ion chamber, and build-up blocks. There is also a mechanism in these equipments which can be used to mount to the head of actual treatment machines.

The system has a specific test apparatus that can be used to test the isocenter point for the treatment machine (an "isocheck").

It has an apparatus that can check the monitor unit controls of a linac teletherapy unit (a "monicheck").

It also has a "linear array" apparatus for dynamic wedge and MLC measurements.

Solid water phantom (RW 3). This is used for absorbed dose measurements of photon and electrons. It has dimensions of $40 \times 40 \times 40$ cm, and utilizes layers with thicknesses of 1 mm, 0.5, 1 cm.

1.10.8 Penumbra

The penumbra is defined as the region of steep dose rate decrease at the edge of radiation beam, noting that the dose rate decreases as a function of the distance from the central axis (Fig. 1.58) [33]:

Types of Penumbra

The *physical penumbra* is the penumbra measured in the dose profile. It is the distance between the points at which the 20 and 80% isodose curves cross the x-axis at D_{max}.

There are several components to the physical penumbra:

- **Geometrical penumbra.** This occurs due to the size of the source; large sources have larger geometrical penumbras.
- **Transmission penumbra.** This occurs due to the beam emerging from the edges of blocks or collimators. It can be decreased by making sure that the shapes of the focalized blocks take into account the beam divergence.

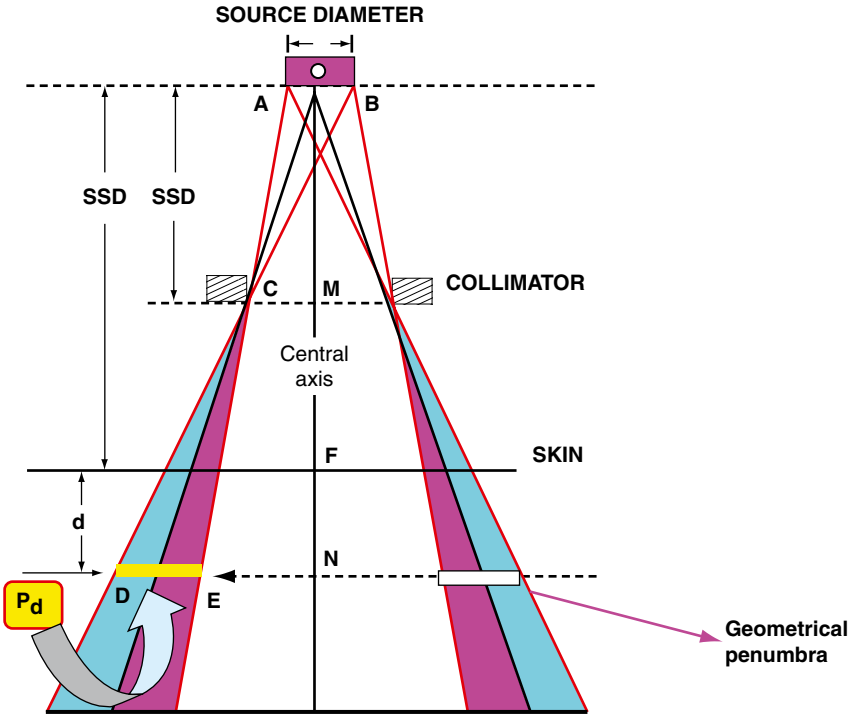

Fig. 1.58 Penumbral parameters and the calculation of the penumbra

$$P = \frac{s(\mathrm{SSD} + d - \mathrm{SCD})}{\mathrm{SCD}} \tag{1.7}$$

P: penumbra
S: source diameter
SCD = SDD: source–collimator distance (= source–diaphragm distance)
d = depth
Field size does not affect penumbra.

Factors that increase the penumbra:
Increase in SSD
Increase in source diameter
Increase in SDD (SCD)
Factors that decrease the penumbra:
Decrease in SSD
Decrease in source diameter
Increase in SDD (SCD)

1.10.9
Inverse Square Law

This is the decrease in radiation intensity with the square of distance from the source (Fig. 1.59) [34]. For instance, when the distance from the source triples, the surface dose decreases ninefold (Fig. 1.60). In tissues, the depth into the tissue thickness is another factor that must be considered in addition to the distance from the source, and the dose decreases exponentially with depth into the tissue.

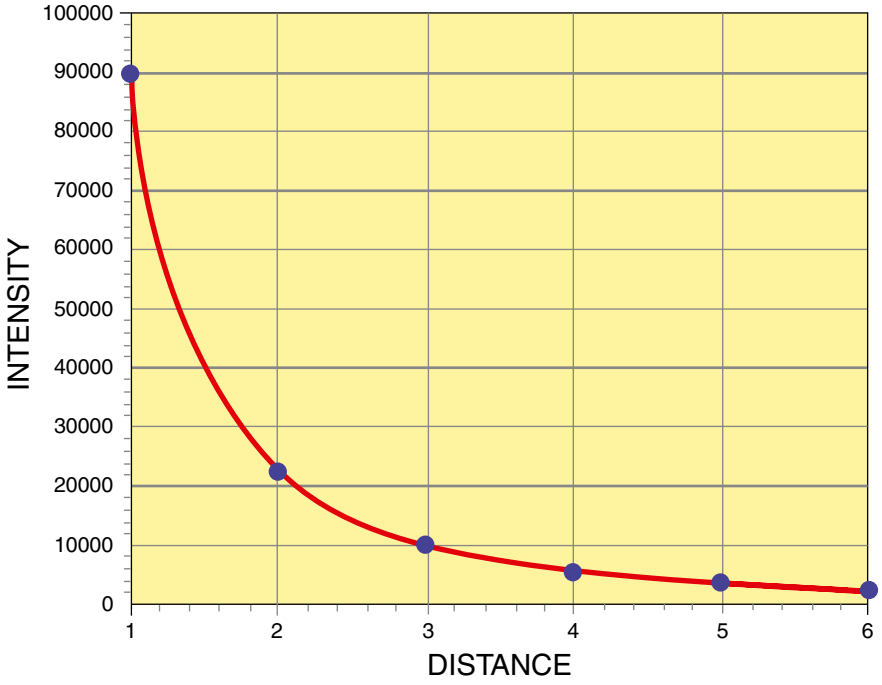

Fig. 1.59 The relationship between intensity and distance from the source

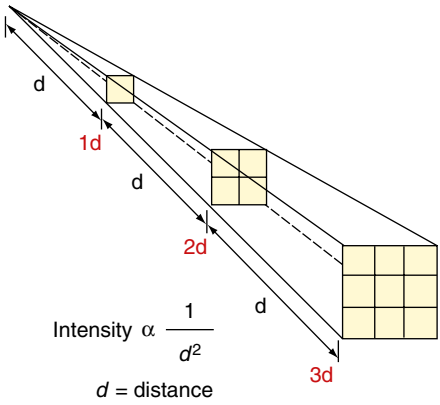

Fig. 1.60 Inverse square law

The inverse square law is very important in both radiotherapy and protection from radiation. Since radiotherapy treatments are applied at a short distance from the source, the dose drops off rapidly with distance due to the inverse square law. This situation is observed for both brachytherapy and external radiotherapy.

Most external radiotherapy is delivered as teletherapy (at a distance of 80–120 cm). Thus, the dose fall-off due to distance is relatively small.

Brachytherapy isodose curves show a rapid dose decrease → rapid fall-off
Here, the isodose curves are narrow, so isodose distances are short
Teletherapy isodose curves show a slow dose decrease → slow fall-off
Here, the isodose curves are wide, so isodose distances are long
Isocentric treatment (constant SAD) is affected more by the inverse square law than the SSD technique.

1.10.10 Backscatter Factor (BSF)

In a phantom, the ratio of the dose maximum to the dose in air at the same depth is called the backscatter factor (BSF) [35]:

$$\mathrm{BSF} = \frac{D_{\max}}{D_{\mathrm{air}}} \tag{1.8}$$

BSF

- Increases as the energy increases (gets closer to 1)
- Increases as the field size increases (gets closer to 1)
- Is independent of SSD

Since the energy of the scattering photon increases as the energy increases, BSF increases.

- At >2 MV, the BSF approaches 1
- The depth at which the BSF is measured depends on the energy
- The BSF measurement depth at energies below that of Co-60 is the surface, since $D_{\max}$ is close to the surface

1.10.11 Tissue to Air Ratio (TAR)

The ratio of the dose at depth d (D_{d}) in a phantom to the dose at the same depth in air (D_{air}) for the distance used in SAD is defined as the tissue to air ratio (TAR) [35]:

$$\mathrm{TAR} = \frac{D_d}{D_{d\text{-air}}} \tag{1.9}$$

The BSF is only defined at D_{max}, whereas TAR can be defined at any depth.

- When $d = D_{max}$, TAR = BSF

TAR

- Increases as the energy increases
- Increases as the field size increases
- Is independent of SSD at low megavoltage energies
- Is dependent on SSD at high megavoltage energies (due to electron contamination)
- The BSF includes primary radiation and scattered radiation; the TAR only includes scattered and absorbed radiation

If $D_d = D_{max}$ in the TAR formula → *peak scatter factor (PSF)*.

1.10.12 Tissue Maximum Ratio (TMR)

The ratio of the dose measured at a depth d (D_d) to D_{max} in a phantom is defined as the tissue maximum ratio (TMR) [36]:

$$\text{TMR} = \frac{D_d}{D_{max}} \tag{1.10}$$

It is defined by performing two measurements in the phantom (i.e., D_d and D_{max} are measured).

The TMR is normalized to D_{max}, in contrast to the TAR.

TMR

- Increases as energy increases
- Increases as the field size increases
- Is independent of SSD at low megavoltage energies
- Is dependent on SSD at high megavoltage energies (due to electron contamination)

$$\text{TMR} = \frac{\text{TAR}}{\text{BSF}} \tag{1.11}$$

The Differences Between TAR and TMR

- TAR uses the dose in air
- TMR uses the dose at D_{max} in phantom.
- TAR is used in isocentric treatment technique.
- TMR calculation is done instead of TAR at energies more than 3 MV.

1.10.13 Scatter Air Ratio (SAR)

The ratio of dose measured at d depth ($D_{d\text{-phantom}}$) in phantom to the dose measured at the same depth in air ($D_{d\text{-air}}$) is defined as SAR [37].

$$\text{SAR} = \frac{D_{d\text{-phantom}}}{D_{d\text{-air}}} \tag{1.12}$$

It is used for the calculation of mean scattered dose.

It is independent on SSD as TAR, but dependent parameter on energy, depth, and field size.

1.10.14 Collimator Scattering Factor (S_c)

The ratio of the dose measured in any field at a depth d in air to D_{max} measured in a reference field (10×10 cm^2) in air is called the collimator scattering factor (S_c or CSF; Fig. 1.61) [38].

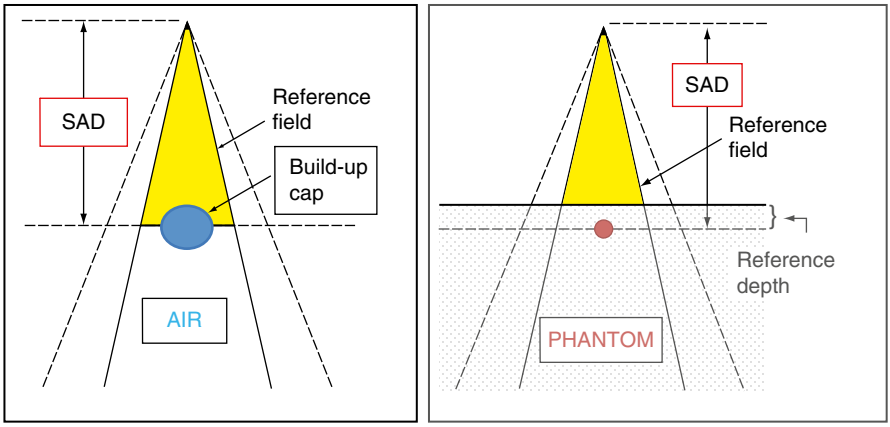

Fig. 1.61 Calculation of the collimator and phantom scattering factor (Fig. 5.3, p 71 of [42])

The collimator scattering factor is also termed the output factor.

S_c is measured in an ion chamber with a build-up cap.

It is:

- Correlated with field size
- Correlated with energy (scattering increases as the field size and energy increase)

1.10.15
Phantom Scattering Factor (S_p)

The ratio of the dose measured in a definite field size at a depth d to D_{max} measured in a reference field (10×10 cm^2) is defined as the phantom scattering factor (S_p) (Fig. 1.62) [37, 38].

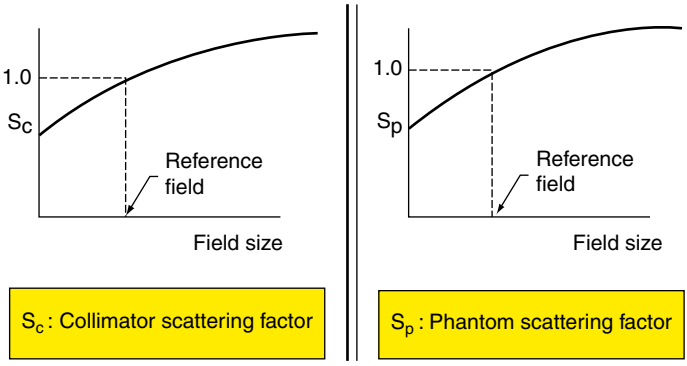

Fig. 1.62 The measurement of CSF and S_p, and how they relate to the field size

The ratio of the BSF calculated in any field at a depth d to the BSF in a reference field in a phantom is another way of defining S_p.

S_p is important for determining scattered radiation from a phantom.

$$\text{Total scattering factor} = S_c + S_p \tag{1.13}$$

1.10.16
Monitor Unit (MU) Calculation in a Linear Accelerator

Monitor units are the units in which the output of a linac is measured. Linacs are calibrated to give 1 cGy at a SAD distance of 100 cm, for a field size of 10×10 cm, and at the depth corresponding to D_{max}, and this calibration dose is defined as one monitor unit (MU).

MU Calculation in the SSD Technique [39] (Nonisocentric Technique)

$$\text{MU} = \frac{\text{TD} \times 100}{K \times (\text{DD}\%)_d \times S_c(r_c) \times S_p(r) \times \text{SSD}_{\text{factor}}} \tag{1.14}$$

If a tray or wedge is used, a tray factor (TF) or a wedge factor (WF) is added to the denominator as a multiplier.

$$r_c = r\frac{\text{SAD}}{\text{SSD}} \tag{1.15}$$

(*continued*)

(continued)

$$\mathrm{SSD}_{\mathrm{factor}} = \left(\frac{\mathrm{SCD}}{\mathrm{SSD} + t_0} \right)^2 \tag{1.16}$$

TD: fraction dose
K: 1 cGy/MU
t_0: reference depth
S_c: collimator scattering factor
S_p: phantom scattering factor
DD%: percentage depth dose
r: collimator field size
SCD: source–collimator distance
SSD: source–skin distance

MU Calculation in the SAD Technique [39] (Isocentric Technique)

$$\mathrm{MU} = \frac{\mathrm{ID}}{K \times TMR(d, r_d) \times S_{\mathrm{c}}(r_{\mathrm{c}}) \times S_{\mathrm{p}}(r_d) \times \mathrm{SAD}_{\mathrm{factor}}} \tag{1.17}$$

If a tray or wedge is used, a tray factor (TF) or a wedge factor (WF) is added to the denominator as a multiplier.

$$r_c = r \frac{\mathrm{SAD}}{\mathrm{SSD}} \tag{1.15}$$

$$\mathrm{SSD}_{\mathrm{factor}} = \left(\frac{SCD}{SAD} \right)^2 \tag{1.18}$$

ID: fraction dose
K: 1 cGy/MU
t_0: reference depth
S_c: collimator scattering factor
S_p: phantom scattering factor
TMR: tissue maximum ratio
r: collimator field size
SCD: source–collimator distance
SSD: source–skin distance

1.10.17
Treatment Time Calculation in a Co-60 Teletherapy Unit

$$\text{Time (min)} = \frac{\text{TD} \times 100}{D_0 \times (DD\%)_d \times S_c(r_c) \times S_p(r) \times \text{SSD}_{\text{factor}}} \tag{1.19}$$

$$r_c = r \frac{SAD}{SSD} \tag{1.15}$$

$$SSD_{factor} = \left(\frac{SCD}{SSD + t_0} \right)^2 \tag{1.16}$$

TD*:* fraction dose
D_0: dose rate (specific SAD in phantom at D_{max})
t_0*:* reference depth
S_c: collimator scattering factor
S_p*:* phantom scattering factor
DD%*:* percentage depth dose
r: collimator field size
SCD*:* source–collimator distance
SSD*:* source–skin distance

1.11
Beam Modifiers

1.11.1 Bolus

Bolus is used for tissue compensation, and is put on the skin at right angles to the beam axis. It is made from a tissue-equivalent density material (Fig. 1.63) [40]. Bolus use leads to increased effects of radiation scattered into the skin. Thus, the entrance dose to the skin increases. Secondary electrons produced by the bolus also increase the skin dose, since the bolus is in contact with skin (→ the depth corresponding to D_{max} gets close to the surface).

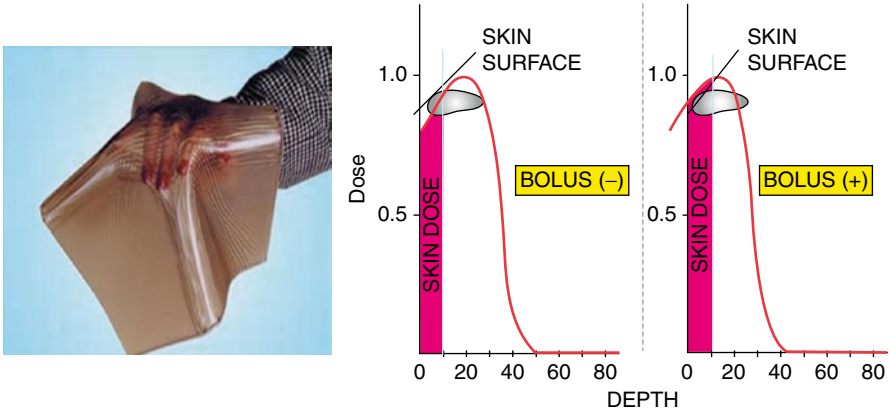

Fig. 1.63 Bolus material and its effect on the skin dose

1.11.2 Compensating Filters

The dose distribution is not homogeneous if the surface of the patient is not flat. Therefore, a compensating filter is positioned between the beam source and the skin to reduce the dose delivered to the area with thinner tissue in order to achieve a homogeneous dose distribution in the irradiated volume (Fig. 1.64) [40]. Compensating filters are made of aluminum–tin or copper–tin mixtures, and are individually designed to compensate for tissue irregularities.

1.11.3 Wedge Filters

Metal wedge filters can be used to even out the isodose surfaces for photon beams delivered onto flat patient surfaces at oblique beam angles (Fig. 1.65) [40]. These wedges can be static, dynamic or motorized. They are most commonly used in tangential irradiation (e.g., the breast, head and neck regions), and they prevent hot spots in vital organs and cold spots in the radiation field. They provide a more homogeneous dose distribution.

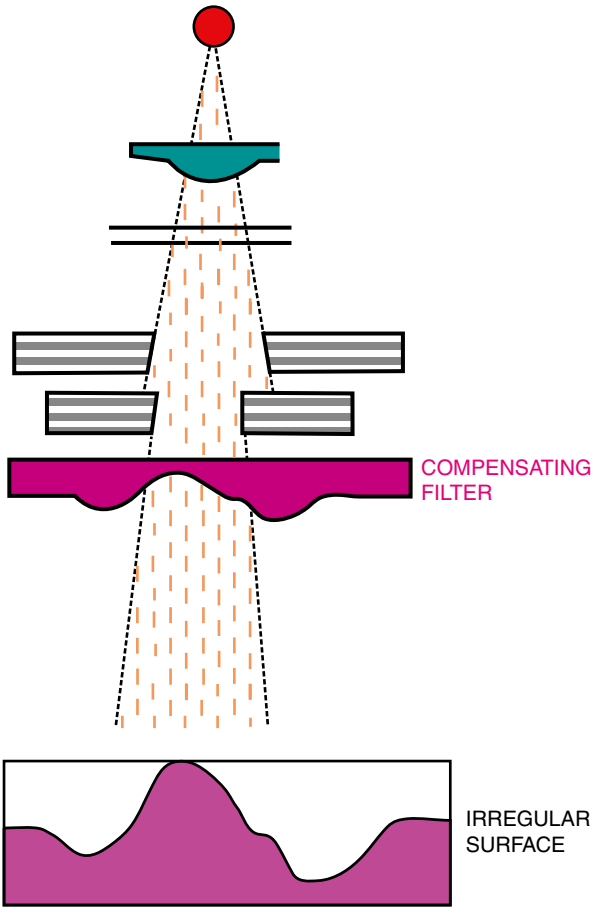

Fig. 1.64 Compensating filter (Fig. 4.11, p 73 of [42])

Wedge angle (θ): the angle between the plane of the ground and the point at which the central axis crosses the 50% isodose line (if $E > 6$ MV, at 10 cm] (Fig. 1.66).

$$\text{Hinge angle } (\Phi) = 180 - 2\theta \tag{1.20}$$

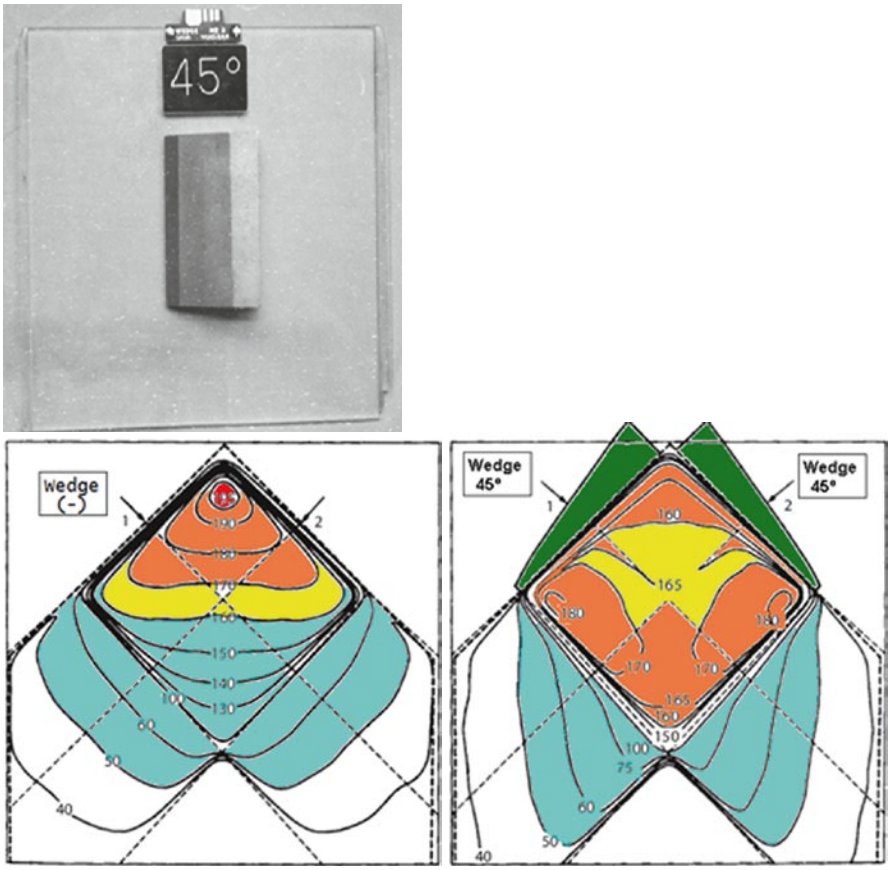

Fig. 1.65 Change in isodose profile resulting from the use of a static wedge filter

1.11.4 Shielding Blocks

These are manufactured in order to shield the normal critical structures in radiotherapy portals. There are two types of shielding block. Standard blocks come with the teletherapy unit, and have various sizes and shapes. They are designed according to the area that needs to be protected. On the other hand, focalized blocks are individually made in mold rooms to shield the areas of the field that need protecting (according to the simulation procedure). Standard blocks are only used in emergencies.

Focalized blocks are made up from lead or Cerrobend® (Fig. 1.67). Cerrobend is a mixture of lead (26.7%), bismuth (50%), zinc (13.3%), and cadmium (10%) that melts at 70ºC has an HVL of 1.3 cm [40].

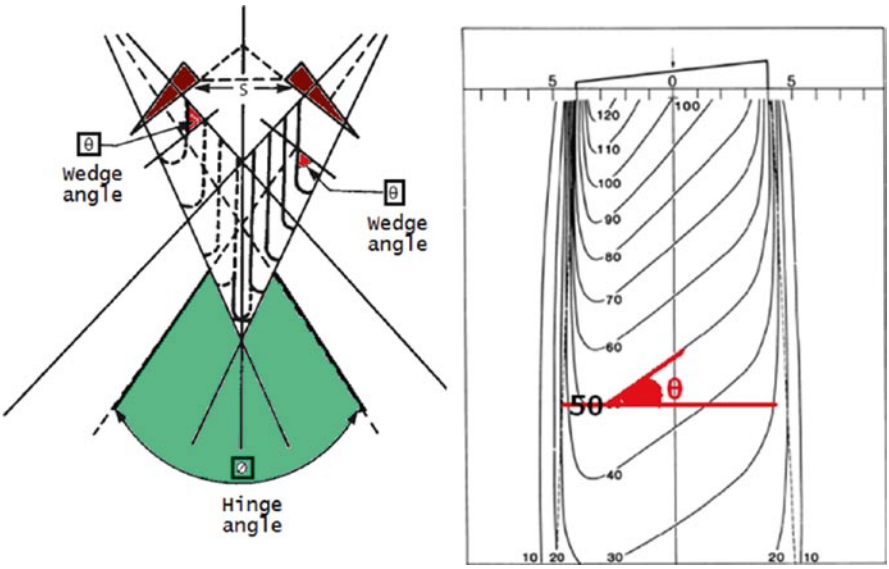

Fig. 1.66 Wedge angle and hinge angle

Fig. 1.67 Block cutter, Cerrobend, and focalized blocks

Focalized blocks have the advantages of providing divergence, a very close fit to the region that needs protecting, and easy setup. However they are time-consuming to make and use, result in an increase work load, and are expensive (Fig. 1.68).

1.11.5 Multileaf Collimator (MLC)

Irregular fields cannot be shaped without focalized blocks in conventional radiotherapy machines. The collimator systems in Co-60 and old linac machines provide only a rectangular field. Multileaf collimators, on the other hand, are composed of many leaves, and each

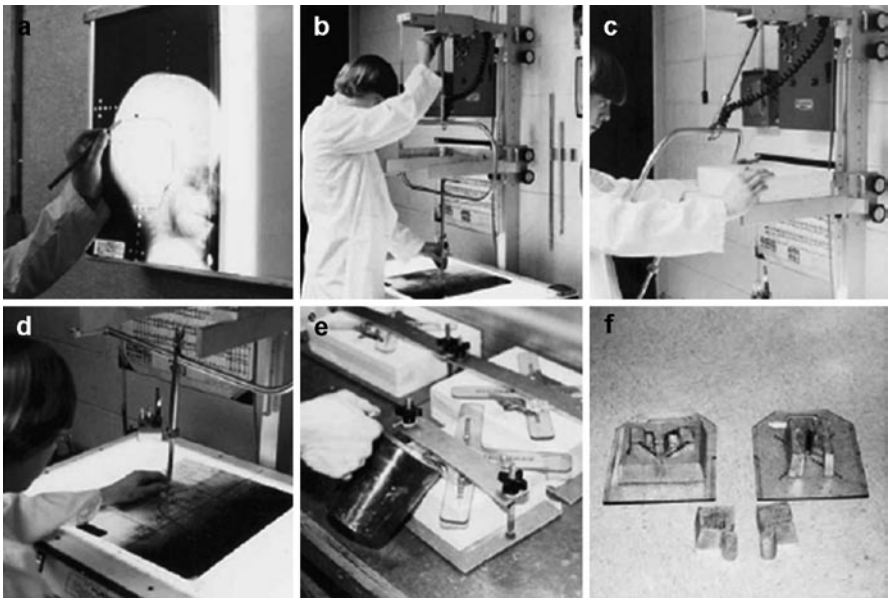

Fig. 1.68 Process of preparing focalized blocks. (**a**) Area to be protected is delineated. (**b**) Block cutter is adjusted according to the parameters of the treatment machine (SSD, SAD). (**c**) Block thickness is adjusted according to the energy and the treatment machine. (**d**) Block mold is cut by hot-wire. (**e**) Cerrobend is poured into block mold. (**f**) Focalized blocks after cooling

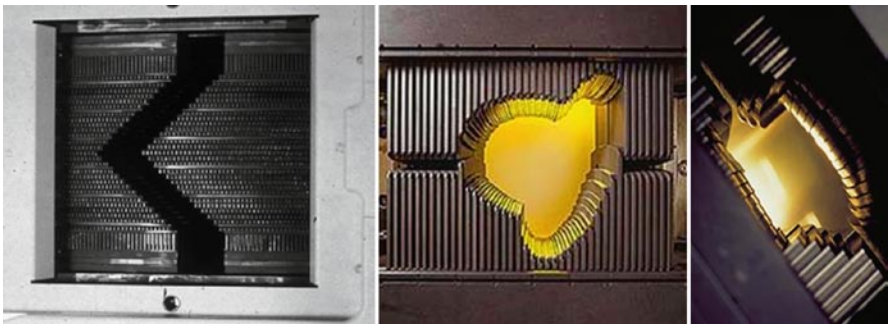

Fig. 1.69 Various types of multileaf collimator systems

leaf can move independently (Fig. 1.69) [41]. By arranging these leaves appropriately, irregular fields that a required by the treatment plan can easily obtained without using blocks (Tables 1.8–1.10).

Table 1.8 Some radiation-associated units and their features

Parameter	Radiation type	Medium in which measurement is performed	Unit	Specific unit
Exposure	X-rays and gamma rays	Air	C/kg	R (roentgen) = 2.58×10^{-4} C/kg
Absorbed dose	All radiation types	Everywhere	erg/g, J/kg	1 rad = 100 erg/g 1 Gy = 1 J/kg
Equivalent dose	All radiation types	Human	erg/g, J/kg	1 REM = 100 erg/g × WR 1 Sv = 1 J/kg × WR

WR weighting factor, formerly known as the quality factor (*Q*)

Table 1.9 Summary of photon–matter interactions

Photon–electron interactions	Photon–nucleus interactions
Interaction with bound electrons Photoelectric effect Coherent effect	Direct interaction with nucleus Photodisintegration
Interaction with free electrons Compton effect	Coulomb interaction with nucleus Pair production

Note that bremsstrahlung is not a photon–matter interaction; it is the interaction of a charged particle (an electron) with matter

Table 1.10 Advantages and disadvantages of various radiations used in external radiotherapy

Radiation	Advantages	Disadvantages
Photon	Wide range of use Skin-sparing effect	Entrance dose > tumor dose High-dose region during the exit of the radiation from the patient
Electron	Sparing of normal tissues beyond the tumor due to their limited ranges	Large penumbra due to scattering Only used in superficial tumors
Proton	No dose beyond tumor Very low dose proximal to the tumor	Large penumbra at 20 cm depth Limited use Expensive

1.12 Pearl Boxes

The skin sparing effect and penetrating ability increase at high energies.

The depth (in cm) of the 10% isodose line for electrons is nearly half of their initial energy in MeV → $E/2$. This is known as the *penetration range* of electrons. It is important for determining an energy that cannot reach spinal cord while selecting a boost dose in head and neck radiotherapy.

The penetration range of electrons triples in lung tissue → because of the air present!

The depth (in cm) of the 80% isodose line for electrons is nearly one-third of their energy in MeV → $E/3$. This is known as the *therapeutic range* ofelectrons.

The depth (in cm) of the 90% isodose line for electrons is nearly one-quarter of their energy in MeV → $E/4$.

The build-up point (i.e., that corresponding to the dose maximum, d_{max}, in cm) for electrons corresponds practically to $E/6$.

- For example, for 6 MeV, $D_{max} = 6/6 = 1$ cm.

This formula is valid up to 16 MeV; at 16 MeV and over d_{max} is ≤ 1.5 cm).

Common features of X-rays and gamma rays in their interaction with tissue are the production of ionization and high speed electrons, depositing energy, and undergoing scattering.

The Compton effect is dominant in linacs, while the photoelectric effect is dominant in Co-60 treatment machines.

The Co-60 source is 2 cm in diameter, which means that it has a larger penumbra than a linac, so the side of the treated field is sharper in a linac.

Physical penumbra → directly proportional to energy

For Co-60 → 5 mm
For 6 MV → 3 mm
For 25 MV → 2 mm
Geometrical penumbra → directly proportional to source diameter and SSD

The skin dose increases as the electron energy increases.
The skin dose decreases as the photon energy increases.

The TAR is difficult to measure at Co-60 and 6 MV photon energies, so the TPR is used instead of TAR in dose calculations.

An advantage of TLD over ion chamber is that it can be used in vivo.

Silver bromide crystals exposed to radiation in film dosimeters change color, and this color change is measured through optic densitometry.

The kerma is greatest at the surface, and decreases with depth. The absorbed dose increases until the depth at D_{max}, and decreases as the depth increases beyond that.

The maximum block thickness for electrons is 1 cm.

The (lead) block thickness for electrons → 0.5 cm (5 mm) for each MeV.

Block thicknesses (lead):
For Co-60, → 5 cm
For 6 MV X-rays → 6 cm
For 25 MV X-rays → 7 cm
5 HVL : 3.125% of radiation passes under block in Co-60. For a linac, block thickness → 4 HVL.

The old unit of exposure, the roentgen, cannot be used for particulate radiation. It is only used for exposure to X-rays and gamma rays.

An electron loses 2 MeV of energy as it propagates through each centimeter of soft tissue.

Frequencies:
Co-60 (mean 1.25 MV) → 3×10^{20} cycles/s (Hz)
6 MV X-rays → 12×10^{20} cycles/s (Hz)
25 MV X-rays → 60×10^{20} cycles/s (Hz)

Photons travel at the speed of light, since they have no mass; electrons are slower, since they have mass.

Tyratron → this is present in all linacs, where it converts DC current to pulse current. It activates the klystron or the magnetron and the filament of the electron gun.

Energy	D_{max} (cm)	50% isodose (cm)
250 keV	On the surface	7
1.25 MeV	0.5	11
4 MeV	1	14
6 MeV	1.5	16
18 MeV	3	21
25 MeV	3.5	23

Since electrons show a rapid fall-off and a finite range, tissues beyond the target are spared and a uniform superficial dose is provide when electrons are used.

Delta electrons → electrons produced by the interactions of secondary electrons with atoms.

Trimmer bars → satellite collimators used in teletherapy machines to decrease the penumbra.

Hardening the X-ray beam → eliminating low-energy photons within the beam using selectively absorbing filters.

TVL (tenth-value layer) → thickness of absorbent that decreases the incoming radiation dose by 90% (TVL = 3.32 HVL).

Divergence → the tendency of a radiation beam to widen as it propagates farther from the source.

Electron energies are calibrated in an ion chamber at the reference depth of the 50% isodose line.

Possible scenarios in which an atomic particle hits a target:

- Nuclear reaction
- Elastic scattering

In elastic scattering, the particles after collision are identical to those before the collision.
The total kinetic energy of the particles does not change during the collision.
A small fraction of the total kinetic energy is transferred to the target.
Radiation is not produced in elastic scattering.

- Inelastic scattering

In inelastic scattering, the particles after the collision are identical to those before the collision.
Most of the total kinetic energy is transferred to the target.
Radiation is produced in inelastic collisions.

Possible Scenarios When a Photon Enters the Human Body

– No interactions occur
– Photon–matter interactions occur, which divert the photon from its original path
– Scattered photons may produce secondary photon–matter interactions

Bragg Peak (Fig. 1.70)

Protons with energies of 200 MV enter the body with a speed of 180,000 km/s. Their range in the body is only 25–30 cm. The energy transferred by the protons moving through the tissue is inversely proportional to their velocities. Thus, the protons lose most of their energy in the region 1–4 mm before they are stopped completely, and create a kind of "energy explosion" (known as the Bragg peak) at the target point. This peak in the dose delivered to tissues in the Bragg peak region can be seen in Fig. 1.70. On the other hand, the most effective dose is delivered just beneath the surface in classical radiotherapy using X-rays, and the dose decreases further into the tissue. Thus, healthy tissues before and beyond the target are exposed to unwanted radiation.

- This phenomenon was first described by Sir William Henry Bragg

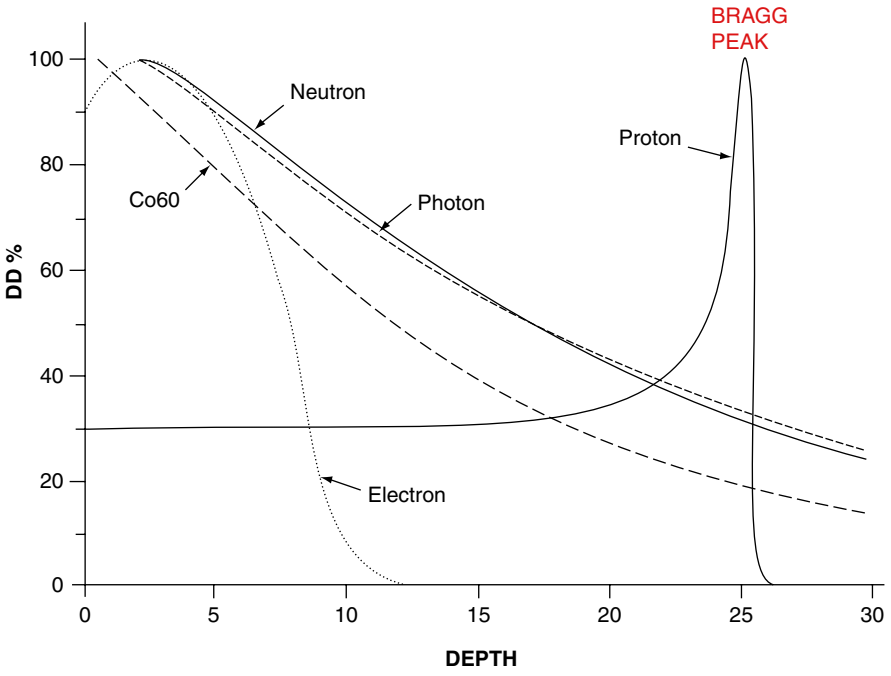

Fig. 1.70 Bragg peak

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Radiobiology

2

Murat Beyzadeoglu, Gokhan Ozyigit, and Cuneyt Ebruli

2.1 Cell Biology and Carcinogenesis

Radiobiology, in general terms, is the science that evaluates the effects of radiation in living organisms. In the field of radiation oncology, it is defined as the science that investigates the interactions between ionizing radiation and living systems, and the consequences of these interactions.

2.1.1 Cell Structure

Atoms form molecules, molecules make macromolecules, macromolecules build complex organic structures, and then cells – which are the main structural component of tissues, and reflect all features of life – are formed. All cells have generally similar structures. However, they specialize according to the location of the tissue (i.e., according to the functions of that tissue). The basic structures of all organisms are formed from these cells. In humans, there are approximately 10^{14} cells [1].

All cells are surrounded by a cell membrane, and they have a liquid-like cytoplasm and organelles within the membrane (Fig. 2.1).

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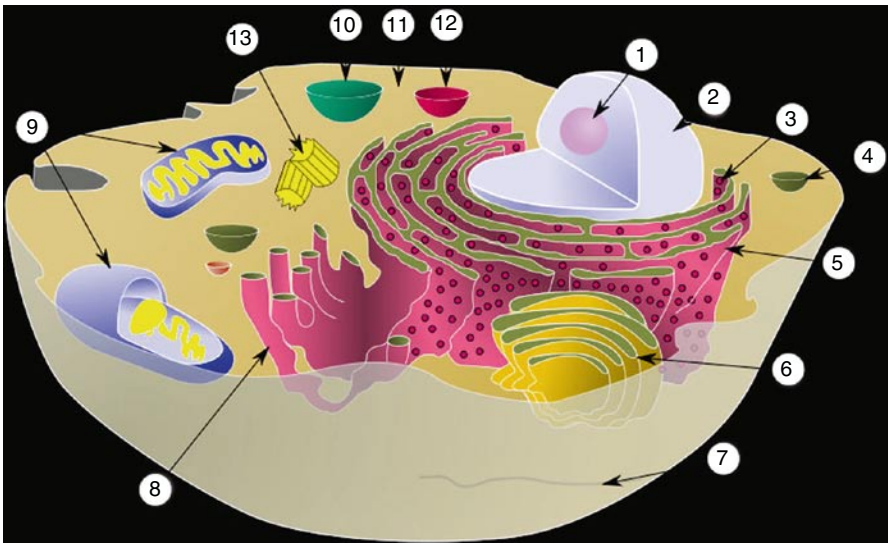


Fig. 2.1 Schematic illustration of a eukaryotic cell. *1*, Nucleolus; *2*, nucleus; *3*, ribosome; *4*, vesicle; *5*, rough endoplasmic reticulum (ER); *6*, Golgi apparatus; *7*, cytoskeleton; *8*, smooth endoplasmic reticulum; *9*, mitochondria; *10*, vacuole; *11*, cytoplasm; *12*, lysosome; *13*, centrioles within a centrosome

2.1.2 Cell Types and Organelles

Cells can be simply divided into two categories: prokaryotic cells and eukaryotic cells [2].

- **Prokaryotic cells.** Bacteria and blue–green algae belong in this group. These cells have no nucleus and are surrounded with a nuclear membrane. In addition, they do not have any membranous organelles, such as mitochondria. DNA – genetic material – is scattered within the cytoplasm. These cells do have ribosomes. The vital functions of this type of cell are performed in the cytoplasm and cellular membrane.
- **Eukaryotic cells.** These cells have membranous organelles, so their nuclear material is not scattered within the cytoplasm, and they have a real nucleus. Eukaryotic cells are more highly developed than prokaryotic cells – the cells of animals, plants, fungi and protists are eukaryotic. These cells have organelles in their cytoplasm. Chromosomes, consisting of DNA and proteins, are located in the cell nucleus. Eukaryotic cells divide by mitosis.

Cytoplasm. The cytoplasm is a semifluid matrix that fills the space between the cell membrane and the nucleus. All vital events occur in the cytoplasm in a living organism. It generally forms a homogeneous transparent mass.

Mitochondria. These are ellipsoidal or cudgel-shaped organelles of length 2–3 μm and diameter 0.5 μm. They are the energy-generating unit of cells. The citric acid cellular respiration cycle (the Krebs cycle) occurs in this organelle. The energy released by breaking the chemical bonds of organic molecules is transformed into ATP within mitochondria.
Lysosome. This is a round organelle surrounded by a membrane, and it contains hydrolytic enzymes. They perform the function of digestion in the cell, clearing away excessive or harmful intracellular structures.
Golgi apparatus. The Golgi apparatus or complex consists of a combination of membranous tubes or saccules. It is generally close to the nucleus, and is particularly conspicuous in actively secreting secretory cells. Its main function is believed to be the storage of proteins secreted by the cell. It performs the functions of secretion and packing.
Endoplasmic reticulum. The endoplasmic reticulum ensures that nutrition circulates in the cytoplasm and synthesizes lipids and hormones. It is a complex serial channel system located between the cell membrane and the nuclear membrane. If it does not contain ribosomes it is called "smooth endoplasmic reticulum." This secretes steroid hormones in steroid-secreting cells and performs detoxification in others.
Ribosome. Ribosomes are located along the channels of the endoplasmic reticulum and are found scattered within the cytoplasm. They perform protein synthesis. They are approximately 150 Å in diameter. Their structures are composed of 65% RNA (ribonucleic acid) and 35% protein. Proteins synthesized by ribosomes are sent to either intracellular or extracellular regions with the aid of the endoplasmic reticulum.

Cell nucleus. This has a granular and fibrous structure (Fig. 2.2). Most of the genetic information of the cell is located in the cell nucleus within chromosomes, which are long, linear, folded DNA molecules formed through the collection of many proteins like histones. The genes located in these chromosomes comprise the nuclear genome of the cell. The role of the cell nucleus is to maintain the integrity of these genes and to control cellular functions by arranging gene expression.
Nuclear membrane. This is the outer covering of the nucleus. Ribosomes are stuck in the nuclear membrane, and it contains pores.
Chromatin. This is the structure that transforms into chromosomes during division and when moving towards poles.
Nucleolus. This is the center of the nucleus, and it synthesizes proteins and ribosomes.
Nuclear matrix. This fills the space between the chromatin and the nucleus, and contains proteins and ions.

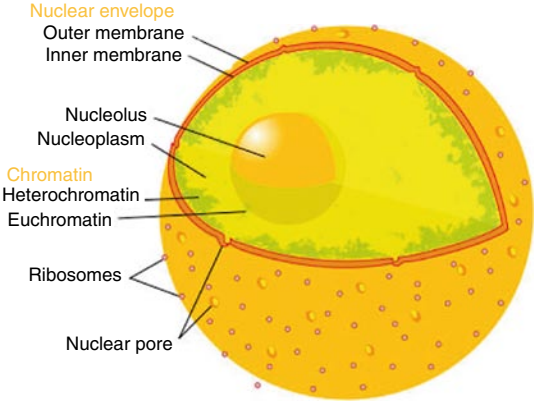


Fig. 2.2 Eukaryotic cell nucleus

Chromosome [3]. The nucleus contains most of the genetic material in the cell (Fig. 2.3). This genetic material actually consists of multiple linear DNA molecules called chromosomes. Chromosomes are found in the form of a complex combination of DNA and proteins termed chromatin during most of the cell cycle, and chromatin forms the chromosomes of one karyotype during division (Fig. 2.4).

A small number of cellular genes are found in mitochondria:

1. Chromatid
2. Centromere
3. Short arm
4. Long arm

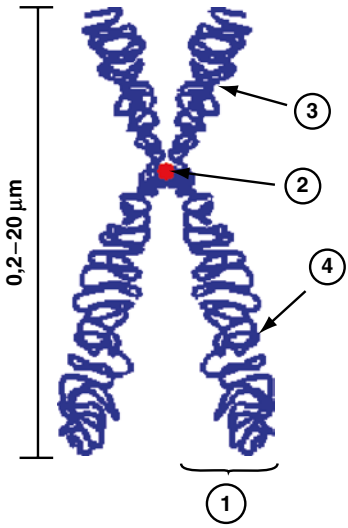


Fig. 2.3 The structure of a chromosome

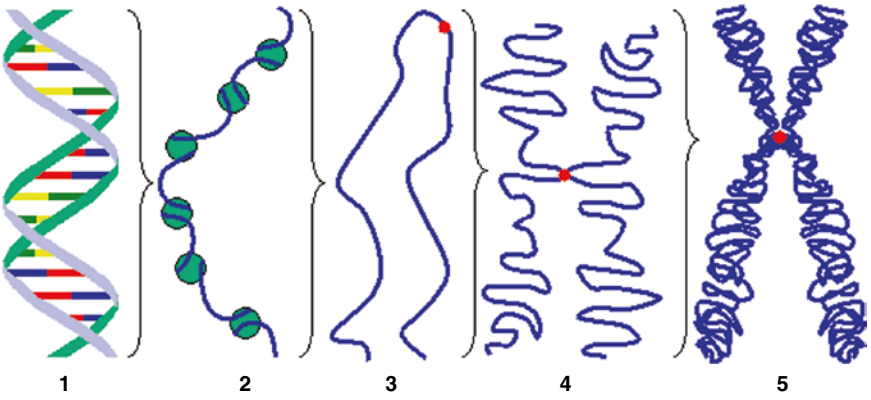


Fig. 2.4 Relationship between DNA and chromosomes. *1*, DNA; *2*, DNA+protein; *3*, chromatin; *4*, chromatids; *5*, chromosome. DNA molecules combine and make proteins, proteins form chromatins, chromatins mate with each other during division and become chromatids, and chromatids combine and forms chromosomes

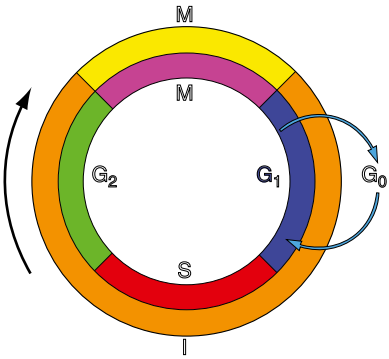
2.1.3 Cell Cycle

During its life, a cell generally exhibits a long period or phase (interphase) during which no division occurs, and a division phase (mitosis). This is called the cell cycle [4]. The cell cycle is repeated at each cellular stage, and the length of time corresponding to a cell cycle varies with cell type (Fig. 2.5). The interphase is very long in some cells, and these types of cells never divide during the life period of the organism (an example is a neuron). Generally, cells grow until they reach a certain size, then they divide.

M: Mitosis
- Prophase
- Metaphase
- Anaphase
- Telophase

I: Interphase
- G_1
- S
- G_2
- G_0

Fig. 2.5 Cell cycle and its stages



The Stages of Mitosis [4]

Mitosis is the division of a cell into two cells through the mating of its genome. Mitosis is only observed in eukaryotic cells. Somatic cells are formed via mitosis, whereas germ cells are formed by meiotic division.

1. **Prophase** (Fig. 2.6)
   The nuclear membrane and endoplasmic reticulum disappear.
   The chromosomes shorten and thicken.
   Centrosomes move towards opposite poles.
   The nucleolus disappears.
   Spindle cells form from the poles to the center.
2. **Metaphase** (Fig. 2.7)
   The chromosomes shorten and thicken further.
   Sister chromatids are kept together using centromeres.
   The chromosomes are arranged side-by-side in a row in the equatorial plane.
   The chromosomes hold on to spindle cells with their centromeres.
3. **Anaphase** (Fig. 2.8)
   The contraction and relaxation movements of spindle cells break the centromeres that lock the chromatids together.
   The sister chromatids are separated from each other and are moved to opposite poles.
4. **Telophase** (Fig. 2.9)
   The chromosomes stop moving.
   The chromosomes unwind their helices and become chromatins.
   The nucleolus reappears.
   RNA and protein syntheses start.
   Spindle cells disappear.
   The nuclear membrane forms, and the endoplasmic reticulum takes on a shape again.
   Vital events restart in the cell.
   Cytogenesis occurs, and division finishes.

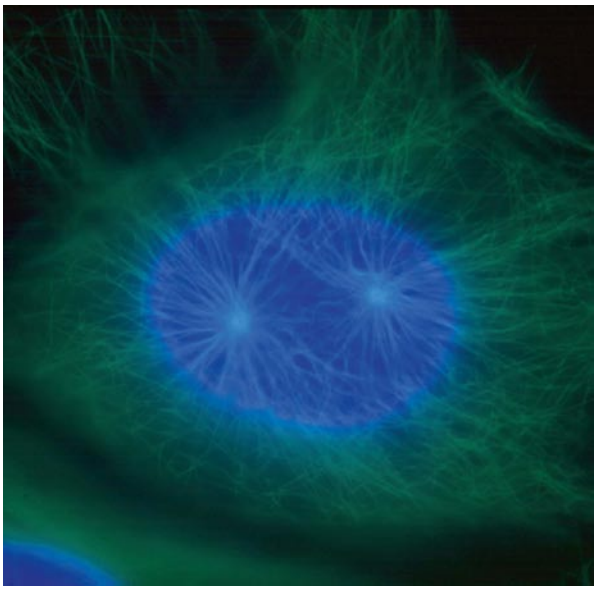


Fig. 2.6 Prophase

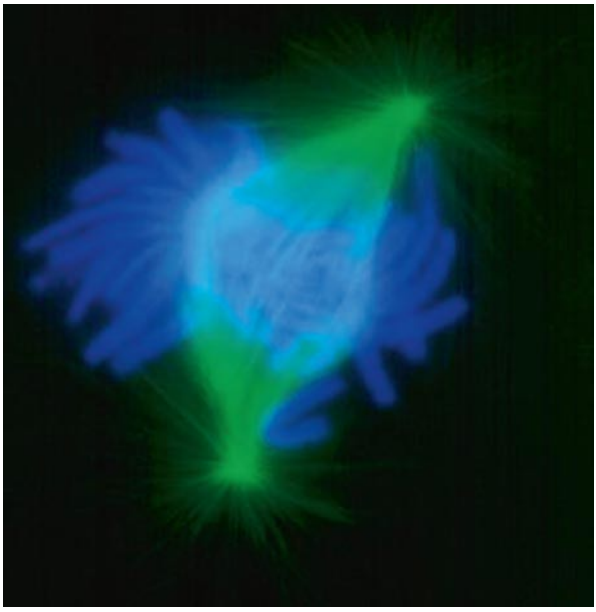


Fig. 2.7 Metaphase

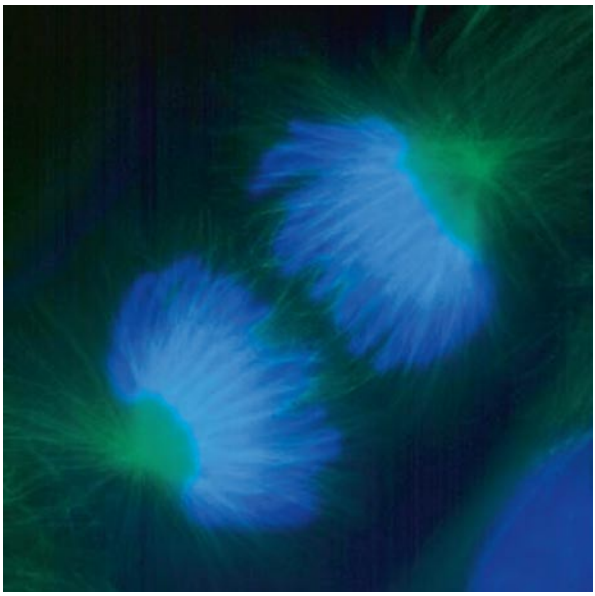


Fig. 2.8 Anaphase

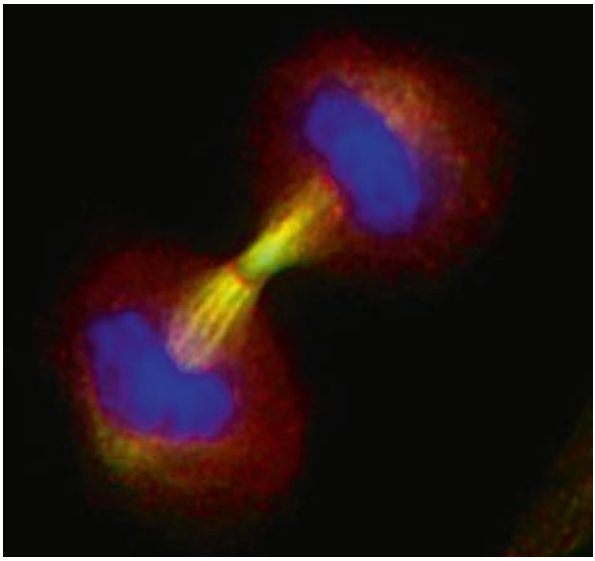


Fig. 2.9 Telophase

Interphase and Its Stages [4, 5]

The interphase is the preparation phase for the redivision of a divided cell. It is the longest phase of the eukaryotic cell cycle. For instance, the interphase of a human skin cell is about 22 h, while the cell cycle of such a cell lasts approximately 24 h. The interphase is divided into three stages.

G_1 → (G: Gap_1)

This occurs just after cytogenesis.

Metabolic events continue intensely.

This is the stage where matter transportation, synthesis, lysis reactions, organelle production, RNA synthesis and tissue functions continue at their highest levels.

It is the longest stage. Dividable cell growth occurs during this stage.

Cells that lose their ability to divide continue with their functions and life activities (e.g., muscle and nerve cells still function at this stage).

S → (S: Synthesis)

DNA is duplicated and the number of chromatins doubles (→ replication).

The most intense protein synthesis is performed at this stage.

The order of centromere duplication is observed.

G_2 → (G: Gap_2)

Enzymes related to division are synthesized.

The number of organelles increases.

DNA synthesis finishes, but RNA synthesis continues.

Centrosome synthesis finishes, and these centrosomes start moving towards opposite poles.

G_0 phase

Cells have a natural mechanism that protects them during difficult developmental conditions. Under these conditions, the cells transiently stop their cellular activities. This phase is called the G_0 phase. In the G_0 phase, some genes in the DNA are covered with various proteins; i.e., the DNA is programmed.

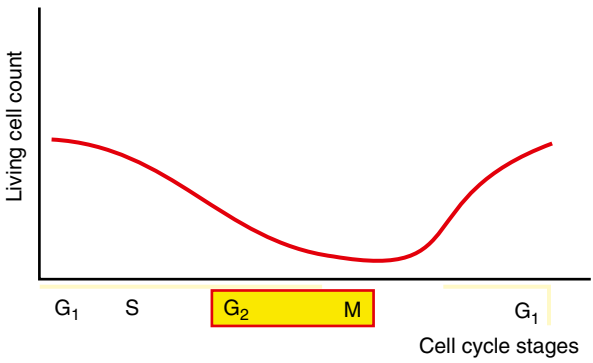


Fig. 2.10 Relationship between cell cycle stages and living cell count

The most radiosensitive stages during the cell cycle are the early G_2 and M stages (Fig. 2.10).

The radiosensitivity of a cell is fourfold greater during the mitotic phase than during the interphase. Radioresistance is high in the S, late G_1 and G_0 phases. The resistance of the S phase is due to the large amounts of synthesis enzymes present, which have the ability to rapidly repair DNA.

2.1.4 Carcinogenesis and the Cell Cycle

Cell proliferation in tissues is a normal function in organisms. Decreasing cell proliferation or increasing the death rate prevents any excessive increase. The replication of cell into two similar cells is prompted by extrinsic biochemical signals, and a series of phases regulated by inner or outer growth factors occur. Some oncogenes and proteins specific to the cell cycle are activated synchronously throughout the cell cycle and are then inactivated.

Oncogenes. Genes that are mutated or synthesized in abnormally excessive amounts and easily transform normal cells into cancer cells are termed oncogenes.

The development of cancer at the cellular level is termed *carcinogenesis*. The combination of mutations that affect biological events such as cell survival, growth control and differentiation is the basis for carcinogenesis. Tumor cells gain several phenotypic features during the development of cancer. Those changes cause the rapid and uncontrolled proliferation of tumor cells, as well as their spread to surrounding tissues. In addition, those cells can survive independently in specific microenvironments and have the ability to metastasize.

Cyclins [6]. These are specific proteins that activate various phases of the cell cycle. Most cells with proliferative abilities divide as a response to external signals like growth factors, some hormones, and antigen histocompatibility complexes that affect cell surface receptors. These cell surface receptors transmit the received signal to the nucleus and the cell divides. Tyrosine kinases are an important component of cascade reactions, which are initiated by proliferative signals from extracellular growth factors, and propagate to the nucleus. Cyclins combine with specific tyrosine kinases called cyclin-dependent kinases, activating them as well as regulating their effects. Various cyclins are synthesized throughout the different phases of the cell cycle, and their levels either increase or decrease synchronously during each phase of the cell cycle.

Cells with proliferative capacity normally stop at certain checkpoints. The most important of these is the first, which occurs just before DNA synthesis, and the second, which occurs just prior to mitosis. These histologic resting periods probably occur due to the decreased activity of cyclin-dependent kinases and tumor suppressor proteins. Actually, since cells in these phases of the cell cycle synthesize the proteins used in the next phases, they are biochemically active. At these checkpoints, any genetic defects are repaired. In summary, while the cell progresses through the cycle, it stops at two checkpoints and is controlled. Normal cells have mechanisms for detecting errors in the DNA sequence. A group of repair mechanisms replace damaged nucleotides with normal molecules when the DNA is damaged. These mechanisms ensure that the genetic material in each of the two daughter cells is the same as that of the mother cell.

The first checkpoint of the cell cycle [7]. This is located in the late G_1 phase just prior to the S phase. DNA should be error-free before it exits from G_1, and even extracellular signals specific for DNA synthesis and all of the mechanisms should work properly. If any damage is detected, the cells try to either repair the damage or die by apoptosis. The protein p53 plays a prominent role in checking for DNA damage at this checkpoint.
The second checkpoint of the cell cycle [7]. This is located just prior to the M phase. Cell cycle inhibitors stop the cell cycle until they are sure that the new daughter cells will have perfect genetic copies of the DNA in the original cell. If DNA replication does not finish entirely and correctly, or all of the proteins, spindle cells and other materials needed for mitosis are not formed completely, the cell cycle stops at this checkpoint until all errors have been corrected. It then enters the M phase.

A small proportion of the normal cell population consists of immortal cells (i.e., they have the capacity for unlimited division). These cells can renew themselves based on signals from other parts of the organism; they also mature and differentiate into new cells that perform the required functions of the organism. However, only a few tissue types can differentiate; most lose their survival abilities, passing into the resting period after aging, and consequently die. Eukaryotes have four populations of cells.

Eukaryotic Cell Populations [8]

Germ cells. These have the capacity for unlimited proliferation, probably due to meiotic division. Unlike cancer cells, these cells form immortal cell lines through meiotic division.

Stem cells. These cells have two functions. The first is proliferation; the second is differentiation and then to carry out the required specific functions of the organism. Unlike cancer cells, these cells can only pass through a limited number of cell cycles.

Partially differentiated cells. These have a limited capacity for proliferation, and their daughter cells are fully differentiated with no proliferative ability.

(*continued*)

(continued)

Fully differentiated cells. These cells never proliferate.

- Differentiated normal cells, in contrast to immortal cancer cell lines, have a biological timer that counts the number of cell divisions. When a certain number of divisions have occurred, the cell cannot divide any further. For instance, human fibroblast cells divide approximately 50 times in cell lines. After that, they cannot divide, regardless of the nutritive conditions present.

2.1.5 Features of Cancer Cells

Cancer is a disorder characterized by the continuous proliferation of cells [9]. This event happens when the increase in the number of excessively proliferating cells is not balanced by normal cell loss. These cells continuously invade and damage the organs of organisms. Although cancer cells die more quickly than the normal cells they derive from, new cell formation occurs so quickly that the cancer cells accumulate. This imbalance arises from both the genetic abnormalities of cancer cells and the inability of the organism to recognize and destroy these cells.

Unique Features of Cancer Cells [9, 10]

Clonal origin. Most cancer cells originate from just one abnormal cell. However, some cancers arise from more than one malign clone. These clones are formed because of either field damage (tissue cells exposed to more than one carcinogen) or heritable defects in some genes.

Immortality. Most normal cells can undergo a limited number of divisions. On the other hand, cancer cells can undergo an unlimited number of divisions and form endless numbers of cells. One of the mechanisms for immortality is associated with telomeres, which are the tips of chromosomes. During normal cell differentiation in, these telomeres shorten. However, the telomeres are renewed by the effect of the enzyme telomerase in cancer cells and stem cells. Telomerase activity normally decreases during cell differentiation. Since the cell loses its capacity for proliferation, fully differentiated cells enter a resting state and consequently die. However, telomerase retains its efficacy in several cancer types, or it is reactivated. Therefore, the telomere length remains constant in these cells and they proliferate indefinitely (they become immortal).

Genetic instability. This situation is caused by defects in the DNA repair process and in DNA mismatch recognition, which results in the heterogeneity of cancer cells. Cancer cells form clones that gradually respond less and less to the proliferation control mechanism. The ability of these clones to survive in foreign environments also gradually increases, and they gain the ability to metastasize.

Loss of contact inhibition. Normal cells growing in culture medium cannot divide if they do not stick to the bottom layer. Normal cells also lose their ability to divide when they form a layer across the whole surface. They do not divide, even in the presence of all of the required growth factors and other nutritional elements in the Petri dish. Cancer cells, however, divide independently without needing to stick to the bottom layer of the Petri dish. Furthermore, they continue to grow even when they have formed more than one layer in the cell culture.

Continuous increase in proliferation. This situation is a characteristic of cancer cells in culture medium. Although cancer cells consume the required nutrition factors, they continue to grow, and they actually end up killing themselves.

Metastasis. This feature is not found in benign tumors and normal cells. Metastasis occurs because of the loss of cellular proteins responsible for adherence to the extracellular matrix, intercellular interaction defects, abnormalities in cell adherence to the basal membrane, abnormalities in basal membrane production, or the destruction of basal membrane by enzymes like metalloproteases.

2.2 Cellular Effects of Radiation

Ionizing radiation injects energy into a material as it passes through it, like a microscopic bullet, until the radiation is stopped by the material due to absorption [11]. In addition, radiation breaks the molecular bonds of the material in its path, and changes the structure of the material. If the material consists of long molecular chains, the chains that are broken by the radiation form new bonds at random. In other words, radiation cuts long molecules at various positions, like a welding flame, and reconnects them in different ways.

Living cells commonly consist of long protein chains, and some of these molecules can be broken by exposing the cell to radiation. The molecular fragments can then rebond in various ways, resulting in new molecules. These new molecules cannot function like the original molecules, and so they need to be repaired. Otherwise, these defective molecular structures will accumulate in the cell, changing the cell's metabolism; if the defective molecule is DNA, it can result in the formation of a cancer cell. Cells have certain repair mechanisms that they can employ for this type of damage. Cells in developed organisms can even check their molecules one by one, and they prefer to rebuild these molecules at certain intervals rather than repairing any damage. However, the capacity for cell repair is limited, and if this limit is exceeded, the damaged molecules will start to accumulate and affect the vital survival functions of the cell.

There is no such thing as a fully radioresistant cell. Structures that form the cell, such as the nucleus, and particularly chromosomes undergoing division, are more radioresistant than the cell cytoplasm. One of the most prominent effects of radiation at the cellular level is the suppression of cell division. The growth of cells that are exposed to radiation, particularly during cell division (mitosis), is interrupted.

The presence of ionizing radiation increases mutation frequency. Mutation frequency is linearly related to dose (Fig. 2.11). Since low mutation rates occur with low doses, this relation is not linear at low radiation doses. Dose rate (i.e., the amount of radiation received over a specific amount of time) does not affect mutation frequency. In other words, the total number of mutations is the same regardless of the period of exposure to the radiation [12].

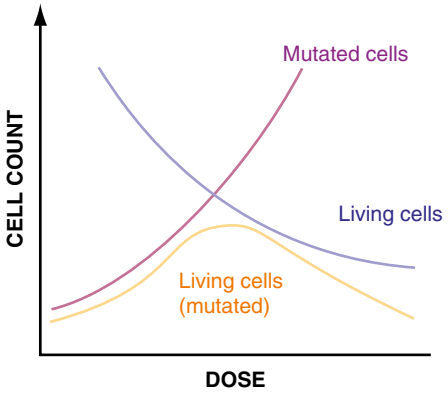


Fig. 2.11 Relationships between dose and mutated cell, living cell, and mutated living cell counts

Ionizing radiation can cause breaking, sticking, clamping and curling in chromosomes. Broken chromosomes can reorganize, remain the same, or combine with other chromosomes. All of these events result in mutations or in eventual cell death (Fig. 2.12).

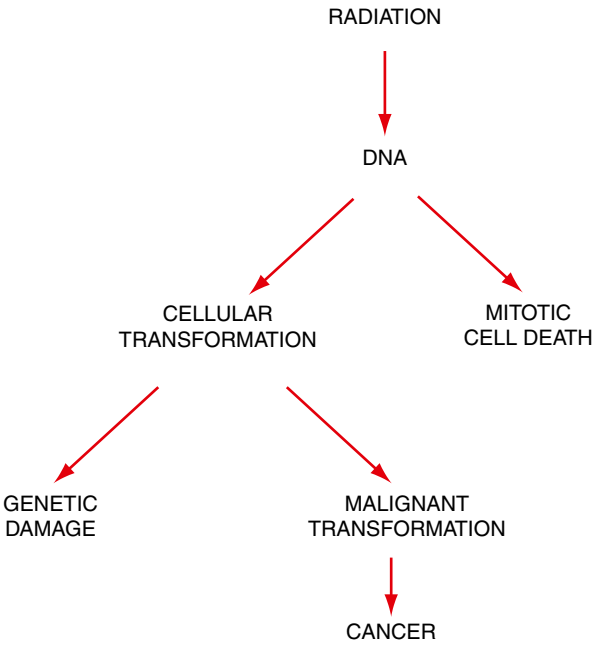


Fig. 2.12 Radiation and carcinogenesis

Although all molecules can be damaged by radiation, DNA molecules that carry genetic information related to cell division and growth are the most probable targets. Radiation may damage or change a small part of the DNA molecule (e.g., only one gene); it can break one or several locations on the DNA helix. The damage is repaired in most cases, but cell death or transformation is observed in some circumstances, and this may result in malign transformations and cause cancer. Dead cells are normally eliminated by the organism. However, if the number of cell deaths exceeds a certain limit, they will affect the proper functioning of the organism and can kill it.

Radiation can have direct and indirect effects on DNA molecules.

2.2.1 The Direct Effect of Radiation at the Molecular Level

Radiation directly affects DNA molecules in the target tissue (Fig. 2.13a) [13]. The direct ionization of atoms in DNA molecules is the result of energy absorption via the photoelectric effect and Compton interactions. If this absorbed energy is sufficient to remove electrons from the molecule, bonds are broken, which can break one DNA strand or both (Fig. 2.13b, c). A single broken strand can usually be repaired by the cell, while two broken strands commonly result in cell death.

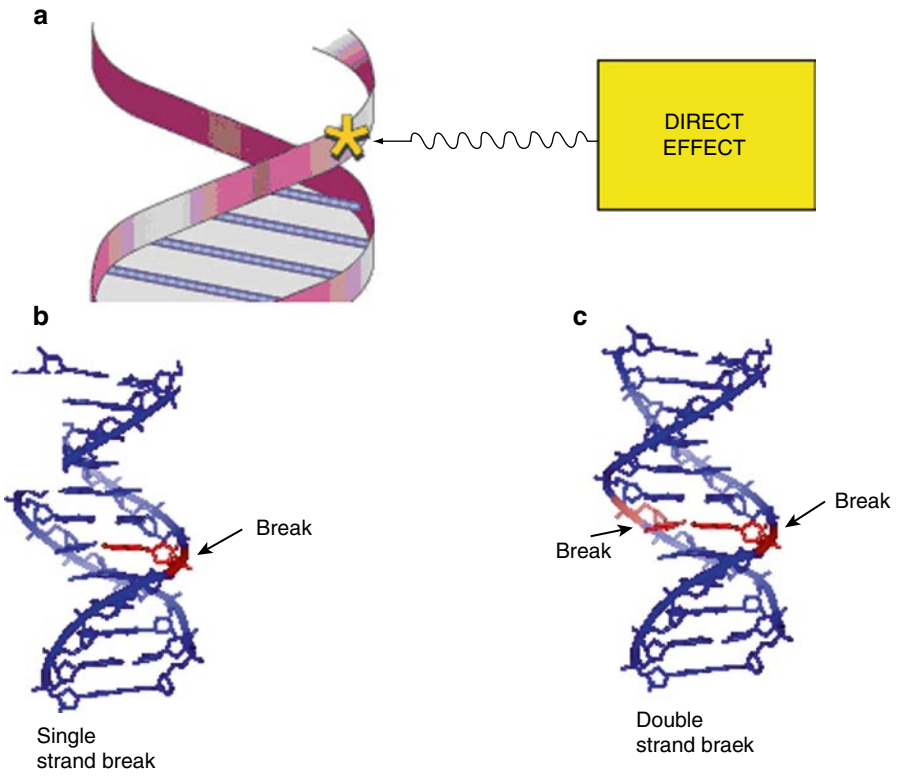


Fig. 2.13 (**a**) Direct effect of radiation. (**b**) Single-strand DNA break. (**c**) Double-strand DNA break

A dose of 2 Gy of X-rays is equal to an energy of 2 J/kg. Since 1 J/kg is equal to 6.25×10^{18} eV/kg [13], 2 Gy is equal to 12.5×10^{18} eV/kg. Since the minimum energy required for ionization is 33 eV, the number of ions per kilogram is calculated by dividing 12.5×10^{18} eV/kg by 33 eV, which yields $\sim 4 \times 10^{17}$ ions/kg. If we apply two doses to the whole body (we know that there are 9.5×10^{25} atoms/kg in the human body), the number of atoms in the whole body ionized by a dose of 2 Gy can be found by dividing the ions/kg by the atoms/kg. The result is nearly 1×10^{-8} (one in a hundred million), which means that the direct effect of X-rays in terms of DNA damage in tissue is relatively minor.

The direct effect of radiation is to ionize molecules in its path. While the direct effect of low linear energy transfer (LET) radiation is largely insignificant (e.g., in terms of DNA damage), the direct effect dominates for high-LET radiation [13].

LET → loss of energy per unit tract length.

When normal cell DNA is damaged by radiation provided in the kinds of doses normally used in radiotherapy, the cell cycle is stopped by the protein p53. The DNA is repaired; the cell then re-enters the cell cycle and continues to proliferate. If the DNA cannot be repaired, the cell enters apoptosis – the programmed cell death pathway. At high radiation doses, the molecules utilized by the DNA repair mechanisms are damaged, so repair is not possible, the cell loses its ability to divide, and it subsequently dies.

A quarter to a third of the damage produced in cellular macromolecules by radiation is due to its direct effect. This means that most of the damage is caused by the indirect effect of the radiation. Damage to cellular proteins following irradiation at biologically relevant doses appears to be of relatively minor importance.

2.2.2 The Indirect Effect of Radiation at the Molecular Level

The indirect effect of radiation on molecules includes the formation of free radicals by energy transfer from radiation, and the resulting molecular damage caused by the interactions of these free radicals with DNA (Fig. 2.14) [13, 14]. This phenomenon is most probably due to the interaction of radiation with water molecules, since the human body is approximately 70% water. Free radicals are electrically neutral atoms that contain “free” (i.e., unbound) electrons. They are highly electrophilic and reactive.

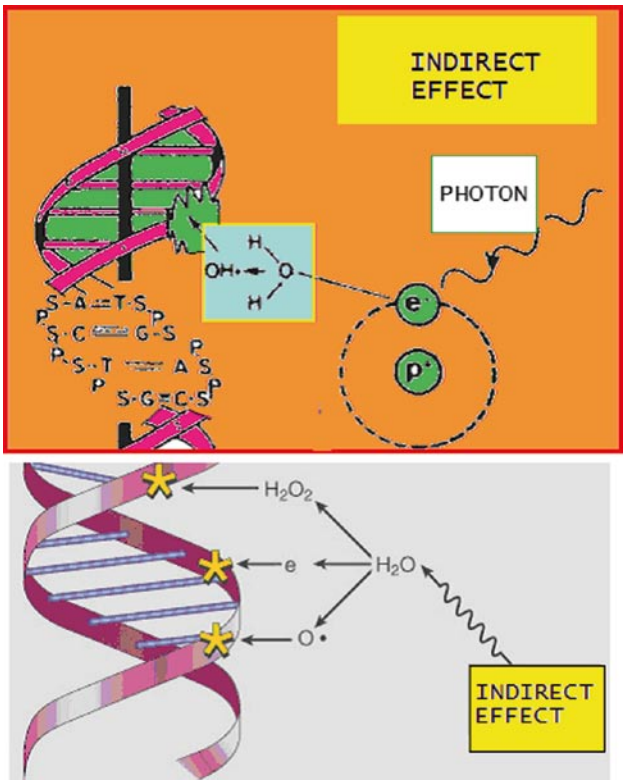


Fig. 2.14 Indirect effect of radiation (Fig. 1.1 of [65])

Water (H_2O) is ionized when exposed to radiation, and as $H_2O \rightarrow H_2O^+ + e^-$, a positively charged water molecule and a free electron are formed [14].

This free electron (e^-) interacts with another water molecule in the reaction $e^- + H_2O^+ \rightarrow H_2O^-$, resulting in the formation of a negatively charged water molecule.

These charged water molecules undergo the reactions $H_2O^+ \rightarrow H^+ + OH$ and $H_2O^- \rightarrow H + OH^-$, yielding H^+ and OH^- ions. These H and OH free radicals may combine with other free radicals or with other molecules.

If the LET of the radiation is high (particularly in the case of alpha particles), the free OH^- radicals do not recombine with H^+ radicals, and so they do not form H_2O. They combine with each other in the reactions $OH^- + OH^- \rightarrow H_2O_2$ and $H^+ + H^+ \rightarrow H_2$, forming hydrogen peroxide and hydrogen gas molecules [14].

Simple free radicals (H or OH) have very short lifetimes (10^{-10}s), and this time span is too short for them to travel from the cytoplasm to the nucleus, where the DNA is located. Therefore, the H combines with O_2 and transforms into a more potent and lethal free radical with a longer lifetime, called hydrogen dioxide (HO_2) [14]. Although hydrogen peroxide,

H_2O_2, has an even longer lifetime (10^{-5}s), it cannot move from one place to another. It oxidizes the surroundings of the cells close to where it is formed, and prevents the nutrition of neighboring tissues or cells. This results in cell death through nutritive deficiency or the isolation of these cells from other tissues.

Free radicals formed by the hydrolysis of water affect DNA. The negative effect of hydrogen peroxide on cell nutrition may be employed as evidence of the indirect effect of radiation.

2.3 Factors Modifying the Biological Effects of Ionizing Radiation

The biological effects of ionizing radiation depend on factors such as the characteristics of the radiation (energy, intensity, content) and the target (structure of irradiated tissue; age, gender, general health of the person exposed to the radiation).

2.3.1 Characteristics of the Radiation

The potential harm to biological materials caused by their irradiation is directly proportional to the efficacy with which the radiation deposits energy in the material. Proton, neutron and alpha particles lose their energies over much shorter distances than X-rays and gamma rays with the same energy.

Linear Energy Transfer (Table 2.1) [15]

The energy transferred to the tissue by ionizing radiation per unit tract length is called the LET.

- The LET is a function of the charge and the velocity of the ionizing radiation.
- The LET increases as the charge on the ionizing radiation increases and its velocity decreases.
- Alpha particles are slow and positively charged. Beta particles, on the other hand, are fast and negatively charged. Therefore, the LET of an alpha particle is higher than that of a beta particle.
- Lethal effects increase as the LET increases.
- The units of the LET are keV/μm.

Since high-LET radiation (particulate radiation) transfers more energy per unit length of material, the probability of causing DNA damage in a short period of time is high. Thus, a

Table 2.1 LET values for various radiation types [15]

Radiation	Energy	Relative LET value (keV/μm)
250 kV X-ray	250 kV	3
3 MV X-ray	3 MV	0.3
Cobalt 60	1.17–133 MV	0.3
Beta 10 kV	10 kV	2.3
Beta 1 MV	1 MV	0.25
Neutron 2.5 MV	2.5 MV	20
Neutron 19 MV	19 MV	7
Proton 2 MV	2 MV	16
Alpha 5 MV	5 MV	100

dose of high-LET radiation is more destructive than the same dose of low-LET radiation (electromagnetic radiation).

Absorbed dose [16]. The basic quantity of radiation measurement in radiotherapy is the "absorbed dose." This term defines the amount of energy absorbed from a radiation beam per unit mass of absorbent material. The unit of absorbed dose is the Gray (Gy). It changes continuously along the path of the radiation because the radiation slows down. In addition, secondary radiation energies occur due to secondary scattering from the particle's path in tissue. The type and effects of each form of radiation type should be known exactly in order to define the total effect of the radiation.

Equivalent dose (= dose equivalent) [16, 17]. Different radiations cause different damages in human tissues. The *absorbed dose* (→ Gy) is not adequate for studies of radiation protection. Thus, the absorbed dose in tissue should be multiplied by the radiation weighting factor for this radiation type. The calculated result is defined as the equivalent dose, measured originally in roentgen equivalent in man units (REMs), but now measured in Sieverts (Sv).

If the mean absorbed radiation dose (Gy) in a tissue or organ is multiplied by the appropriate radiation weighting factor (W_R), the equivalent dose (H_T) is found.

Sv is a large unit, so doses are frequently expressed in millisieverts (mSv) or microsieverts (μSv) for practical purposes.

Radiation weighting factors (W_R) are determined in order to compare the biological effects of different radiation types [18, 19]. These weighting factors are also called radiation quality factors (QF) (Table 2.2).

Table 2.2 Weighting factors for various radiation types (ICRP 1991)

Radiation type	Energy interval	Weighting factor = quality
Photon (gamma and X-rays)	All energy levels	1
Electron	All energy levels	1
Neutron	<10 kV	5
Neutron	10–100 kV	10
Neutron	100 kV–2 MV	20
Neutron	2–20 MV	10
Neutron	>20 MV	5
Proton	>20 MV	5
Alpha particles, heavy nuclei	All energy levels	20

Dose Rate [20]

This is the dose delivered per unit of time. If a radiation dose that causes irreparable damage when delivered over a short time period is delivered over longer periods, the cell or organism may survive.

2.4 Target Tissue Characteristics

Different tissues have different radiosensitivities. Cells that divide frequently (e.g., blood-forming cells in the bone marrow) are frequently affected by radiation more than rarely dividing cells (e.g., connective and fat tissue). Metabolic factors such as the oxygen concentration in the irradiated volume are also important.

The International Commission on Radiological Protection (ICRP) defined a mean reference human in order to estimate the absorbed doses at certain places on the body (Fig. 2.15). In general, the results on radiation absorption obtained in this way can be related to real irradiation. A further simplification was recommended by the ICRP in 1977. The recommended limits on dose equivalence are based on regular irradiation of the whole body. Irradiation of the whole or only part of the body can be expressed as the equivalent whole-body irradiation by taking into account weighting factors for certain organs (Table 2.3) [18, 19].

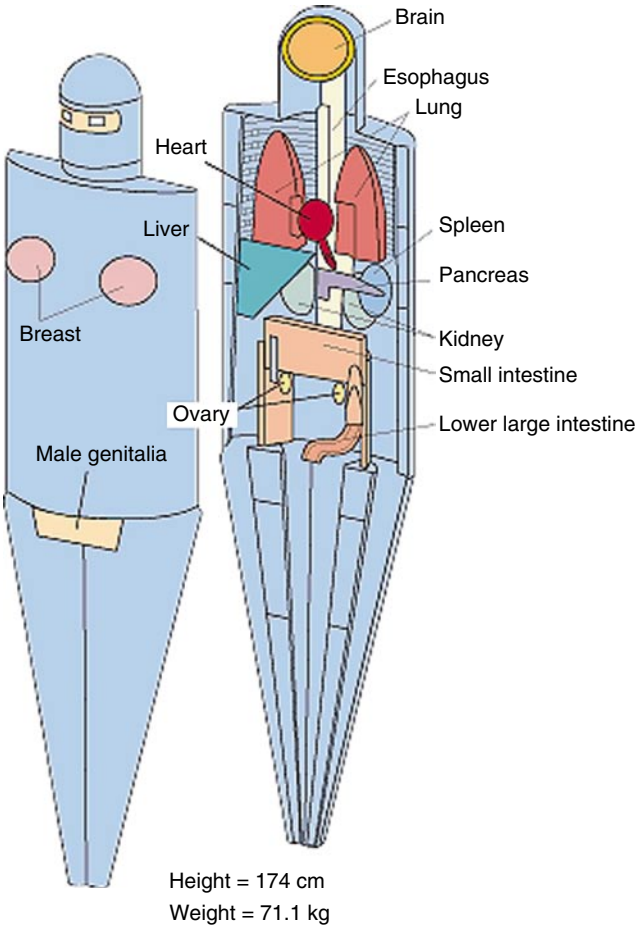


Fig. 2.15 Reference human according to the ICRP (Fig. 4.21 of [66])

Table 2.3 Tissue weighting factors

Tissue	Tissue weighting factor (W_T)
Gonads	0.20
Lung, bone marrow, stomach, colon	0.12
Thyroid, liver, esophagus, breast, bladder	0.05
Bone surface	0.01
Skin	0.01
Other organs	0.05
Total	1

Whole Body Dose Equivalent [17]

$$H_{wb} = \Sigma_T W_T H_T \quad (2.1)$$

H_T: dose equivalent for tissue
W_T: weighting factor for tissue

Effective Dose [17]

This is the dose calculated by multiplying the equivalent dose by the tissue weighting factor (W_T) (Fig. 2.16).

- The units of effective dose are sieverts, just like equivalent dose.

Fig. 2.16 Relationship between exposure and equivalent dose

$$\mathrm{WT} = \frac{\text{Risk at organ or tissue (depending on stochastic effects)}}{\text{Total risk at body (depending on stochastic effects)}} \tag{2.2}$$

Relative Biological Effect (RBE) [21, 22]

The RBE is the ratio of the 250 kV X-ray dose that produces a specific biological effect to the test dose of any radiation that produces the same effect. The RBE is related to the LET.

$$\mathrm{RBE} = \frac{\text{The 250 kV X - ray dose required for a specific effect}}{\text{Tested dose of any radiation required for a specific effect}} \tag{2.3}$$

Overkill Effect

The decrease in the curve of RBE vs. LET at LET values of above 100 keV/μm has been interpreted as an "overkill effect," where the ionization density within a single cell is greater than the two ionization events needed to inactivate the cell (Fig. 2.17). In other words, any dose beyond that needed to produce the two events per cell is, in effect, wasted. Densely ionizing radiation is inefficient at producing the maximum amount of cell death.

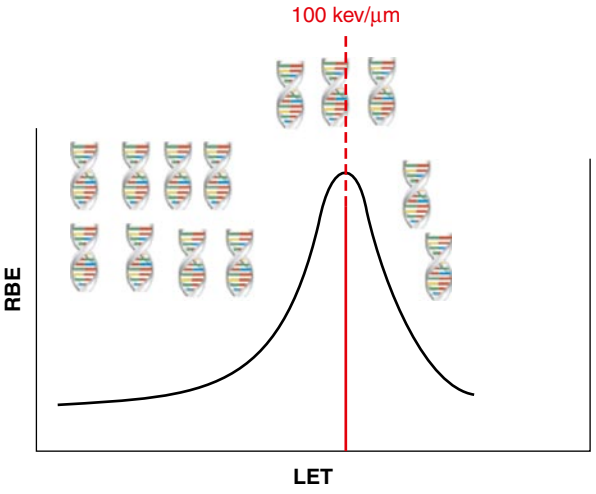


Fig. 2.17 Overkill effect

The durations of physical, chemical and biological events after radiation has penetrated the cell are shown in Fig. 2.18.

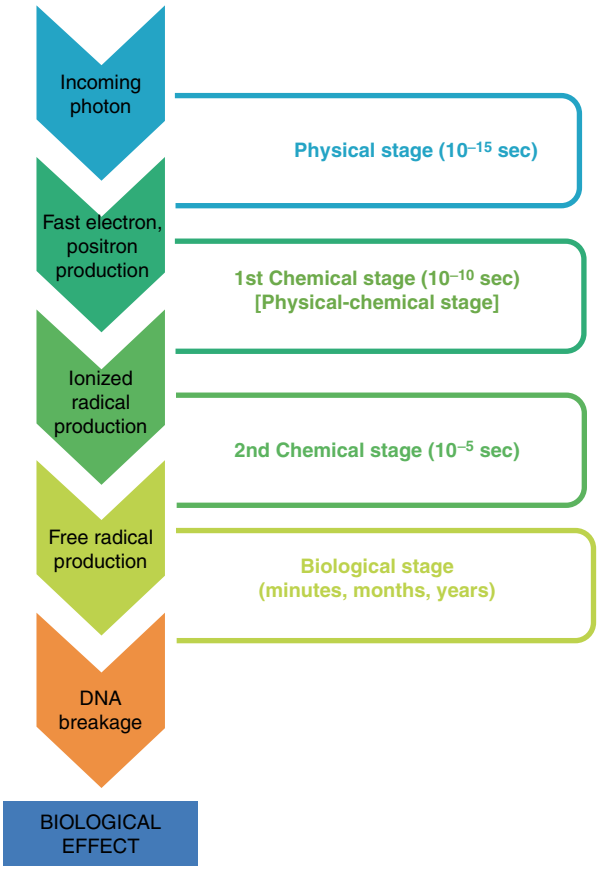


Fig. 2.18 Durations of physical, chemical and biological stages

2.5 Target Theory

The number of DNA or critical target cells "hit" by the radiation depends on random events in target theory, and has no direct relation to the ionizing radiation dose [23]. Therefore, there is no threshold at which the effects of the radiation are observed. Whatever the delivered radiation dose, there is always a chance of it hitting DNA or cells and producing harmful effects. The phenomenon where the effects of the radiation do not depend on dose is known as the "stochastic effect."

Target theory explains the cell damage caused by radiation based on the principles of probability. It assumes that there are certain critical molecules or critical targets within cells that need to be hit or inactivated by the radiation to kill the cell.

Single target–single hit [23, 25]:
Here, there is only one target in the cell that is associated with cell death, and a single hit on this target is adequate to inactivate the target.

- This is a valid assumption for viruses and some bacteria.

Multiple target–single hit [23, 24]:
Here, there is more than one target per cell, and a single hit of any of these targets is required for cell death.

Not all targets are hit; some of them are killed, while others are damaged by low doses. This type of damage is called sublethal damage (SLD). Cells with SLD may repair themselves during interfractional periods.

This is a valid assumption for mammalian cells.

2.6 Cell Survival Curves

The number of cells in cell lines within cell cultures can increase in one of two ways: either arithmetically or exponentially (geometrically).

The number of cells increases linearly (by a constant number) with each generation in an arithmetic increase. In an exponential increase, the number of cells doubles with each generation, and so exponential growth is faster than arithmetic growth (Fig. 2.19).

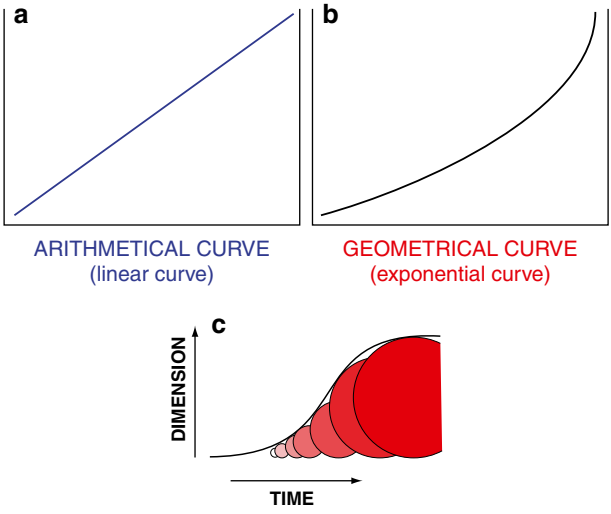


Fig. 2.19 Survival curves: (**a**) arithmetical; (**b**) geometrical (exponential). (**c**) Exponential increase in cell number

When cell culture lines are exposed to radiation, some of them lose their capacity to divide and cannot form colonies (→ reproductive cell death), some only divide to a small degree and form small colonies, some divide slowly and form colonies over longer periods, some lose their capacity to divide but continue to grow and become giant cells, while still others degenerate and die. The remaining cells are not affected by the radiation, and they represent the surviving fraction (SF) after irradiation of the cell culture (→ SF) [26].

Surviving Fraction [26, 27]

The ratio of the number of cells that form colonies to the number of seed cells under normal conditions (i.e., no irradiation) in a cell culture is termed the plating efficiency (PE). The same ratio obtained under irradiated conditions and divided by the PE is called the surviving fraction (SF):

$$\text{Surviving fraction (SF)} = \frac{\text{Colony number}_{\text{rad}}}{\text{Seeded cell number}_{\text{rad}} \cdot \text{PE}} \tag{2.4}$$

- For example, if 100 cells are seeded into an unirradiated culture, and ten colonies are formed, then the PE is 10/100. If there are five colonies after a 450 cGy dose of radiation, the SF is 5/[100 × 10/100] = 1/2. Thus, the SF of 450 cGy is 50%.

If the SF is calculated for various doses, then it can be presented as a cell–dose plot. Combining the points on the plot leads to a cell survival curve.

Curves showing the relation between the radiation dose and SF are termed cell survival curves. If the dose is plotted on the *y*-axis and the SF (as a percentage of the original number of cells in the culture) is plotted on the *x*-axis, a sigmoid curve is obtained (Fig. 2.20a). If the logarithm of the SF is plotted on the *x*-axis, a semilogarithmic curve is obtained (Fig. 2.20b) [27].

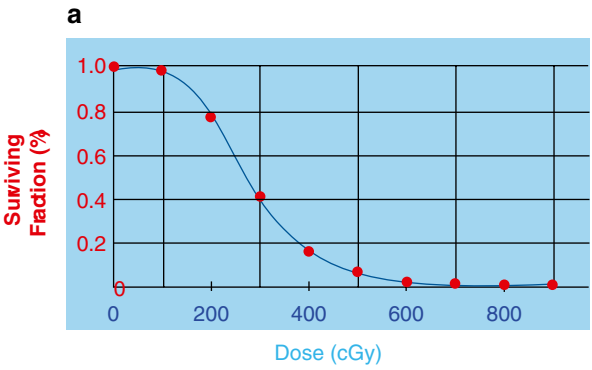
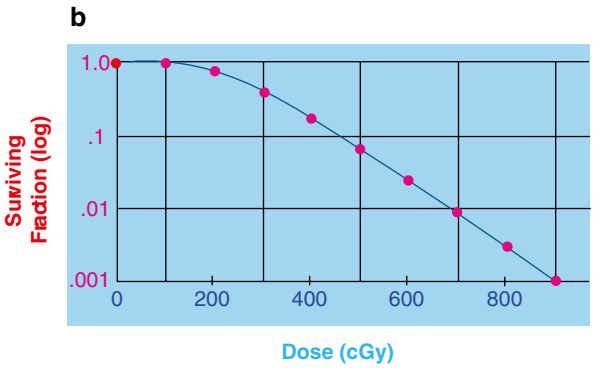


Fig. 2.20 **(a)** Sigmoid curve; **(b)** semilogarithmic curve

Fig. 2.20 (continued)



LD50 value can be obtained from a sigmoid survival curve (LD50 is the dose that kills 50% of cells → lethal dose).

Survival curves are radiobiologically defined using semilogarithmic curves, and these curves provide information on some parameters such as the number of cells killed by the radiation and cell radiosensitivity.

2.6.1 Exponential Survival Curves

These are the survival curves resulting from the single target–single hit hypothesis of target theory (Fig. 2.21) [16, 26–28]. They show that cell death due to irradiation occurs randomly. At certain doses with one unit increase, both same number of cell deaths and same proportion of cell death occur.

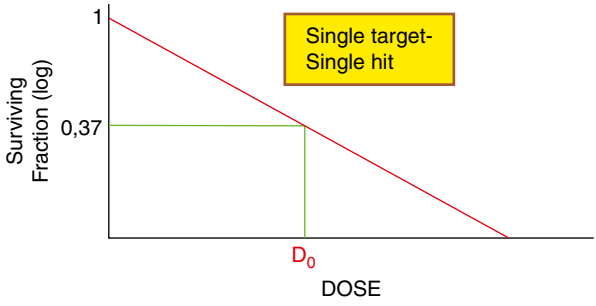


Fig. 2.21 Single target–single hit hypothesis

After 100 radiation "hits," the probability that one of the hits will be a target → e^{-1} ($e \approx 2.718 \ldots$).

- e^{-1} is approximately 37%. In other words, 63% of the targets will be hit after 100 hits, while 37% of the targets will survive.
- This corresponds to the survival curve observed for viruses and some bacteria.
- Some cells are observed to be very sensitive to radiation (for example, germ cells) also show this behavior.
- It may also be observed at very low dose rates and for high-LET radiation.

D_0 = dose that decreases the surviving fraction to 37%.

This is the dose required to induce an average damage per cell.

A D_0 dose always kills 63% of the cells in the region in which it is applied, while 37% of the cells will survive.

$1/D_0$ = the slope of the survival curve.

As the value of D_0 decreases → $1/D_0$ increases → slope increases → *radiosensitive cell.*
As the value of D_0 increases → $1/D_0$ decreases → slope decreases → *radioresistant cell.*

For exponential survival curves, SF is given by

$$SF = e^{-D/D_0} \tag{2.5}$$

This can be used to determine the proportion of the original cells that will survive if a dose D is delivered.

2.6.1.1 Shouldered Survival Curves with Zero Initial Slope

These survival curves are based on the multiple target–single hit hypothesis of target theory [16, 26–28]. They are produced by the hypothesis of requiring multiple targets per cell, and only one of these targets needs to be hit to kill the cell (Fig. 2.22).

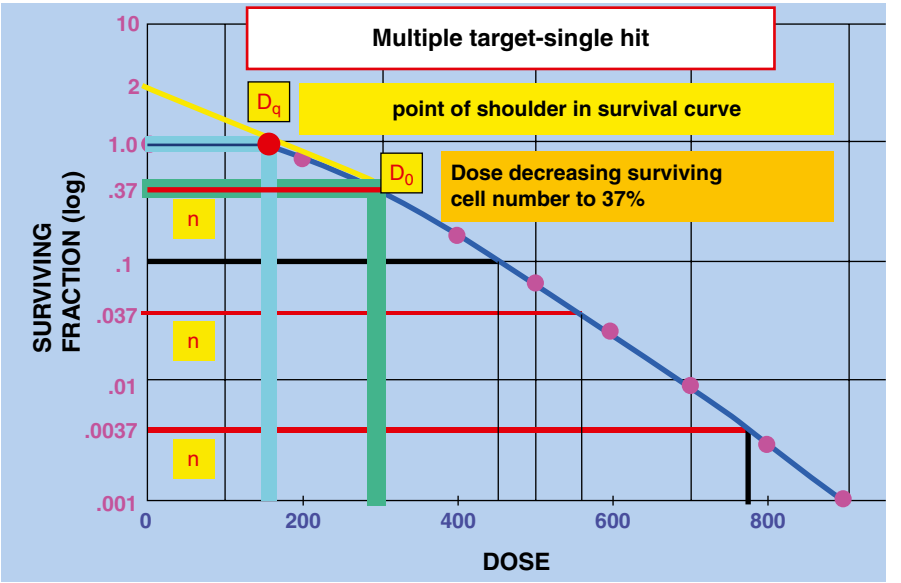


Fig. 2.22 Multiple target–single hit hypothesis

D_0: the dose that yields a surviving fraction of 37%.
D_q: half-threshold dose → the region of the survival curve where the shoulder starts (indicates where the cells start to die exponentially) (= quasi-threshold dose).
n: extrapolation number (the number of D_0 doses that must be given before all of the cells have been killed).

SF for shouldered survival curves with zero initial slope:

$$SF = 1 - \left[1 - e^{-D/D_0}\right]^n \tag{2.6}$$

This gives the proportion of the original cells that survive if a dose D is delivered.

D_q → the width of the shoulder region.

$$D_q = D_o \log_n 2.7 \tag{2.7}$$

If n increases → D_q increases → a wide shouldered curve is observed.
If n decreases → D_q decreases → a narrow shouldered curve is observed.
If D_q is wide and D_0 is narrow, the cell is radioresistant.
The D_0 and D_q values for the tumor should be smaller than those of normal tissue to achieve clinical success.

2.6.1.2 Shouldered Survival Curves with Nonzero Initial Slope

If we carefully examine the shouldered survival curve with an initial slope of zero, the curve is straight when the dose is small [26–28]. This indicates that there is a threshold dose where the radiation starts to exert an effect. However, studies have demonstrated that the radiation has an effect regardless of the radiation dose. The model that takes this observed behavior into account has two components with a nonzero initial slope.

Components of Shouldered Survival Curves with Nonzero Initial Slope (Fig. 2.23) [16, 27, 28]

- Component corresponding to the single target–single hit model (blue in the figure)
  This shows lethal damage.
  This shows the cells killed by the direct effect of the radiation.
  This shows the effect of high-LET radiation.
- Component corresponding to the multiple target–single hit model (red in the figure)
  This shows the accumulation of SLD.
  This shows the cells killed by the indirect effect of the radiation.
  This shows the effect of low-LET radiation.

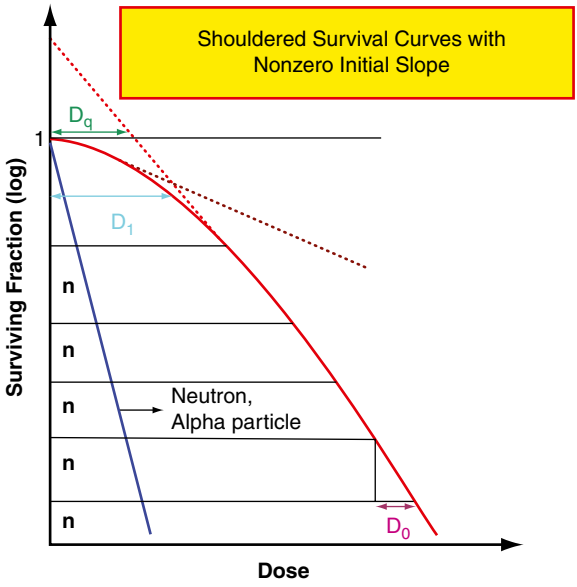


Fig. 2.23 Shouldered survival curves with nonzero initial slope

$1/D_1$: the slope of the component corresponding to multiple target–single hit (the slope of the initial region).
D_q: the dose at which the shoulder starts for the multiple target–single hit component (the quasi-threshold dose).
$1/D_0$: the slope of the terminal region of the multiple target–single hit component.
n: extrapolation number.

SF for shouldered survival curves with nonzero initial slope:

$$SF = e^{-D/D_1}\left[1-(1-e^{-D/D_0})^n\right] \tag{2.8}$$

2.6.2 Linear–Quadratic Model (LQ Model)

In this model, developed by Douglas and Fowler in 1972, it was assumed that cell death due to ionizing radiation has two components (Fig. 2.24) [29].

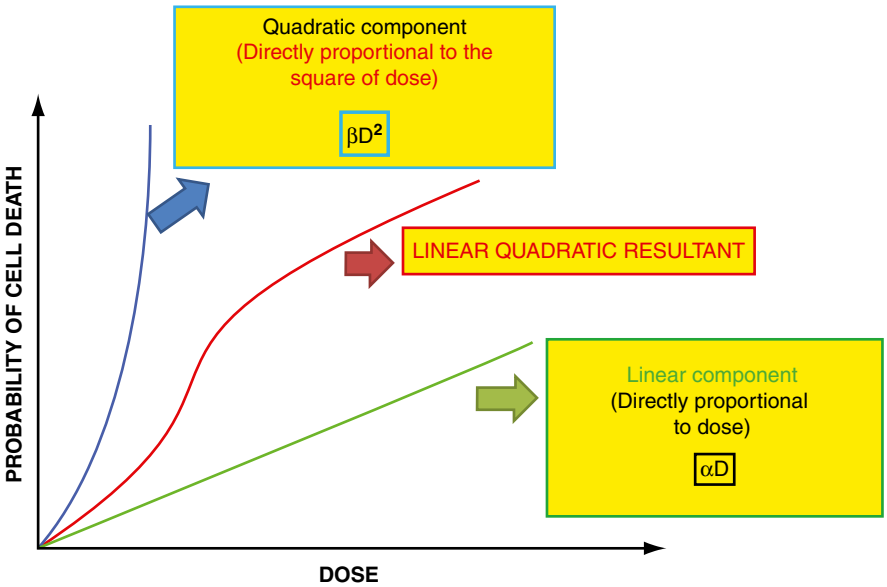


Fig. 2.24 Components of the linear–quadratic model

The first component
Directly proportional to dose → D
- Linear component

The second component
Directly proportional to the square of the dose → D^2
- Quadratic component

If we transform the cell death probability curve into an SF curve, the linear–quadratic model assumes a linear–quadratic relation between fraction dose and fraction number.

If the effect with one radiation hit is *p1*, then

- $p1 = \alpha D.\alpha$ → initial slope of the survival curve (low-dose region)
  α → linear coefficient (Fig. 2.25).
- Corresponds to the cells that cannot repair themselves after one radiation hit.
- Important for high-LET radiation.

Apoptotic and mitotic death are dominant.

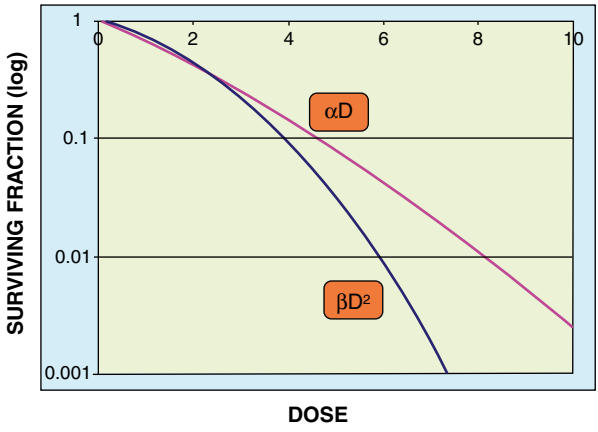


Fig. 2.25 Relation I between dose and surviving fraction in the LQ model

If the effect of two radiation hits is *p2*, then
- $p2 = \beta D^2$

β → quadratic coefficient.

- Corresponds to cells that stop dividing after more than one radiation hit, but can repair the damage caused by the radiation.
- Important for low-LET radiation.
- Mitotic death is dominant.

$$\text{Total effect } p1 + p2 = \alpha d + \beta d^2 \tag{2.9}$$

$$\text{SF} = e^{-(\alpha d + \beta d^2)} \tag{2.10}$$

α → shows the intrinsic cell radiosensitivity, and it is the natural logarithm ($\log_e$) of the proportion of cells that die or will die due to their inability to repair radiation-induced damage per Gy of ionizing radiation.

β → reflects cell repair mechanisms, and it is the natural logarithm of the proportion of repairable cells due to their ability to repair the radiation-induced damage per Gy of ionizing radiation.

What is the LQ model used for?

To formulate equivalent fractionation schemes.

To calculate additional doses after breaks from radiotherapy.

To get information on acute and late responses.

$$E = n\,(\alpha d + \beta d^2) \tag{2.11}$$

$$E = nd\,(\alpha + \beta d) \tag{2.12}$$

$$E/\alpha = nd\left(1 + \frac{d\beta}{\alpha}\right) \tag{2.13}$$

$$E/\alpha = nd\left(1 + \frac{d}{\alpha/\beta}\right) \tag{2.14}$$

$$BED = \frac{E}{\alpha} \tag{2.15}$$

$$BED = nd\left(1 + \frac{d}{\alpha/\beta}\right) \tag{2.16}$$

$$E = nd\left(\alpha + \beta d\right) + \log_e 2\left(T - T_k\right)/T \tag{2.17}$$

$$(\log_e 2 = 0.693)$$

$$BED = E/\alpha = nd\left(1 + \frac{d}{\alpha/\beta}\right) - \frac{0.693}{\alpha T_p}\,(T - T_k) \tag{2.18}$$

E = $\log_e$ of the total cell number, including irreparable cells (α) or partially repairable cells (β)
n = fraction number
d = fraction dose
BED = biological effective dose = extrapolated tolerance dose = response dose.
T = overall treatment time
T_k = kick-off time (repopulation start time)
T_p = potential tumor doubling time

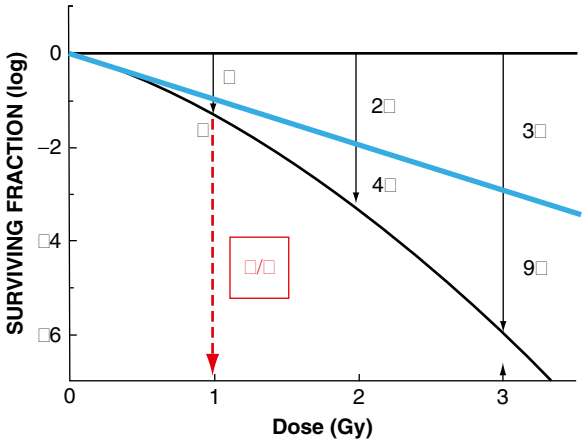


Fig. 2.26 Relation II between dose and surviving fraction in the LQ model (Fig 1.1, p 9 of [67])

α/β → dose for which the number of acutely responding cell deaths is equal to the number of late-responding cell deaths (the dose for which the linear and quadratic components of cell death are equal) (Fig. 2.26).

Tumor response and acute effects in normal tissues → α/β = 10 Gy.

Late effects in normal tissues → α/β = 3 Gy.

The α/β ratio may differ among tumor types; e.g., it is 1.5 for melanoma and 1.5–3.5 for prostate adenocarcinoma.

- This model does not take into account the effect of treatment time.

Models Used Before the LQ Model

1. **Strandqvist model** [30, 31]. This was developed by Magnus Strandqvist in 1944. Here, the relationship of skin tolerance to radiation dose for a particular skin cancer treatment time is plotted using a logarithmic curve. The slope of this curve is constant and equal to 0.22. Cohen showed that this slope value was valid for skin cancer, but he was observed that the slope was 0.33 for skin erythema. In summary, this model assumed that the tolerable fraction dose was related to the treatment time T as $T^{0.33}$.
2. **Ellis model** [31, 32]. This was developed by Ellis in 1966. While only the total dose is important in the Strandqvist model, the dependence of the tolerable dose on the number of fractions and the overall treatment time is accounted for in this model. The dose obtained using this model is termed the nominal standard dose (NSD), and so the model is known as the NSD model.

- The NSD is the dose required to cause maximum tumor damage without exceeding the tolerance levels of healthy tissues.

$$D = \mathrm{NSD} \times N^{0.24} \times \mathrm{T}^{0.11} \tag{2.19}$$

$$\text{NSD} = D \times N^{-0.24} \times T^{-011} \quad (2.20)$$

D: total dose at skin level
NSD: nominal standard dose
N: fraction dose
T: overall treatment time

3. **Orton–Ellis model** [31]. This is a modified form of the NSD model. It is also known as the TDF (time–dose factor) model. It can be summarized as:

$$\text{TDF} = d^{1.538} \times X^{-0.169} \times 10^{-3} \quad (2.21)$$

X = treatment time/fraction number
d = fraction number

If a total dose of 66 Gy is given in 30 fractions comprising 2 Gy daily fraction doses for 6 weeks, what are the BED values for acute effects, tumor response, and late effects ($\alpha/\beta = 3$ for late effects, $\alpha/\beta = 10$ for acute effects and tumor response)?

$\text{BED} = nd\,(1 + d/[\alpha/\beta])$.

$\text{BED}_{10} = 2 \times 30 \times (1 + 2/10) = 72$ Gy.

$\text{BED}_{10} = 72$ Gy for acute effects and tumor response.

$\text{BED}_{3} = 2 \times 30 \times (1 + 2/3) = 100$ Gy.

$\text{BED}_{3} = 100$ Gy for late effects.

The BED formulation is less reliable for fraction doses of more than 3 Gy.

In Head and Neck and Lung Cancers

BED calculation for tumor response:
$T_k = 21$ days and $T_p = 3$ days.
BED calculation for normal tissue:
$T_k = 7$ days and $T_p = 2.5$ days.
In prostate for late effects, $\alpha/\beta = 1.5$ Gy.
In CNS and kidney for late effects, $\alpha/\beta = 2$ Gy.

- Tissues that respond early to irradiation (radiosensitive)
  These die linearly.
  The α/β ratio is large.
- Tissues that respond late to radiation (radioresistant)
  These die quadratically.
  The α/β ratio is small.
  This hypothesis is valid for both tumor and normal tissues (Fig. 2.27).

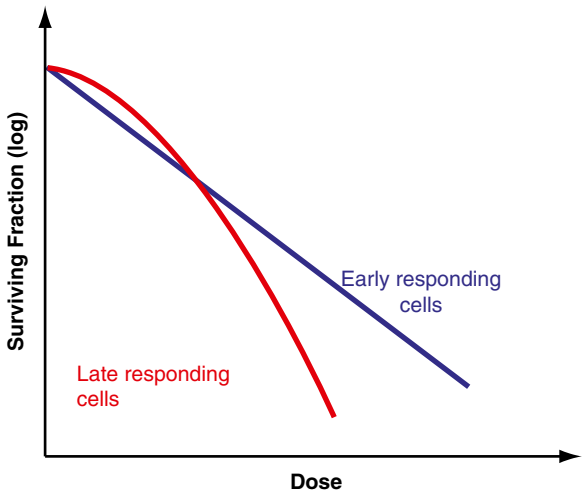


Fig. 2.27 Relation between SF and radiosensitivity

The BED formula utilizing the LQ model can be employed to compare two different radiotherapy schedules:

$$n_2 d_2 = n_1 d_1 \frac{\alpha/\beta + d_1}{\alpha/\beta + d_2} \tag{2.22}$$

$n_1, d_1 \rightarrow$ fraction dose and number of fractions in the first scheme.
$n_2, d_2 \rightarrow$ fraction dose and number of fractions in the second scheme.

2.6.3 Types of Cellular Damage Due to Radiation

1. **Lethal damage** [33, 34]. This is irreversible, irreparable damage, resulting in cell death.
- This usually results from the direct effect of radiation.
- Double strand breakage in DNA (+).
- Particularly observed in high-LET radiation.
2. **SLD** [33, 34]. SLD can be repaired within hours under normal conditions, unless an additional radiation dose is given (inducing further SLD).
- This generally occurs due to the indirect effect of radiation.
- Single strand breakage in DNA (+).
- Observed in low-LET radiation.
3. **Potentially lethal damage** [34]. This is repairable, depending on the changes in the cell environment after exposure to radiation.

- Under normal conditions, this type of damage is lethal to cells undergoing mitosis that are exposed to radiation.
- However, such damage can be repaired in suboptimal environmental conditions after exposure to radiation because the cell gets the signal of that suboptimal conditions that are not suitable for mitosis are present. The cell then prefers to repair this potential damage rather than initiate mitosis.

2.6.4 Factors Affecting the Cell Survival Curve

1. **Cell cycle.** Duration of each phase in the human cell cycle: G1 = 1.5–14 h, S = 6–9 h, G2 = 1–5 h, M = 0.5–1 h.
- The responses of cells in different phases to radiation vary (Fig. 2.28).
- The most radiosensitive cell phases are late G2 and M.
- The most radioresistant cell phases are late S and G_1.

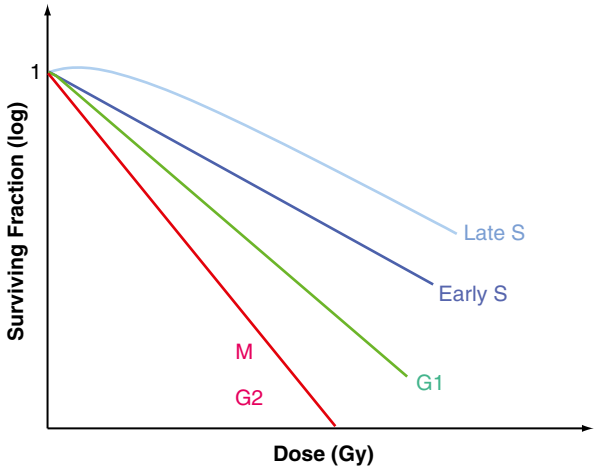


Fig. 2.28 Cell cycle and SF

2. **LET.** Radiosensitivity increases with high-LET radiation (Fig. 2.29).
- The slope of the survival fraction (SF) curve ($1/D_0$) is large for high-LET radiation.
- The slope of the SF curve ($1/D_0$) is small for low-LET radiation.

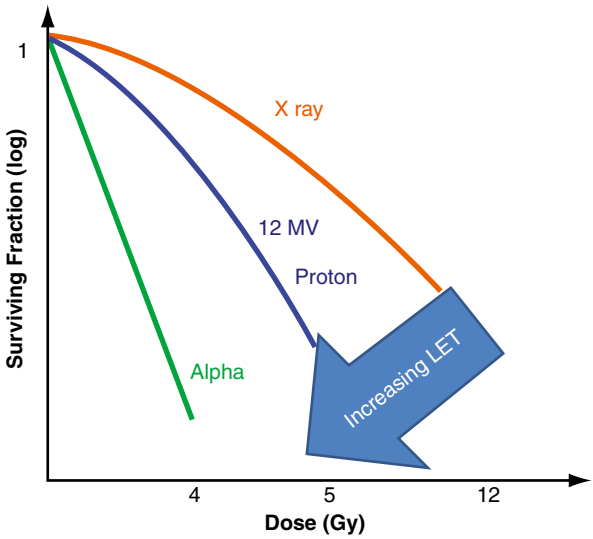


Fig. 2.29 Linear energy transfer and SF

3. **Repair of sublethal damage (SLDR)** [35]. SLD is usually repaired 2–6 h after the delivery of radiation (Fig. 2.30).

- SLD is not fatal, but the second dose increases radiosensitivity.
- It can be lethal if there is an insufficient repair period between two fractions.
- Repair abilities differ among normal tissues and tumors.
- Inhibition of SLDR is the rationale for the additive effect of chemoradiotherapy.
- SLDR depends on dose rate, and it is evident between dose rates of 0.01–1 Gy/min.

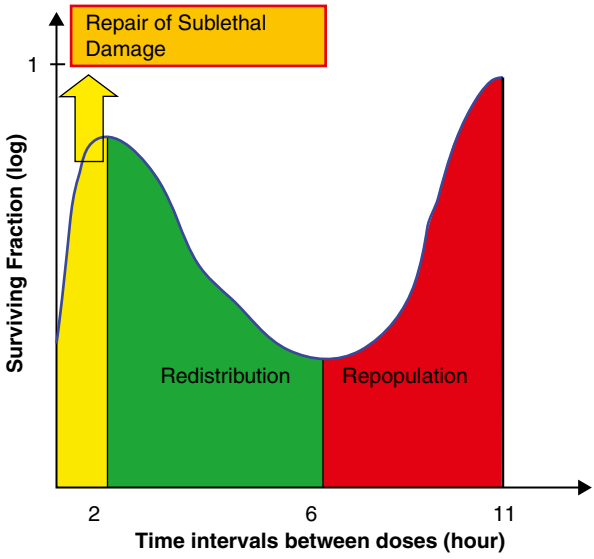


Fig. 2.30 Repair of sublethal damage and SF

4. Repair of potentially lethal damage (PLDR) [36].
Some damage that is lethal during normal growth can be repaired under suboptimal conditions (Fig. 2.31).

- The first human DNA repair gene to be discovered is located in the 18th chromosome.
- Mitomycin C, which selectively affects hypoxic tumor cells, acts through this gene and inhibits PLDR.

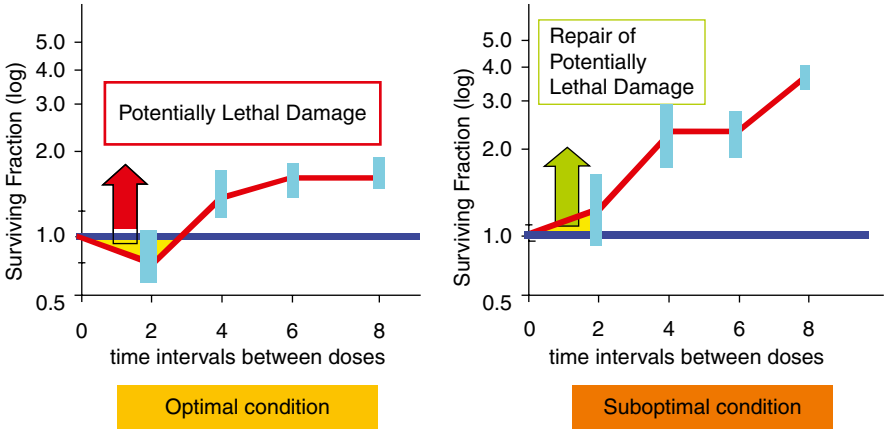


Fig. 2.31 Repair of potentially lethal damage and SF

5. Dose rate. Cell survival is greater for a delivered radiation dose if the dose rate is decreased (Fig. 2.32).

- This is due to the proliferation of undamaged living cells and SLD repair during radiotherapy.
- This effect is very important in brachytherapy applications. The dose rate in external therapy is 100 cGy/min. Low dose rates are used in brachytherapy, and high doses can be given due to normal tissue repair and repopulation.

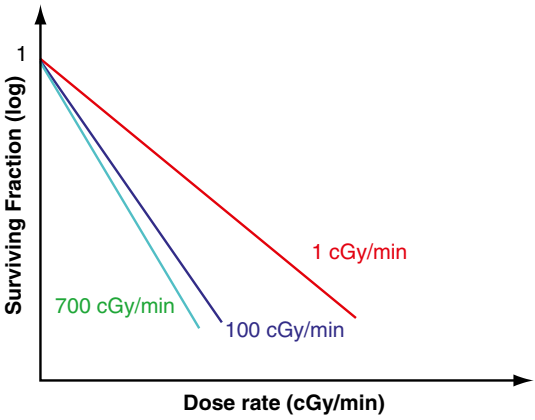


Fig. 2.32 Dose rate and SF

6. **Oxygenation** [37]. Soluble oxygen in tissues increases the stability and toxicity of free radicals. The increase in the effect of radiation after oxygenation is defined as the oxygen enhancement ratio (OER) (Fig. 2.33).

$$\text{OER} = \frac{\text{Required dose under hypoxic conditions}}{\text{Required dose under oxygenated conditions}} \tag{2.23}$$

The maximum value of the OER is 3. Oxygenation can modify the indirect effect of free radicals. However, the OER plays no role in the direct effect of high-LET radiation; OER is 1 in this case.

Tumors become less hypoxic during fractionated radiation schedules.

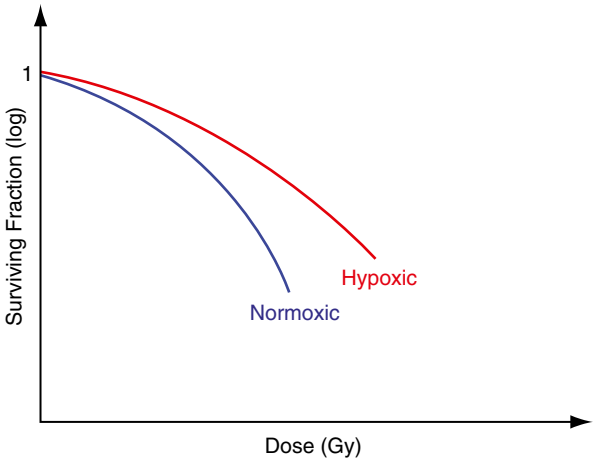


Fig. 2.33 Oxygenation and SF

7. **Temperature.** Most cells are more sensitive to radiation at high temperatures. However, there are more chromosome aberrations at low temperatures (probably due to the suppression of the DNA repair processat low temperatures).
8. **Chemical agents**

(a) *Radioprotective agents* [38]. Free radical scavengers are radioprotective agents.

- Thiol compounds, sulfhydryl amines like cysteine, cystamine and isothiouronium, dimeric compounds containing excess sulfhydryl (SH) radicals, and antioxidants like vitamins A, C and E can decrease radiation damage.

These compounds protect cells by neutralizing free radicals, producing hypoxic conditions, and forming disulfide bounds in proteins, strengthening protein structure.

Thiols, on the other hand, transiently inhibit DNA synthesis, giving the cell time to repair SLD using repair enzymes. However, they are not used prophylactically as radioprotective agents due to their side effects.

Alcohol, morphine and tranquillizing agents decrease respiration, thus increasing radioresistance.

Amifostine (WR-2721). The results of phase III trials have confirmed the safety and efficacy of amifostine as a radioprotective agent that reduces xerostomia in patients with head and neck cancers who are receiving radiotherapy. It is also a cytoprotectant that prevents cisplatin-induced renal toxicity and neutropenia in patients with ovarian cancer.

(b) *Radiosensitizers* [39]. Oxygen is the leading radiosensitizer. Oxygen mimetic agents with electron affinity (metronidazole, misonidazole, nitroimidazoles, etanidazole (SR-2508)), DNA analogs (actimomycin D, adriamycin, methotrexate, 5-flourouracil), and caffeine can increase the damaging effects of radiation.

2.7 Tissue and Organ Response to Radiation

Tissue is defined as a collection of similarly functioning cells that have the same origin and are similar in shape and structure. Tissues form organs. The response of a tissue to radiation is determined by its precursor cells (Table 2.4).

Table 2.4 Radiosensitivities of various tissues

The most sensitive	Lymphocyte Immature hematopoietic cells Intestinal epithelium Spermatogonia Ovarian follicle cells
Sensitive	Bladder epithelium Esophagus epithelium Gastric mucosa Epidermal epithelium Optic lens epithelium
Moderately sensitive	Endothelium Growing bone and cartilage Fibroblast Glial cells Mammary gland epithelium Lung epithelium Renal epithelium Hepatic epithelium Pancreas epithelium Thyroid epithelium Surrenal gland epithelium
Less sensitive	Mature erythrocyte Muscle cell Mature connective tissue Mature bone and cartilage Ganglion cell

Bergonie and Tribondeau Law [40]

The radiosensitivity of a tissue depends on:

- The excess amount of less-differentiated cells in the tissue
- The excess amount of active mitotic cells
- The duration of active proliferation of the cells

According to the Bergonie and Tribondeau law, the effect of radiation on undifferentiated divided cells with high mitotic activity is much greater than the effect of radiation on undivided differentiated cells.

Michalowski Tissue Sensitivity Classification [41]

Hierarchical tissues. These tissues are divided into two compartments containing differentiated and undifferentiated cell groups, respectively. The cells in these tissues are H-type cells.

- These are cells that can continuously divide, such as stem cells and intestinal epithelial cells.
- They respond acutely to radiation.
- *Flexible tissues*. These are tissues that are not divided into compartments containing different cells. The cells die together during tissue damage, and they are F-type cells.
- These are tissues that consist of cells that divide if necessary, such as liver and thyroid cells.
- They are late-responding tissues.

Many tissues respond to radiation in a manner that can be considered a hybrid of these two tissue types. The response of a tissue to radiation derives from both parenchymal cells and vascular stromal cells. Cells that cannot renew themselves (such as central nervous system (CNS) cells and striated muscle cells) are less sensitive to radiation, and radiation damage is most likely due to the effect on vascular stroma. A radiation dose that kills most of the stem cells in the parenchymal compartment of a tissue activates the repopulation of functional mature cells, and mature cells originating from stem cells play an important role in re-establishing tissue function after irradiation.

Flexure dose (D_f). This is the dose calculated by multiplying the α/β ratio of acutely responding tissue by 0.1 in the LQ model.

It refers to the maximum dose at which F-type tissues are protected.

It is important in hyperfractionation.

D_f is the maximum dose at which late-responding tissues are protected but early-responding tissues die. It is the dose attained just before the death of the first cell.

If D_f is high, late side effects decrease and acute side effects increase. The total dose may increase. If D_f is high, the suitability for hyperfractionation increases.

Factors Determining Radiation Damage According to Ancel and Vintemberger [42]

Biological stress in the cell.

Biological stress is important in cell division. While radiation damage to rapidly dividing cells is observed early, damage to slowly dividing cells is seen in late.

Cell status before and after radiation dose.

This indicates the environmental conditions of the cell → the radiation response of a cell changes in optimal and suboptimal conditions:

- Radiation response increases in optimal conditions.
- Radiation response decreases in suboptimal conditions.

Well-differentiated cells show a reduced capacity to divide compared to undifferentiated ones. This indicates that undifferentiated cells accrue more damage from radiation. For instance, bone marrow cells, intestinal crypt cells, and basal skin cells are undifferentiated cells; these are damaged early and at low doses.

Rubin and Casarett Tissue Sensitivity Classification [43]

This classifies tissues according to proliferation kinetics:

Tissues consisting of vegetative intermitotic cells (VIM).

These consist of undifferentiated cells.

These cells have a very short cell cycle.

– Examples include stem cells and intestinal stem cells
– These have short lifetimes but can continuously repopulate.
– These are the most radiosensitive tissues.

Tissues consisting of differentiated intermitotic cells (DIM).

These consist of cells with a partial proliferative capacity.

Their mitotic activity stops when they become mature.

- An example is spermatogonia

Multipotential connective tissues (MPC).

These consist of cells with relatively long lifetimes.

These cells divide at irregular intervals.

- The most prominent example is the fibroblast.

Tissues consisting of reverting postmitotic cells (RPM).

These cells do not divide under normal conditions; they only divide if necessary.

These tissues consist of cells with long lifetimes.

- Examples include liver parenchymal cells, pulmonary cells and renal cells.

Tissues consisting of fixed postmitotic cells (FPM).

These cells never divide.

These tissues consist of cells with very long lifetimes.

(*continued*)

(continued)

- Examples include CNS cells, muscle cells and erythrocytes.
- These are the most radioresistant tissues.

The radiosensitivities of tissues are variable, except in the cases of VIM and FPM.

The α/β ratio for acute-responding tissues is high (~10).
The α/β ratio for late-responding tissues is low (~3).
The α/β ratio in human tumors varies between 1 and 25.

Tissue and organ radiation tolerance is an important clinical parameter. The tolerance doses of normal tissue and organs surrounding the tumor are very important in radiotherapy planning. The tolerance dose depends on the delivered fraction dose and the irradiated tissue volume.

TD5/5: this defines the minimum tolerance dose, which is the dose that yields a complication rate of less than 5% over 5 years.
TD50/5: this defines the maximum tolerance dose, which is the dose that yields a complication rate of 50% over 5 years.

Dose-limiting organs are classified into three classes according to their radiation tolerances: I, II and III (Tables 2.5–2.7).

Tolerance doses are determined for 2 Gy daily fraction doses and for 5 days/week.

Table 2.5 Class I organs: radiation damage is morbid and/or highly fatal [44]

	Damage	TD 5/5 (Gy)	TD50/5 (Gy)	Irradiated field size or volume
Bone marrow	Aplasia, pancytopenia	25 35	4.5 40	Total Segmental
Liver	Acute and chronic hepatitis	25 15	40 20	Total Total thin band
Stomach	Perforation, bleeding	45	55	100 cm^2
Small intestine	Perforation, bleeding	45 50	55 65	400 cm^2 100 cm^2
Brain	Infarction, necrosis	60 70	70 80	Total 25%
Spinal cord	Infarction, necrosis	45	55	10 cm
Heart	Pericarditis, pancarditis	45	55	100 cm^2
Lung	Acute and chronic pneumonia	30 15	35 25	60% Total
Kidney	Acute and chronic nephrosclerosis	15 20	20 25	Total Whole thin band
Fetus	Death	2	4	Total

Table 2.6 Class II organs: radiation damage is of low–moderate morbidity, or occasionally fatal [44]

	Damage	TD5/5 (Gy)	TD50/5 (Gy)	Irradiated field size or volume
Oral cavity and pharynx	Mucositis, ulceration	60	75	50 cm^2
Skin	Acute and chronic dermatitis	55	70	100 cm^2
Esophagus	Esophagitis, ulceration	60	75	75 cm^2
Rectum	Ulcer, stricture	60	80	100 cm^2
Salivary glands	Xerostomia	50	70	50 cm^2
Bladder	Contracture	60	80	Total
Ureters	Stricture	75	100	5–10 cm
Testis	Sterilization	1	2	Total
Ovaries	Sterilization	2–3	6–12	Total
Growing cartilage	Growth retardation	10	30	Total
Child bone	Dwarfism	10	30	10 cm^2
Adult cartilage	Necrosis	60	100	Total
Adult bone	Fracture, sclerosis	60	100	10 cm^2
Eye				
Retina	Retinopathy	55	70	Total
Cornea	Keratopathy	50	60	Total
Lens	Cataract	5	12	Total/partial
Endocrine glands				
Thyroid	Hypothyroidism	45	150	
Surrenal	Hypoadrenalism	60	20–30	Total
Hypophysis	Hypopituitarism	45		
Peripheral nerves	Neuritis	60	100	Total
Ear				
Middle ear	Serous otitis	50	70	Total
Vestibule	Meniere's syndrome	60	70	

Table 2.7 Class III organs: radiation damage is not morbid or is reversibly morbid [44]

	Damage	TD5/5 (Gy)	TD50/5 (Gy)	Irradiated field size or volume
Muscle	Fibrosis	60	80	Total
Lymphatics	Atrophy, sclerosis	50	70	Total
Large artery–vein	Sclerosis	80	100	10 cm^2

(*continued*)

Table 2 7 (continued)

	Damage	TD5/5 (Gy)	TD50/5 (Gy)	Irradiated field size or volume
Joint cartilage	–	500	500	
Uterus	Perforation, necrosis	100	200	Total
Vagina	Ulcer, fistule	90	100	Total
Breast (adult)	Atrophy, necrosis	50	100	Total

Serial Organs [45]

The functional subunits (FSUs) of serial organs are structured serially (Fig. 2.34).

- If critical damage due to radiation occurs in any functional subunit, complications are observed in the whole organ.
- Examples include the spinal cord, esophagus, rectum and coronary arteries.

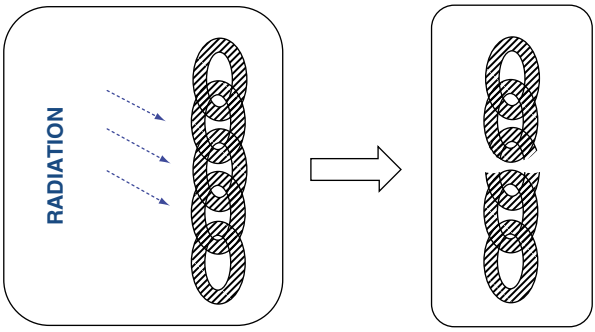


Fig. 2.34 Response to radiation in serial organs (Fig. 5.7, p 101 of [20])

Parallel Organs [45]

Their FSUs are parallel in structure (Fig. 2.35).

- If critical damage due to radiation occurs in any functional subunit, complications are only observed in that subunit, and the organ continues its function.
- Examples include lungs, liver, and myocardium.

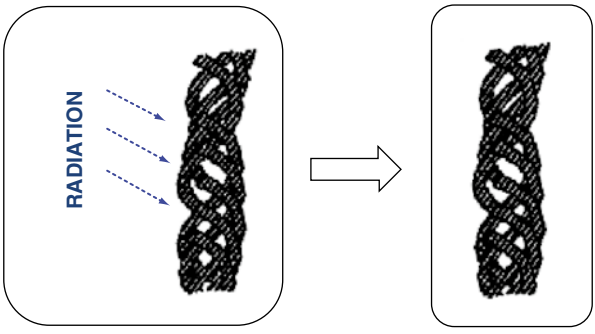


Fig. 2.35 Response to radiation in parallel organs (Fig. 5.8, p 102 of [20])

2.8 Stochastic and Deterministic Effects

The effects of radiation on tissues and organs can be classified into three groups: acute, subacute and chronic [46].

Acute effects: changes that occur in the first 6 months.

If the radiation dose is high enough, the organ's parenchymal tolerance is exceeded and organ death occurs. If the dose is low, the organ continues to function fully or partially, even in the presence of parenchymal damage.

Subacute effects: changes that occur between 6 and 12 months.

Secondary parenchymal degeneration resulting in decreased resistance to radiation is observed.

Chronic effects: changes that occur after 12 months.

Carcinogenesis, genetic mutations and chromosomal aberrations occur.

Deterministic Effect [46]

- The acute and subacute effects of radiation are known as deterministic effects (non-stochastic effects) (Fig. 2.36). The intensities of these effects are directly proportional to the dose.

They have a specific threshold dose.

Effects appear at higher doses than the threshold dose.

There is a relationship between dose and individual effects.

Cataract, skin erythema, sterility, radiation myelitis, and fibrosis are all examples of deterministic effects.

For example, if the total body irradiation dose is >5 Gy, bone marrow suppression is observed, but this suppression is not observed for a dose of <5 Gy.

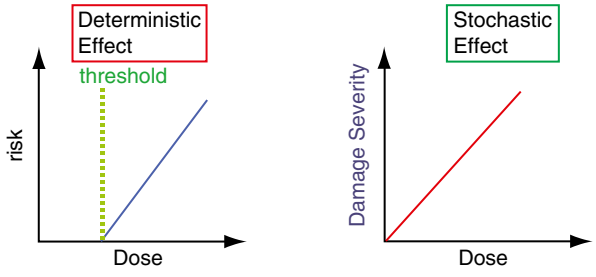


Fig. 2.36 Deterministic and stochastic effects of radiation

Stochastic Effects [46]

- The chronic effects of radiation are known as stochastic effects (Fig. 2.37).

These are statistically measurable effects.
There is no threshold dose for these effects.
There is no relationship between the dose and individual effects.
Carcinogenesis, genetic mutations and chromosome aberrations are all stochastic effects.
Stochastic incidence → the incidence of cancer is 250 cases per 1 million for 1 REM radiation.

2.9 Tumor Response to Radiation

The aim of radiotherapy is to annihilate the tumor tissue while minimizing damage to the normal surrounding tissues. Thus, the radiosensitivities of the tumor and its surrounding tissues are important considerations when determining the best treatment. It is well known that cells in tumor tissues have chaotic growth patterns and various radiosensitivities. Furthermore, tumor cells exhibit a variety of size, chromosome structures, and cytoplasms. However, this is not true of neighboring normal tissue cells. The principle of *primum non nocere* is always valid in radiotherapy. In light of this principle, several concepts for destroying the tumor while protecting healthy tissues have been developed in the field of radiation oncology.

2.9.1 Therapeutic Index

The therapeutic index defines how the tumor control probability (TCP) relates to the normal tissue complication probability (NTCP) for different doses [47]. Normal tissues may get damaged by the dose required to control the tumor; on the other hand, the tumor may not receive an adequate dose if the normal tissues require protection. Achieving the optimal balance between TCP and NTCP is a basic aim of radiotherapy. All new technologies are directed towards this aim.

TCP and NTCP curves are sigmoid in shape. The purpose of treatment is to move the TCP curve to the left and the NTCP curve to the right (Fig. 2.37).

- The therapeutic index (= therapeutic window) increases if the region the between two curves becomes large, and the expected benefit from treatment increases.

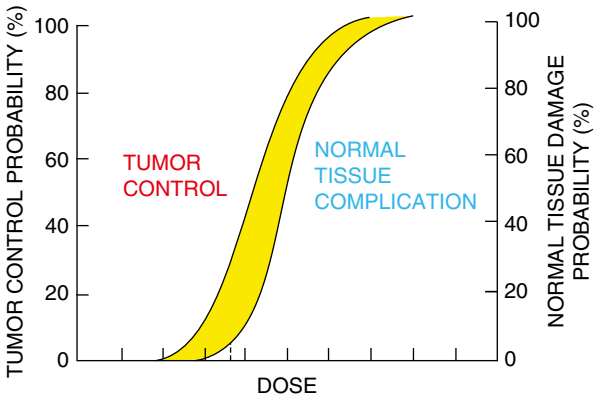


Fig. 2.37 TCP and NTCP curves

When the fraction dose is increased from 2 to 2.5 Gy, the total dose to control the tumor decreases. Since the maximum tolerable dose is constant, the total dose received by normal tissue increases and the therapeutic window narrows. Therefore, the treatment scheme in the second graphic in Fig. 2.38 is unacceptable compared to that in the first graphic.

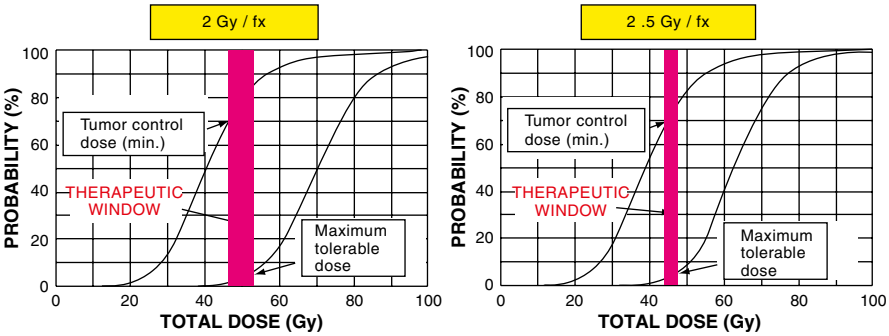


Fig. 2.38 Relationships between fraction dose, total dose, and therapeutic window

2.9.2 Tumor Control Probability (TCP)

The efficacy of radiotherapy treatment is evaluated by the locoregional TCP and the treatment-related NTCP [49].

TCP is directly proportional to the dose and inversely proportional to the number of cells in the tissue (or the volume of the tumor). The total dose required to control the subclinical disease in epithelial cancers is 40–50 Gy, whereas it is 60–70 Gy for clinically observable gross disease. The most important dose-limiting factor is the tolerance of the surrounding tissues to radiation.

Local tumor control. This is the destruction of tumor cells, where they are determined. It is also defined as the death of the last clonogenic cancer cell.

Radiation affects tumor cells in a very similar way to normal tissue and organs; its effect is nonspecific.

Tumoral factors affecting the TCP:

- Intrinsic radiosensitivity
- Location and size of tumor
- Cellular type of tumor
- Effect of oxygen

Treatment-related factors affecting the TCP:

- Dose–time fractionation
- Radiation quality (RBE, LET)
- Dose rate
- Use of radiosensitizers
- Combination of radiotherapy with surgery and/or chemotherapy
- Technique (e.g., small field sizes)
- Treatment modality (e.g., brachytherapy, conformal RT, IMRT, IGRT, targeted RT

The tumor volume decreases if a dose d_1 is delivered to a volume v_1. If we assume that a second dose d_2 is delivered to a new volume v_2, the total TCP will be as follows:

$$TCP = TCP(d_1,v_1).TCP\,(d_2,v_2).TCP(d_3,v_3)... = \prod_{i=1}^{n} TCP\,(d_i,v_i) \tag{2.24}$$

$$\mathrm{TCP}\,(D) \approx \mathrm{e}^{N.\mathrm{e}^{-(\alpha d+\beta d^2)}} \tag{2.25}$$

$$\mathrm{TCP} = \mathrm{e}^{-(SF\times N)} \tag{2.26}$$

where SF = surviving fraction and N = clonogenic cell number.

$$P(D) = \frac{1}{1+\left(\frac{D_{50}}{D}\right)^{k}} \tag{2.27}$$

k = slope of dose–response curve
D = total dose
D_{50} = tolerance dose
$P(D)$ = expected probability of cure for the given total dose (%)
$\mathrm{TCD}_{50} = D_{50} = \mathrm{ED}_{50} = \mathrm{TD}_{50}$

- The tissue tolerance dose is equal to the dose that kills 50% of clonogenic cells (Fig. 2.39).

$$(\mathrm{TCD}_{50} = \mathrm{TD}_{50})$$

$$\mathrm{TCD}_{50} = \mathrm{TCP}\,(1 - \mathrm{NTCP}) \qquad (2.28)$$

$$\mathrm{TCD}_{50} = D_{50} = \mathrm{ED}_{50} = \mathrm{TD}_{50}$$

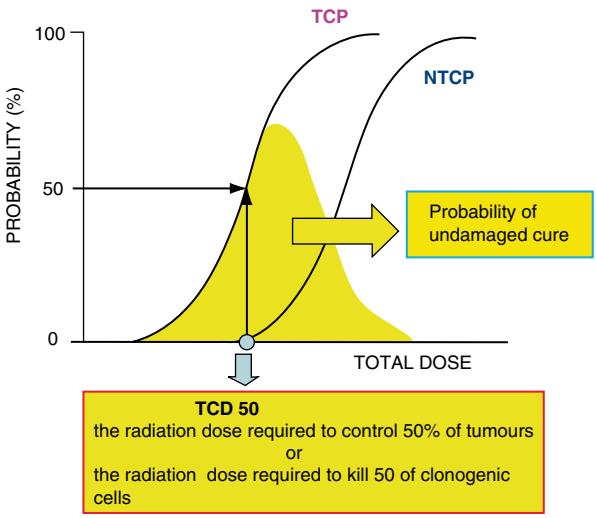


Fig. 2.39 Relationship between TCP, NTCP, and TCD50

- The dose needs to be increased threefold to increase the TCP from 10 to 90%.

If the TCP and NTCP curves are close to each other → tumor is radioresistant.
If the TCP and NTCP curves are far from each other → tumor is radiosensitive (Fig. 2.40).

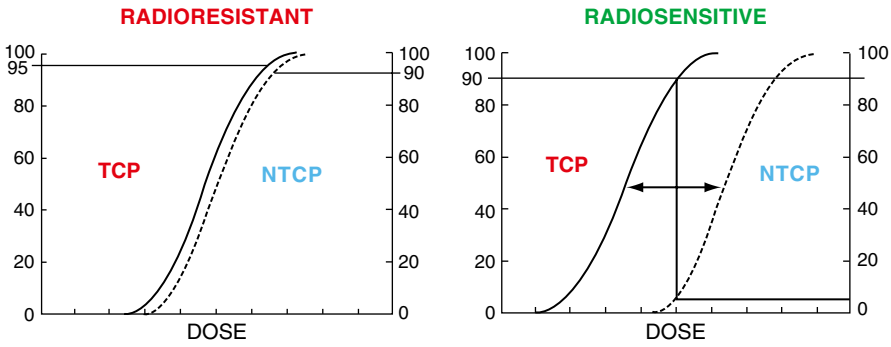


Fig. 2.40 Relationship between TCP, NTCP, and radiosensitivity

2.9.3 Normal Tissue Complication Probability (NTCP)

The TCP is a function of the total dose, fraction dose, irradiated volume including the whole tumor, and treatment reproducibility [49, 50]. The NTCP is a function of the total dose, fraction dose, fraction number and the volume of tissue exposed to the radiation [49, 50].

The Lyman model is used in NTCP calculations [51]. This model is highly complex. It is a mathematical model of biological effects based on the use of algebraic definitions.

- The volume of irradiated normal tissue and its radiosensitivity make this model more complex.
- In addition, tissue types (parallel or serial organs) as well as the FSUs of tissues are added to this formulation, making the model even more complex [51].

$$P(D) = \sum_{k=M+1}^{N} \binom{N}{k} \cdot P_{FSU}^{k} \cdot (1 - P_{FSU})^{N-k} \tag{2.29}$$

- However, the most important issue is not the formulation, but the knowledge of TD50, and not to exceed this limit during planning.

$$\mathrm{NTCP} = \frac{1}{1 + \left(\frac{D_{50}}{D}\right)^{k}} \tag{2.30}$$

Factors affecting NTCP [51]:
Factors related to organ tissue

- Tissue radiosensitivity
- The volume of organ tissue within the radiotherapy portal
- Organ type: serial or parallel

Factors related to treatment

- Dose–time fractionation
- Quality of radiation (RBE, LET)
- Dose rate
- Use of radioprotectors
- Combination of RT with surgery and/or chemotherapy
- Technique (e.g., addition of boost field)
- Treatment modality (e.g., brachytherapy, conformal RT, IMRT, IGRT, targeted RT)

TCP and NTCP calculations are mechanistic models. The *critical volume model* was developed by Niemierko in 1997. This model is used empirically for 3D treatment plans that involve calculating the *equivalent uniform dose* (EUD). This model is based on the hypothesis that clonogenic cells that have the same survival curves can be irradiated with same uniform dose. The α/β ratios, clonogenic cell number, dose, number of fractions, type of tissue and type of tumor, as well as the SF2 are fed into this formulation. The EQD2 (equivalent dose at 2 Gy) is derived in addition to the SF2, and this is used to compare different fractionation schemes [52].

- SF2 = surviving fraction after 2 Gy irradiation → as SF2 increases, TCP decreases

$$EQD_2 = D \times \left[d + \frac{\alpha/\beta}{2} + \alpha/\beta \right] \tag{2.31}$$

where D = total dose and d = fraction dose.

The value of the EUD lies between the minimum dose and the mean dose for tumor control (Fig. 2.41). A decrease in the TCP dose was observed when the EUD was calculated and used.

$D_{min} \leq \text{EUD} \leq D_{mean}$

As the irradiated volume increases, the normal tissue tolerance dose decreases due to the increase in functional subunit number.

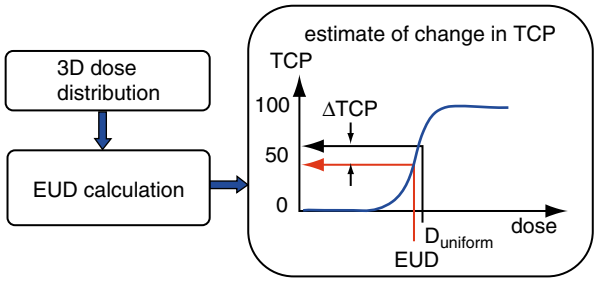


Fig. 2.41 Relationship between TCP and EUD

The essential parameters of the NTCP are the irradiated tissue volume and the dose delivered (Figs. 2.42 and 2.43).

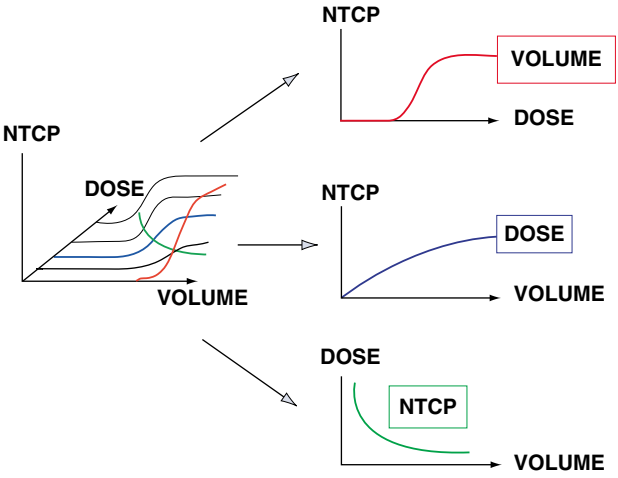


Fig. 2.42 The essential parameters of NTCP and its relationships (Fig. 5.4, p 97 of [20])

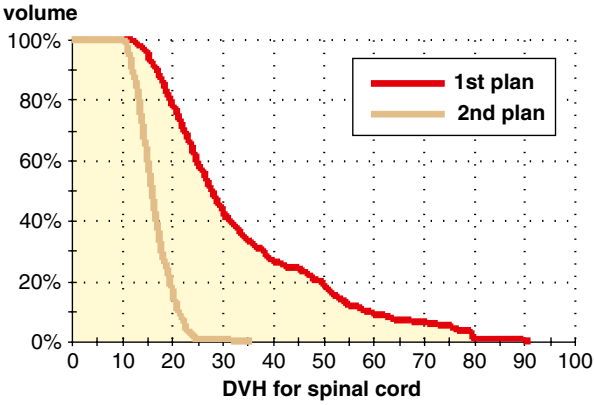


Fig. 2.43 DVH curves for spinal cord in two different treatment plans (Fig. 5.6, p 100 of [20])

Major references for NTCP estimation models:

- Lyman model: Burman C, Kutcher GJ, Emami B, Goitein M (1991) Fitting of normal tissue tolerance data to an analytic function. Int J Radiat Oncol Biol Phys 21:123–135.
- Critical volume model: Stavrev P, Stavreva N, Niemierko A, Goitein M (2001) The application of biological models to clinical data. Phys Medica 17(2):71–82.

The Clinical Importance of TCP and NTCP [50–52]

- The TCP and NTCP can be used to estimate the treatment success and side effects in particular.
- Dose–volume histograms created by treatment planning systems (particularly 3D-conformal radiotherapy and IMRT) as well as TCP and NTCP mathematical modeling are very useful for graphically demonstrating normal tissue damage ratios within the treated tumor volume, and can be used to guide clinicians during treatment planning (Fig. 2.43).

Therapeutic Ratio

TR = normal tissue tolerance dose/tumor control dose.

2.10 The Five R's of Radiotherapy

The delivery of radiation in small daily fractions is known as fractionated radiotherapy. Fractionated radiotherapy studies were started after it was realized that single, high-dose radiotherapy is ineffective for tumor control and has serious side effects. Claudius Regaud observed that ram spermatogenesis decreased after fractionated doses, but there were no side effects on the scrotal skin.

Although Regaud started the first fractionation studies, the first radiation oncologist, Grubbe, treated a breast cancer patient (Mrs. Rosa Lee) with radiotherapy for 1 h each day for 18 days in 1896. He found beneficial responses, but did not publish them since he was just a medical student. However, Grubbe published two scientific articles 50 years after his first use of radiotherapy.

Grubbe EH (1946) X-ray treatment; its introduction to medicine. J Am Inst Homeopath 39(12):419–422.

Grubbe EH (1947) The origin and birth of X-ray therapy. Urol Cutaneous Rev 51(5):375–359.

Coutard, a colleague of Regaud, applied fractionated radiotherapy to head and neck cancers in 1934, and obtained successful results [53]. He emphasized the importance of the time–dose concept in radiotherapy (Fig. 2.44).

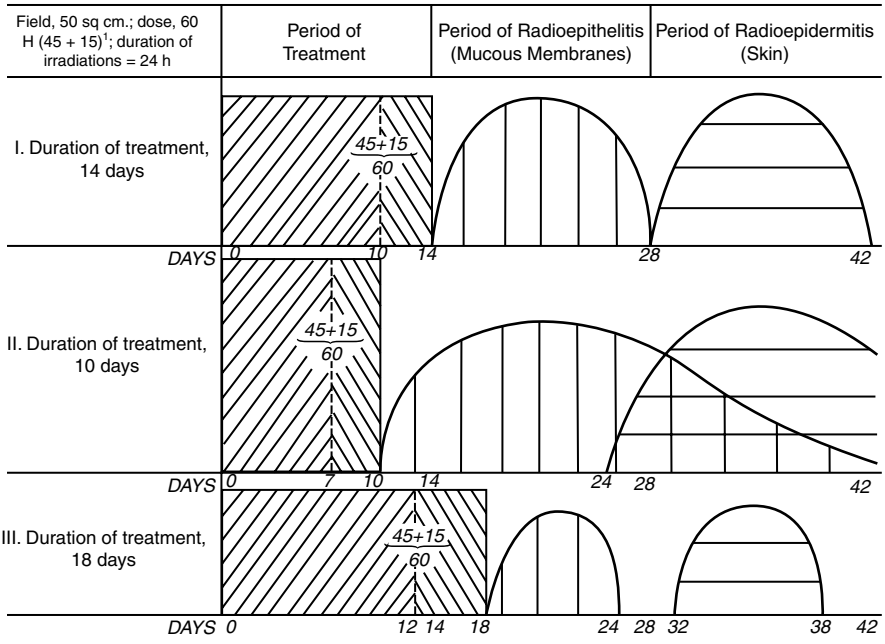


Fig. 2.44 Relationship between mucosal reaction and time as well as dose (from Coutard)

Coutard observed that skin and mucosal reactions seen during radiotherapy of pharyngeal and laryngeal cancers depend on the dose and the duration of radiotherapy.

Fractioned radiotherapy is founded on five main features:

- Repopulation
- Repair
- Redistribution (= reassortment)
- Reoxygenation
- Radiosensitivity (intrinsic radiosensitivity)

Biological factors that affect the responses of normal and tumor tissues in fractionated radiotherapy were defined as repair, reassortment (redistribution), repopulation and reoxygenation by Withers in 1975. A fifth "R," radiosensitivity, was added to this list by Bernard Fertil in 1981. All of these are important for estimating the responses of normal or tumor tissues to radiotherapy.

2.10.1 Repopulation

Both tumor and healthy normal cells continue to proliferate even when they are exposed to radiation [54, 55]. This proliferation is a physiological response of tumor and normal tissues to decreases in cell number.

The Consequences of Proliferation

- Increases the number of tumor cells to be destroyed → against treatment
- Increases the number of normal tissue cells following irradiation → in favor of treatment

This repopulation enables tumor cells to partially resist the lethal effects of radiotherapy. The time required for the tumor cell number to double is known as the "tumor doubling time," T_p. This doubling time is less than two days for most tumors. This period can also be considered the repopulation time, and it varies during radiotherapy. Repopulation is slow at the beginning of radiotherapy, but it speeds up after the first doses of radiation therapy. This increase in repopulation rate is termed "accelerated repopulation," and the time taken for it to begin is termed the "kick-off time" (T_k). This accelerated repopulation becomes even faster if the treatment is interrupted after the tumor doubling time for any reason. Normal tissues also repopulate during radiotherapy; this issue is important for the repair of acute side effects. Therefore, radiotherapy schemes should be arranged so as to allow normal tissues to repopulate.

Resting cells in the G_0 phase enter the cell cycle in order to compensate for the cells killed by radiotherapy, and they undergo mitosis → repopulation (Fig. 2.45).

Early-responding tissues repopulate faster than the tumor during interfraction periods.

If the overall treatment time becomes longer than the period required, the tumor enters the accelerated repopulation mode and its response to radiation decreases due to tumoral proliferation.

- Accelerated repopulation begins after 28 days of treatment for head and neck tumors (Fig. 2.46) [55, 56].

Radiotherapy should be completed as soon as possible, within the tolerance limits of acutely responding normal tissues, due to the risk of accelerated repopulation.

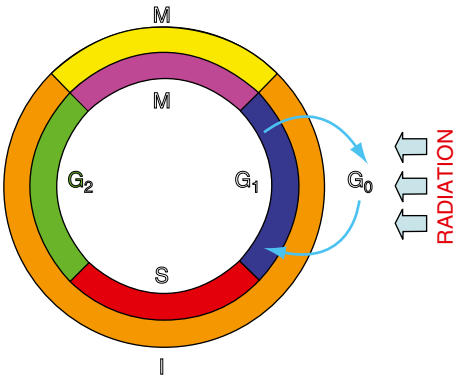


Fig. 2.45 Cell cycle and repopulation

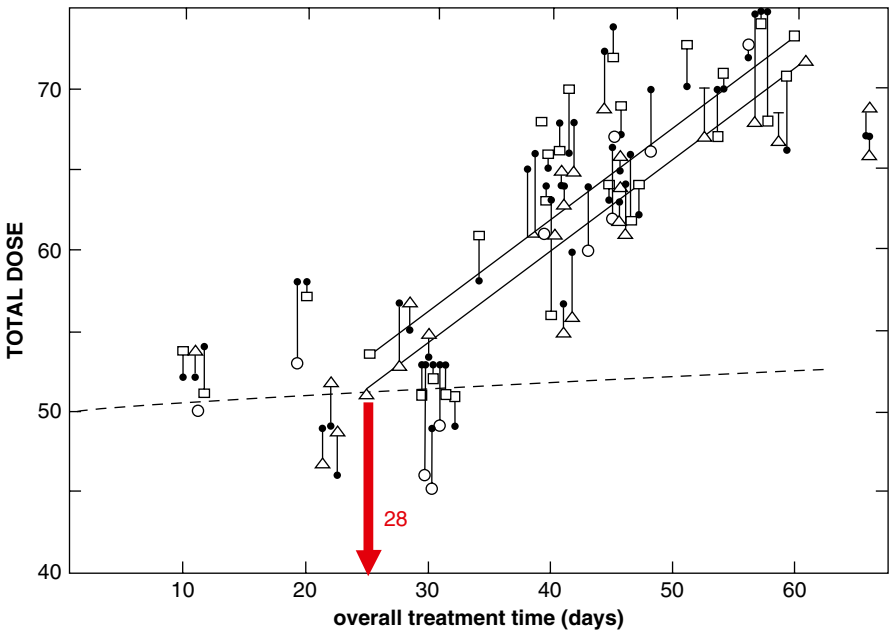


Fig. 2.46 Accelerated repopulation

2.10.2 Repair

Radiotherapy causes lethal damage to tumor cells and SLD in normal tissues. The application of radiotherapy in fractionated doses allows normal tissues time to repair [56, 57].

If an optimal interval is left between fractions (6–12 h), normal tissue cells responding late to radiation have the capacity for faster repair than tumor cells.

According to multiple target–single hit theory, SLD occurs in mammalian cells at low doses, and this damage is repaired during interfraction intervals.

One parameter used in this context is half the time required for cell repair after radiation damage ($t_{1/2}$), and the value of this parameter can be minutes to hours. Therefore, interfraction intervals should be at least 6 h in order to allow normal tissue cells to repair radiation damage.

The repair of SLD in spinal cord is much slower than that in other normal tissues. Thus, the interfraction interval should be at least 8 h in spinal cord irradiation.

Tumor cell SLD repair starts at the initial point of the shoulder (D_q) in the survival curve of the LQ model. Fractionating the next dose prevents this sublethal repair, shifting the dose away from the shoulder. Normal tissue cells, on the other hand, start to repair SLD before D_q, and so are not affected by the use of fractionation (Fig. 2.47). Repopulation and repair → more important for normal tissues than tumor tissues.

As the protection of normal tissues increases, radioresistance increases.

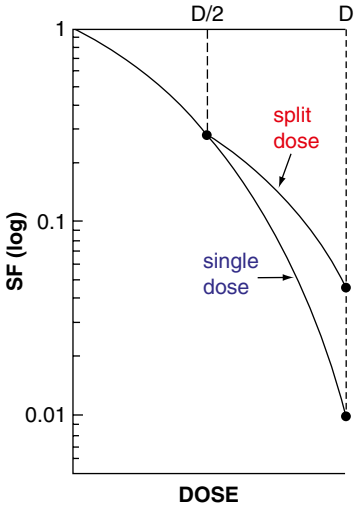


Fig. 2.47 Fractionated radiotherapy and the cell survival curve

Redistribution and reoxygenation → more important for tumor tissues than normal tissues; as more tumor tissue dies, its radiosensitivity increases.

When the total radiation dose is applied by dividing it into small fractions, and if the interval between two fractions is long enough (>6 h), normal tissues can protect themselves from radiation through SLD repair and repopulation.

2.10.3 Redistribution (= Reassortment)

The radiosensitivities of cells vary with the phase of the cell cycle (Fig. 2.48) [55, 58]. The most sensitive phases are M and G_2, while the most resistant is the S phase. Cells in resistant phases of the cell cycle may progress into a sensitive phase during the next dose fraction. Therefore, the probability that tumor cells will be exposed to radiation during a sensitive phase increases, and this probability will continue to increase over the course of the treatment, and so the benefit of the radiation will also increase.

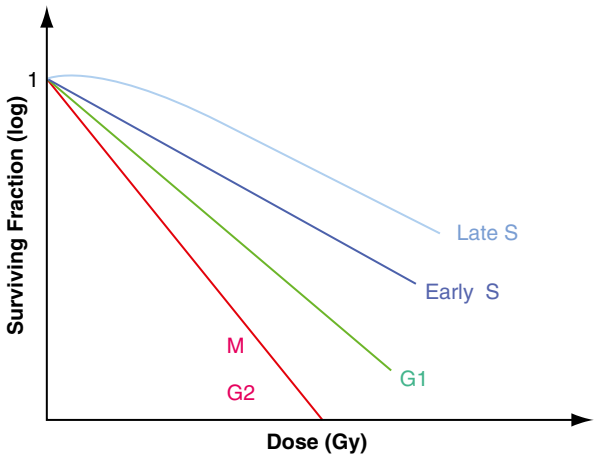


Fig. 2.48 Phases of the cell cycle and the survival curve

The durations of cell cycle phases: G_1 = 1.5–14 h, S = 6–9 h, G_2 = 1–5 h, M = 0.5–1 h

- The most sensitive: M and G_2
- The most resistant: S

2.10.4 Reoxygenation

As the tumor volume increases through the proliferation of tumor cells, the vascularity of the tumor tissue becomes insufficient to meet its requirements, and hypoxic–necrotic regions begin to occur within the tumor tissue [59, 60]. Hypoxic cells are 2–3 times more

resistant to radiation (→ oxygen is required for the indirect effect to occur) (Fig. 2.49). Well-oxygenated cells that are radiosensitive die over the full course of fractionated radiotherapy. Therefore, since the oxygen supply is constant, the hypoxic cells gradually obtain much better vascularity and oxygenation, and their radiosensitivities increase (Fig. 2.50).

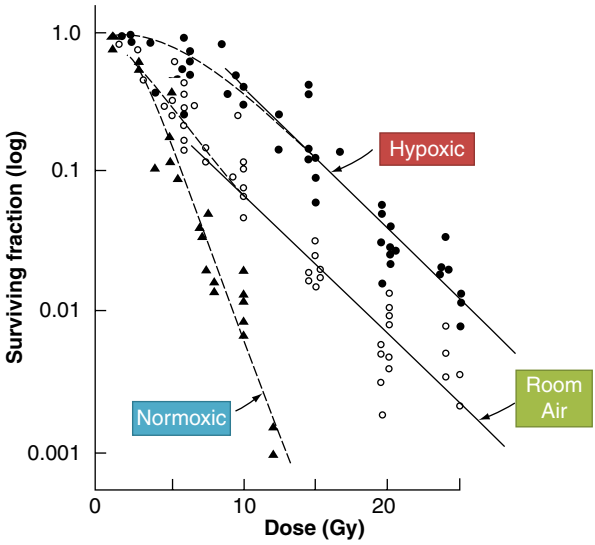


Fig. 2.49 Oxygenation and the cell survival curve

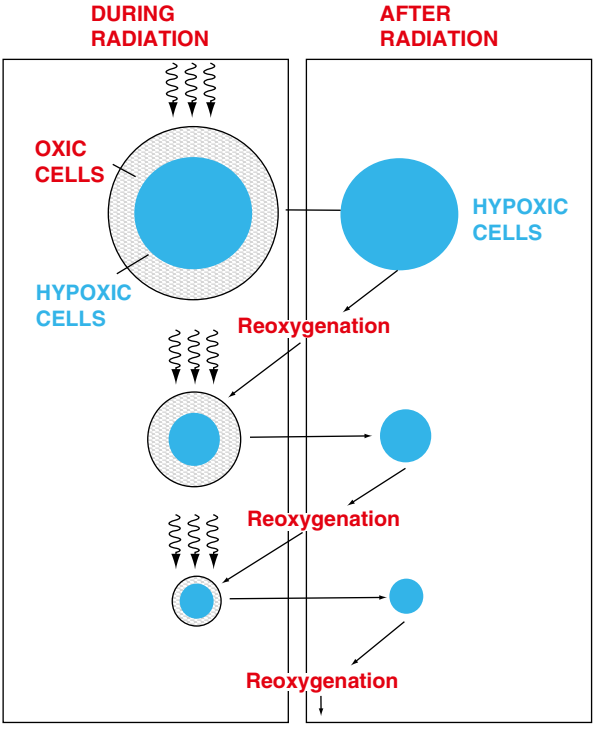


Fig. 2.50 Fractionated radiotherapy and reoxygenation

Oxygenating a tumor from the hypoxic state

- If hemoglobin is low, a blood transfusion may be given.
- High-pressure oxygen or carbogen may be applied during radiotherapy.
- The patient may be prevented from using hypoxic materials like cigarettes during radiotherapy.
- Hypoxic radiosensitizers may be used (e.g., metronidazole).

If the time interval between fractions is *t* and *T* is the overall treatment time, then for:

Reoxygenation	*T* should be minimum
Redistribution	*t* should be minimum
Repair	*T* should be minimum for normal tissues
Repopulation	*T* should be minimum for the tumor

2.10.5 Radiosensitivity (Intrinsic Radiosensitivity)

Radiosensitivity (the fifth R of radiotherapy) is a concept that involves multiple components [52, 60]. Radiosensitivity may be affected by environmental conditions. The term "radiosensitivity" was first defined by Bergonie and Tribendau in 1907; they suggested that radiosensitivity was directly proportional to mitosis and inversely proportional to differentiation. Since radiosensitivity may be affected by external conditions, the term SF_2 was introduced by Fertil in 1981.

SF_2 = surviving cell fraction after a radiation dose of 2 Gy.
As SF_2 increases, radiosensitivity decreases.
SF_2 is represented graphically for some tumor cell lines in Fig. 2.51.

- Radiosensitizers are used to decrease SF_2.

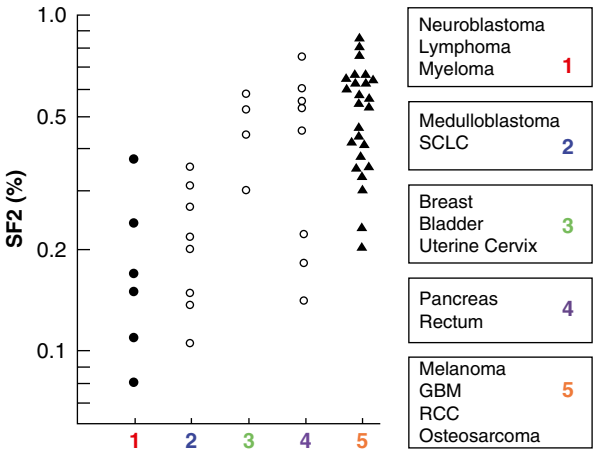


Fig. 2.51 SF_2 in some tumor lines

2.11 Fractionation

The five R's of radiotherapy form the basis for fractionation [47, 61, 62]. The total dose cannot be given in just one fraction, since this would produce serious adverse reactions in normal tissues. Therefore, it is necessary to divide the total dose into fractions. Normal cells can protect themselves from the radiation through repair and repopulation during the interfraction periods, whereas tumor cells are sensitized to the radiation through reoxygenation and redistribution.

Conventional Fractionation

Fraction dose	1.8–2 Gy
Number of fractions per day	1
Number of fractions per week	5
Number of fractions per treatment	25–35
Total dose	45–70 Gy

Hyperfractionation

Fraction dose	1.1–1.2 Gy
Number of fractions per day	>2
Number of fractions per week	10
Number of fractions per treatment	60–70
Total dose	45–70 Gy or >10%

Aims of hyperfractionation

To decrease the fraction dose and increase the total dose

To increase local control

To decrease late effects in normal tissues

In hyperfractionation

Acute side effects are similar or slightly increased compared to conventional fractionation.

Late side effects are decreased compared to conventional fractionation.

Accelerated Fractionation

Fraction dose	1.1–2 Gy
Fraction number/day	>1
Fraction number/week	>5
Fraction number/treatment	25–35
Total dose	45–70 Gy or less

The aim of accelerated fractionation

To decrease overall treatment time, to decrease accelerated repopulation

In accelerated fractionation

Early side effects are more than conventional fractionation.

Late side effects are same as conventional fractionation.

Treatment may be stopped early or the total dose may be decreased due to the excess amount of early side effects → this may cause a decrease in local control.

Hypofractionation

Fraction dose	>2 Gy
Number of fractions per day	≤1
Number of fractions per week	≤5
Number of fractions per treatment	≤25–35
Total dose	<45–70 Gy

The aim of hypofractionation

Hypofractionation is generally used for palliative purposes in the management of metastatic tumors. Late side effects are undervalued and palliation is provided over a very short time period.

In hypofractionation

Early side effects are similar to those associated with conventional fractionation.

Late side effects are increased compared to conventional fractionation.

Split Course. This refers to a fractionated treatment regimen that includes a planned interruption in order to decrease acute side effects. It is no better than conventional fractionation with regard to treatment efficacy.

Concomitant Boost. Here, two fractions are given daily in the fourth week of radiotherapy in order to prevent accelerated repopulation in head and neck cancers. The boost dose is given to the primary tumor site.

Hyperfractionation

Standard regimen:

70 Gy/35 fractions/7 weeks

$BED = D(1 + d/\alpha/\beta)$

$BED_3 = 70\ (1 + 2/3) = 116$ Gy

$BED_{10} = 70\ (1 + 2/10) = 84$ Gy

If we want to give the same total dose using two fractions per day:

$BED_{10} = 84 = X(1 + 1.2/10)$

(*continued*)

(continued)

X = 75 Gy
$BED_3 = 75(1 + 1.2/3) = 105$ Gy
Note that late side effects will increase.
However, 75 Gy/62 fractions = 6 weeks.

Accelerated Fractionation

Standard regimen:
70 Gy/35 fractions/7 weeks
$BED = D(1 + d/\alpha/\beta)$
$BED_3 = 70(1 + 2/3) = 116$ Gy
$BED_{10} = 70(1 + 2/10) = 84$ Gy
If we give 70 Gy/45 fractions/5 weeks with 1.6 Gy fractions and 3 fractions per day:
$BED_3 = 70(1 + 1.6/3) = 107$
$BED_{10} = 70(1 + 1.6/10) = 81$ (total treatment time will decrease).

- Early side effects depend on the total dose.
- Late side effects depend on the fraction dose.

2.12 Radiation Protection

The ICRP, the International Atomic Energy Agency (IAEA), and similar organizations have published many recommendations relating to protection from ionizing radiation over the last 50 years. Although those recommendations are not enforceable by law, many countries have adopted these recommendations and put them into practice.

In principle, protection from all radiation sources is required. However, no practical measure can be taken to protect ourselves against the normal levels of radiation resulting from natural radiation sources and radioactive fallout due to previous nuclear tests. Nevertheless, we can control whether or how nuclear tests will occur in the future. The use of radiation in medicine is a decision that should be made clinically. In this field, it is not suitable to limit personal doses that are delivered for diagnostic or therapeutic reasons. Thus, collective doses are very high in these circumstances. Medical personnel must carefully follow related laws and ICRP recommendations [63].

On the other hand, the principles of radiation protection should be applied fully to all medical and industrial uses of radiation, as well as by all other users of nonnatural radiation, radiation workers and the normal population.

The essential principles of radiation protection, as published in ICRP report 60 and the IAEA document BSS-115 (*Basic Protection Standards*) are:

- *Justification*. Radiation should never be delivered with no benefit, considering its harmful effects.
- *Optimization*. The dose should be as low as possible, considering personal doses, the number of irradiated persons, economical and social factors, except when medical irradiation is performed for therapeutic purposes. This is known as the ALARA (as low as reasonably achievable) principle [63, 64].
- *Dose limits*. Radiation dose to normal individuals should not exceed the permissible organ and tissue equivalent doses.

Dose limits for radiation personnel [63]:

- For the whole body, the effective dose limit for five consecutive years: 100 mSv (i.e., a mean of 20 mSv per year).
- For the whole body, the effective dose limit in any 1 year: 50 mSv.
- For lens, the equivalent dose limit per year: 150 mSv.
- For hands, food and skin, the equivalent dose limit per year: 150 mSv.

Dose limits for the general public [63]:

- For the whole body, the effective dose limit for five consecutive years: 25 mSv (i.e., a mean of 5 mSv per year).
- For the whole body, the effective dose limit in any 1 year: 1 mSv.
- For lens, the equivalent dose limit per year: 15 mSv.
- For hands, food, and skin, the equivalent dose limit per year: 50 mSv.
- *Dose limits for 16–18 year old students and trainees (i.e., in those using radiation for educational purposes)* [63]:
- For the whole body, the effective dose limit in any year: 6 mSv.
- For lens, the equivalent dose limit per year: 50 mSv.
- For hands, foot, and skin, the equivalent dose limit per year: 150 mSv.

Note that radiation workers must be at least 18 years old.

The working conditions for radiation personnel who are pregnant should be arranged to ensure that the dose received by the fetus is as low as possible. The fetal dose for the remaining period of pregnancy should not exceed 1 mSv. Lactating personnel should not be allowed to work in places that incur a risk of radiation contamination.

- Patient visitors and volunteers (during diagnosis/treatment): <5 mSv
- Children visiting patients: <1 mSv

Radiation protection. Methods of protecting from radiation can be grouped into two classes:

1. **Protection from internal radiation.** Internal contamination occurs via the entry of radioactive materials during respiration, digestion, or through damaged mucosa or skin. The radioactive material will radiate throughout the period when it is in the body. Therefore, precautions should be taken to prevent internal radiation from entering the body through media, foods, clothes, respiration and skin that are already contaminated with radioactive materials. These precautions include the use of special respiration equipment, a full face mask and filters, wearing protective clothes, blocking respiratory entry using towels when such equipment is absent, and banning the consumption of food and water in contaminated regions.
2. **Protection from external radiation.** There are three methods that are used to protect from external radiation:
   (a) *Distance*. As radiation intensity is inversely proportional to the square of the distance from the radiation source (inverse square law), increasing the distance from the source is a good protective measure. For instance; if the dose rate is 100 mSv/h at 1 m, it will be 1 mSv/h at 10 m.
   (b) *Time*. As the amount of radiation delivered is directly proportional to the time spent close to the radiation source, the time spent close to the source should be as short as possible. For instance, if the dose rate is 100 mSv/h, and someone stays in this field for 1 h, they will receive a dose of 100 mSv, but the dose will be 1000 mSv if they stay for 10 h.
   (c) *Shielding*. The most effective method of protecting from external radiation is shielding, and protective barriers with suitable features should be placed between the radiation source and the person in order to decrease the dose received. Shielding can be made from highly protective materials like soil, concrete, steel, and lead.

2.13 Pearl Boxes

Radiation hormesis. Although the harmful effects of high-dose ionizing radiation are accepted, some preclinical and clinical data show that low-dose radiation actually stimulates some biological functions. The word "hormesis" derives from the Greek word "hormone," which means "stimulate." Radiation hormesis refers to the stimulating effect of ionizing radiation. This concept is generally defined as the physiological benefits gained from exposure to low-LET radiation in the total absorbed dose range of 1–50 cGy.

- In 1996, Yonezawa et al. observed that 30% of 21-ICR rats lived for 30 days after 8 Gy X-ray irradiation, whereas their life spans increased by 70% after a 5 cGy dose.

Adequate time and the optimal medium (adequate nutrition, oxygen) should be provided between each fraction to allow the repair of SLD (→ for normal tissues!).

- SLD is repaired in 0–2 h
- There is a cell cycle phase change every 2–10 h (→ reassortment = redistribution)
- Repopulation starts after 12 h in tumor tissue

Basic Advantages of Fractionation

- Protects normal tissues from early side effects.
- Provides reoxygenation in tumor cells.

Basic Disadvantages of Fractionation

- Overall treatment time increases.
- Tumor cell proliferation increases during treatment breaks due to increased duration.

Molecular oxygen should be present in the medium during radiotherapy to ensure maximum cell death through the fixation of free radicals. Therefore, hypoxia decreases cellular radiosensitivity. This condition provides the basis for some applications, such as the delivery of oxygen at 3 atm pressure (hyperbaric) to patients during radiotherapy, the use of hypoxic cell sensitizers like nitroimidazole, and the use of high-LET radiation that decreases the inverse effect of hypoxia on tumor cells.

Bystander Effect

The bystander effect is where cells that are not exposed to radiation, but which are in close proximity to cells that are, show similar biological effects to the cells exposed directly to radiation.

- This effect is thought to occur due to intercellular communication and cytokines.

Abscopal Effect

The occurrence of systemic side effects in the regions that are far away from the irradiated area. Increasing the fraction size over 2 Gy per fraction increases abscobal effect in parallel tissues.

Avalanche Phenomenon

The avalanche phenomenon refers to the fact that, when the number of flexible tissue cells has dropped to a certain level (point F in Fig. 2.52) after the cells have been exposed to radiation, the remaining cells die more rapidly. This effect is more prominent at high doses and with additional treatments (chemotherapy, surgery). This dose dependency is due to not only cell turnover but also the entry of other lethally irradiated cells into the cell proliferation mode, and cell death occurs as an avalanche or cascade.

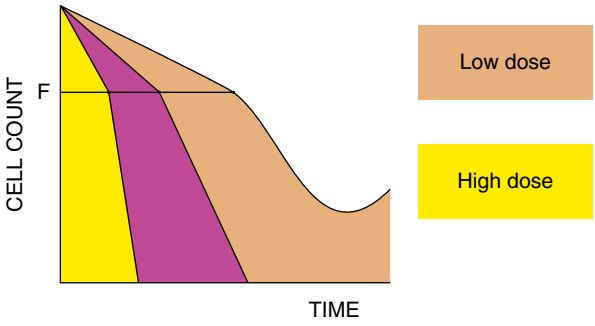


Fig. 2.52 Avalanche phenomenon

Radiation Recall Phenomenon. This is a severe reaction that is observed in particular in the skin of the irradiated area during chemotherapy after the end of external radiotherapy. Skin edema, erythema, rashes and discoloration are seen. The mechanism that causes this is the interaction of basal layers of the irradiated skin with cytotoxic agents secreted from dead cells due to chemotherapy. In general, this effect is observed in patients receiving chemotherapy after a long period of radiation (weeks, months). The chemotherapeutic agents that most often cause this phenomenon are actinomycin, doxorubicin, methotrexate, fluorouracil, hydroxyurea, and paclitaxel.

The half-life of a free radical is longer (microseconds) than that of an ion radical. Free radicals can diffuse and so damage regions outside of the primary radiation pathway. They play an important role in the oxygen effect. They are the basis for the indirect effect of radiation.

Two hundred meV proton radiation and 1.1 MV gamma radiation are examples of low-LET radiation, like 250 kVp X-rays.

The components of cosmic rays are high-LET radiations, like Fe ions and carbon ions, while solar flares are composed largely of energetic protons (which are a low-LET radiation).

Telomeres shorten during each period of mitosis due to the low telomere activity in primary human fibroblasts and most other somatic cells.

- This shortening generally causes a loss of replicative potential and G_1 arrest, which is also known as replicative cell aging.
- Primary human fibroblast aging can occur due to various mechanisms, including exposure to ionizing radiation. Some somatic cells may undergo additional divisions before a proliferative block, and this condition is termed a crisis. The crisis includes extensive genetic instability and ends in cell death in most situations.

The quadriradial-type aberrant chromosome number increases in Fanconi aplastic anemia. An increase in this type of chromosome is also observed upon exposure to radiation. A prominent increase is also seen upon the use of chemotherapeutic agents that create crosslinkages, like mitomycin.

SLD repair and the value of the β parameter in the cell survival curve decreases as the dose rate decreases.

If there is no shoulder in the cell survival curve, $n = 1$ and $D_{37} = D_0$.

In high-LET radiations, the extrapolation number (n) decreases until it reaches 1 as LET increases.

D_q and n are more predictive regarding the effect of fractionation on survival than D_0.

As n increases with dose rate, D_{10}, D_0, and α/β all decrease.

- D_{10} is the dose that decreases the SF to 10%

- A dose rate of 1–0.1 Gy/min allows cellular repair.
- A dose rate of 0.1–0.01 Gy/min allows redistribution.
- A dose rate of 0.01−0.001 Gy/min allows repopulation.

In cases of ataxia telangiectasia, the α component of the cell survival curve is larger than it is in the normal population.

Inhibiting SLD selectively increases double-hit kill and the β component of the cell survival curve increases.

Skin infections occur due to microvessel damage during and after radiotherapy; infections in oral mucosa arise due to decreased saliva, loss of the antibacterial effect of saliva, and increases in oral acidity.

In cell culture, 90% of cells growing exponentially die after receiving a D_{10} dose. The remaining cells are cells in the S phase, which is the radioresistant phase of the cell cycle.

The differences in intrinsic radiosensitivity among several types of cancer cells are mainly due to variations in the α component. Variations in the β component do not affect radiosensitivity so much.

According to animal experiments, the most sensitive fetal phase to radiation is just after conception and before the implantation of the embryo into the uterus.

Irradiation in the early fetal period, corresponding to weeks 8–15 of human gestation, mostly increases the risk of mental retardation.

The main risks of irradiation during preimplantation, organogenesis and the late fetal period are prenatal death, congenital malformation, growth retardation and carcinogenesis, respectively.

The effects of irradiation during gestation (other than inducing cancer) are deterministic, not stochastic. Since there is a threshold dose for deterministic effects, the severity of such an effect depends on the dose. Since the developing embryo/fetus is particularly radiosensitive, the dose received by the fetus should be minimized. Unfortunately, 36% of the 40 million radiological tests performed per year were performed in fertile women until the 1980s.

The most radiosensitive phase of human gestation regarding neonatal deaths is 2–6 weeks, the phase of organogenesis. Some congenital malformations that can occur at this stage are not compatible with life.

The time required for SLD repair in most tissues ($T_{1/2}$) → 1.5 h.

Normalized Total Dose ($NTD_{2\,Gy}$)

This is used to convert a BED to an LQ equivalent dose in 2 Gy fractions. The NTD is very useful for deriving hypofractionated regimens in LQ equivalent doses (stereotactic radiotherapy, hypofractionation in prostate cancer and breast cancer, etc.). $NTD_{2\,Gy}$ is the total dose in 2 Gy fractions that would give the same log cell kill as the schedule being analyzed.

$$RE = 1 + \frac{d}{\alpha/\beta}$$

Here, RE = relative effectiveness, d = fraction dose, and α/β = alpha/beta ratio.
Prostate tumor α/β = 1.5 Gy
RE for 2 Gy fractions: 1 + 2/1.5 = 2.33

Divide $BED_{1.5\ Gy}$ by this RE (2.33) to get $NTD_{2\ Gy}$
For example, 7.30 × 5 fractions = 36.5 Gy
$BED_{1.5\ Gy} = 36.5(1 + 7.3/1.5) = 214.13$
$NTD_{2\ Gy} = 214.13/2.33 = 91.9$ Gy
Reference: Fowler JF (2005) The radiobiology of prostate cancer including new aspects of fractionated radiotherapy. Acta Oncolo 44:265–276.

Normal Tissue Toxicity After Stereotactic Body Radiation (SBRT)
SBRT doses per fraction for serial organs:
Spinal cord: 8–10 Gy/1 fraction, 5–6 Gy/3 fractions, 4–5 Gy/5 fractions
Trachea and bronchi: 7–9 Gy/5 fractions
Brachial plexus: 8–10 Gy/5 fractions
Esophagus: 6–8 Gy/5 fractions
Chest wall and ribs: 10–15 Gy/3 fractions, 6–8 Gy/5 fractions
Small bowel: 10–12 Gy/1–2 fractions, 6–8 Gy/5 fractions
Note that therapeutic or close to therapeutic doses with 1–3 fractions are not recommended for trachea, bronchi, brachial plexus and esophagus.
SBRT doses per fraction for parallel organs:
Lung: 20 Gy/1 fraction, 20 Gy/3 fractions, 8–10 Gy/5 fractions
Liver: 25 Gy/1 fraction, 20 Gy/3 fractions, 8–10 Gy/5 fractions
SBRT dose–volume limits for parallel organs:
Lung: 700–1,000 mL of lung not involved with gross disease, V_{20} of 25–30%
Liver: 700–1,000 mL of liver not involved with gross disease, two-thirds of normal liver <30 Gy
Kidney: minimize the region receiving >20 Gy, two-thirds of one kidney <15 Gy (assuming that there is another functional kidney)
Reference: Milano MT et al (2008) Normal tissue toxicity after small field hypofractionated stereotactic body irradiation.

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Clinical Radiation Oncology

3

Murat Beyzadeoglu, Gokhan Ozyigit, and Cuneyt Ebruli

3.1 Introduction

Radiation was first applied in a clinical setting by an American medical student, Emil Grubbe, on 29th January 1896. Grubbe, the son of German immigrants, introduced the term "radiotherapy" in 1903: "He had been interested in comparing the effects of phototherapy and radiotherapy" [1]. Since then, the field of radiation oncology has developed rapidly in parallel with technology, and has become indispensable in the treatment of cancers.

Initially, naturally radioactive radium was applied in every situation where medicine was deficient; radium extracts were assigned a trademark and sold in markets (Fig. 3.1). However, the serious side effects of their use were understood, and so the application of radium was regulated by strict rules and laws. Finally, the fields of the diagnostic use and the therapeutic use of radiation were separated, and that of radiation oncology, a branch of internal medicine that uses ionizing radiation of various types and energies for the treatment of cancer and some benign diseases, was established.

Radiation oncology made use of several treatment modalities and machines in its infancy. All of these new treatment modalities blazed a trail in the medical community (Fig. 3.2); this process of development continues even today in the field of radiation oncology.

Fig. 3.1 Various industrial compounds that included radium from the beginning of the twentieth century

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DOI: 10.1007/978-3-642-11666-7_3, © Springer-Verlag Berlin Heidelberg 2010

NEW WEAPON AGAINST CANCER

Seven hundred thousand volts will be made easily available to the California Institute of Technology scientists by two new giant X-ray transformers made by engineers of the General Electric Company. One of these, shown above, has already been shipped to the coast and the other is nearing completion.

SCIENCE NEWS LETTER *for October 7, 1933*

Better Cancer Treatment May Result From Powerful X-Rays

Super-Radiations Will Affect Cancer Cells Leaving Normal Cells Unharmed Because of Immunity Built by Cosmic Rays

The American Journal of Nursing, Vol. 83, No. 11 (Nov., 1983), pp. 1567–1569

RADIATION ALTERNATIVE TO MASTECTOMY

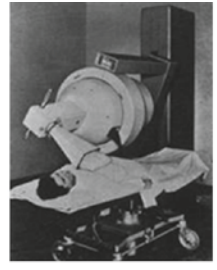
Excision of the tumor, combined with two stages of radiation treatment, seems to be as effective

Roswell Park Memorial Institute

RADIATION THERAPY—Dr. Walter Murphy is shown administering a radiation dose to a young child at Roswell Park Memorial Institute, Buffalo, N.Y., using a two million electron-volt X-ray machine. The Institute is ranked as one of the world's largest and best equipped cancer research centers.

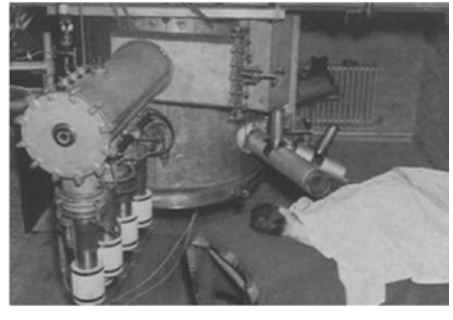
TREATMENT

Powerful gamma rays from a radium "bomb" penetrate the body tissues to kill deep-seated cancer cells which threaten life. Hines Hospital owns three grams of precious radium, valued at $25,000 at current prices.



MAXITRON 250—The "three-in-one" therapy X-ray machine demonstrates treatment to the breast. The bolus bag scatters secondary radiation back into the part of the body being treated.

COBALT 60 MACHINE—Shown here is General Electric's tele-therapy unit—a machine that, instead of X-rays, uses four tiny "wafers" of radioactive cobalt giving off high-powered, penetrating radiation. Enough radium to give off the same amount of radiation would cost $26,000,000. Cost of the cobalt wafers is estimated at $18,000.



TO BATTLE CANCER

The outlet tubes of this giant X-ray machine, directed at the patients, permit only a narrow beam of X-rays to strike them at the proper places for the therapy.

Fig. 3.2 Historical articles and treatment machines

Approximately 50–60% of all cases of cancer require radiotherapy at some stage during their treatment. The radiation oncologist decides whether radiation therapy is indicated. However, it is best to take a multidisciplinary approach (surgery, medical oncology, nuclear medicine, radiology) when deciding on the final treatment in clinical practice.

Radiotherapy Types According to Aim

Curative radiotherapy. This is the application of radiotherapy alone to cure. Used in cases of early-stage Hodgkin's lymphoma, nasopharyngeal cancer, some skin cancers, and early glottic cancers (curative radiotherapy = definitive radiotherapy) for example.
Palliative radiotherapy. This is the alleviation of cancer symptoms by applying palliative doses of radiation. Used in cases of brain and bone matastases and superior vena cava syndrome for example.
Prophylactic (preventive) radiotherapy. This is the prevention of possible metastases or recurrences through the application of radiotherapy. An example is whole-brain radiotherapy for acute lymphoblastic leukemia and small cell lung cancer.
Total body irradiation. This is the ablation of bone marrow by radiation in order to suppress the immune system, eradicate leukemic cells, and clear space for transplant cells during bone marrow transplantation conditioning.

Radiotherapy Types According to Timing

Adjuvant radiotherapy. Radiotherapy given after any kind of treatment modality.

- If given after surgery → *postoperative radiotherapy*

Neoadjuvant radiotherapy. Radiotherapy given before any kind of treatment modality.

- If given before surgery → *preoperative radiotherapy*

Radiochemotherapy (chemoradiotherapy). Radiotherapy given concurrently with chemotherapy.

Radiotherapy Types According to Mode

External radiotherapy (teletherapy/external beam radiotherapy). Radiotherapy applied to the body externally using a treatment machine.
Brachytherapy (endocurietherapy/sealed-source radiotherapy). Radiotherapy performed by placing temporary or permanent radiation sources into body cavities.

(*continued*)

(continued)

Intraoperative radiotherapy (IORT). Radiotherapy given under intraoperative conditions, usually by electron beams or low-energy X-rays. It is delivered to the tumor bed just after the resection of the primary tumor, and external radiotherapy is generally required afterwards.
Stereotactic radiotherapy (SRT). Radiotherapy delivered by several beams that are precisely focused on a three-dimensionally localized target. A special frame or a thermoplastic mask is used for CNS tumors, while a body frame may or may not be used for extracranial sites.

- If given in one-five fractions in ablative doses → *stereotactic radiosurgery (SRS)*
- If given in more than five fraction → *SRT*

Three-dimensional conformal RT (3D-CRT). A radiotherapy technique where the dose volume is made to conform closely to the target through the use of 3D anatomical data acquired from CT or MRI imaging modalities. The aim is to apply the maximum dose to the target while sparing neighboring structures as much as possible with the aid of advanced computer software and hardware.
Intensity-modulated radiotherapy (IMRT). A highly developed form of 3D-CRT. IMRT provides a highly conformal dose distribution around the target through the use of nonuniform beam intensities. This is achieved through using either static or dynamic segments. The isodose distribution can then be matched closely to the target by modulating the intensity of each subsegment.
Image-guided radiotherapy (IGRT). The integration of various radiological and functional imaging techniques in order to perform high-precision radiotherapy. The main aims are to reduce setup and internal margins, and to account for target volume changes during radiation therapy, such as a tumor volume decrease or weight loss (adaptive radiotherapy). This is not an IMRT technique; it enables various radiotherapy techniques, including IMRT, to be delivered more accurately (Fig. 3.3).
Tomotherapy. There are two sorts of tomotherapy: serial and helical tomotherapy. Serial tomotherapy utilizes a special collimator system called a MiMIC that is mounted on a classic linac gantry. The table also has a special device called a crane that allows it to be moved with high precision. IMRT is then performed in several arcs. Helical tomotherapy, on the other hand, uses a dedicated tomotherapy machine. It consists of a 6 MV linac mounted on a CT, and it delivers IMRT with spiral movements similar to those in the CT procedure. Simulations and IMRT are performed within the same machine.
Cyberknife® (robotic radiosurgery). A type of SRT/radiosurgery technique. It provides frameless treatment of tumors at both cranial and extracranial sites, and utilizes a 6 MV linac mounted on a robotic arm (Fig. 3.4), as well as a robotic tabletop. Cyberknife has the ability to perform all sorts of advanced radiotherapy techniques, including IMRT, IGRT, breathing-synchronized radiotherapy, tumor-tracking radiotherapy, and SRS/radiotherapy.

Boron neutron capture therapy. Here, a boron compound that is selectively absorbed by brain tumor cells is given to the patient. The tumor tissues that absorb the boron are then irradiated with slow neutrons. The boron atoms react with these neutrons to generate alpha radiation, which damages DNA via ionization events.
Hyperthermia. This prevents tumoral repair by utilizing a supraadditive (synergistic) effect with radiation: tumor tissues get colder more slowly than normal tissues. Hyperthermia is more effective under hypoxic and acidic conditions. The critical temperature for hyperthermia is 43°C.

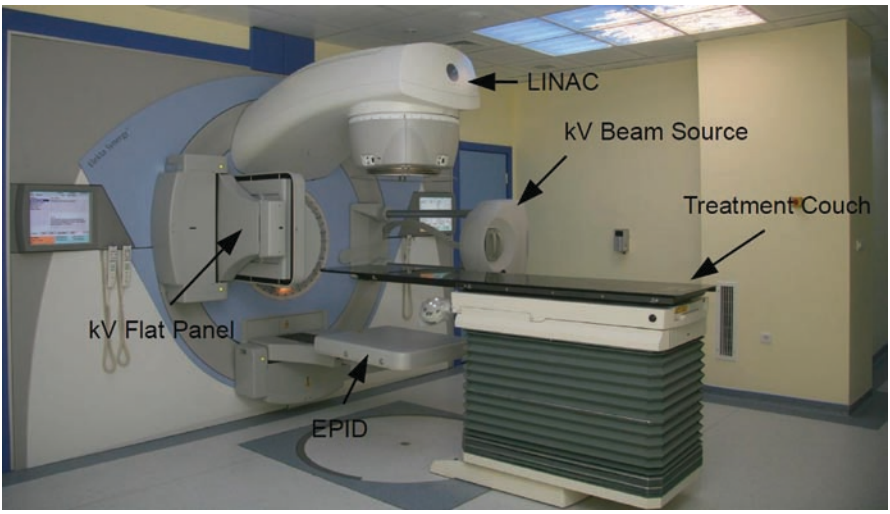


Fig. 3.3 Image-guided radiotherapy unit (courtesy of Gulhane Military Medical Academy)

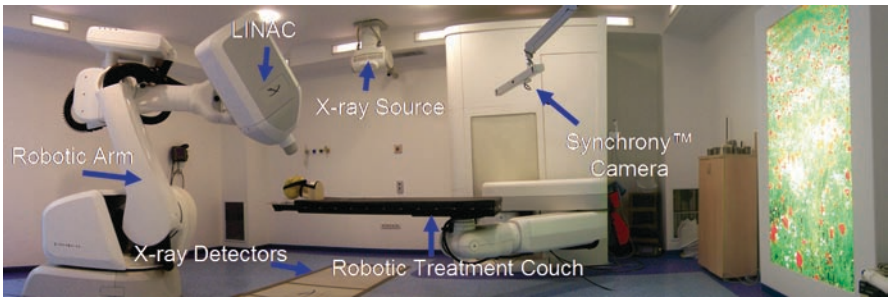


Fig. 3.4 Robotic radiosurgery machine (courtesy of Hacettepe University, Robotic Radiosurgery Unit)

Patients should be informed about the treatment (procedures, duration, acute and late side effects, cost, and alternative modalities) after radiotherapy has been decided upon, and informed consent should be obtained for legal purposes.

Factors that must be taken into consideration before radiotherapy is decided upon:

Aim:
- Palliation
- Cure

RT center:
- Equipment
- Experience
- Inpatient clinic
- Cost

Tumor:
- Stage, histology, location
- Radiosensitivity
- Previous treatments

Patient:
- Age, performance
- Morbidity
- Cosmesis
- Patient preference

3.2 The Radiotherapy Procedure

Radiotherapy is performed by a group of team members, including the radiation oncologist, radiation physicist, radiotherapist, dosimetrist, nurse, psychologist and/or social workers. The treatment success in radiotherapy is highly dependent on adequate technical equipment.

After the decision to use radiotherapy has been taken in a multidisciplinary meeting, the radiation oncologist needs to evaluate reports related to the patient's history, physical exams, and particularly pathology reports, radiograms and reports, as well as nuclear imaging reports, and add such details to the patient's chart. Adding a short summary to the end of chart may prove useful after registry. If there are any prominent and apparent physical signs, they should be photographed and added to the chart, since they may be useful for evaluating the success or failure of treatment. With the patient's consent, such pictures can also be used for academic studies.

Procedures and data that are not recorded on the chart are accepted as non-existent.

The patient should be informed about his disease and treatment according to his education level just after clinical examination. The steps involved in the radiotherapy procedure and their duration, as well as acute and late effects, their starting times, and preventive measures for them should also be told to the patient. The consent form should then be signed by the patient and physician, and one copy should be given to the patient while the other should be added to the patient's chart. After that, the first step in radiotherapy – simulation – is scheduled (immobilization, imaging, and tumor localization) (see Fig. 3.5).

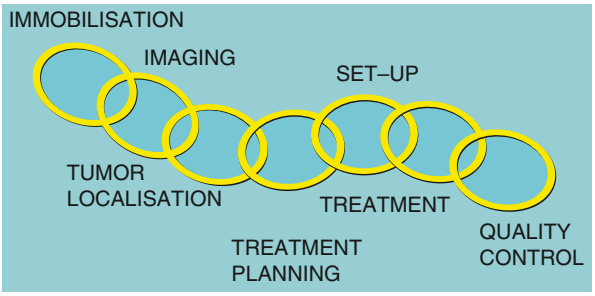


Fig. 3.5 The steps involved in radiotherapy

3.2.1 Simulation

Simulation is radiotherapy field determination using a diagnostic X-ray machine with similar physical and geometrical features to the actual teletherapy machine. The patient is immobilized before simulation and then the tumor is localized either in a direct scopy X-ray machine or in serial CT slices. The simulation can be performed by CT, MRI, or rarely by PET–CT (Fig. 3.6 and Fig. 3.7).

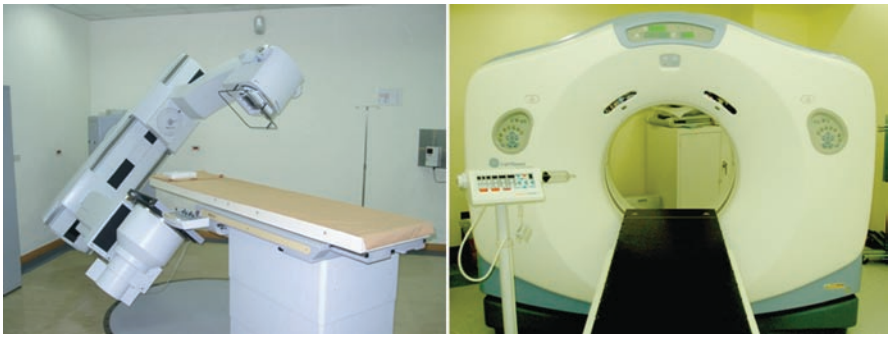


Fig. 3.6 Various simulator types: conventional simulator and CT simulator (courtesy of Gulhane Military Medical Academy)

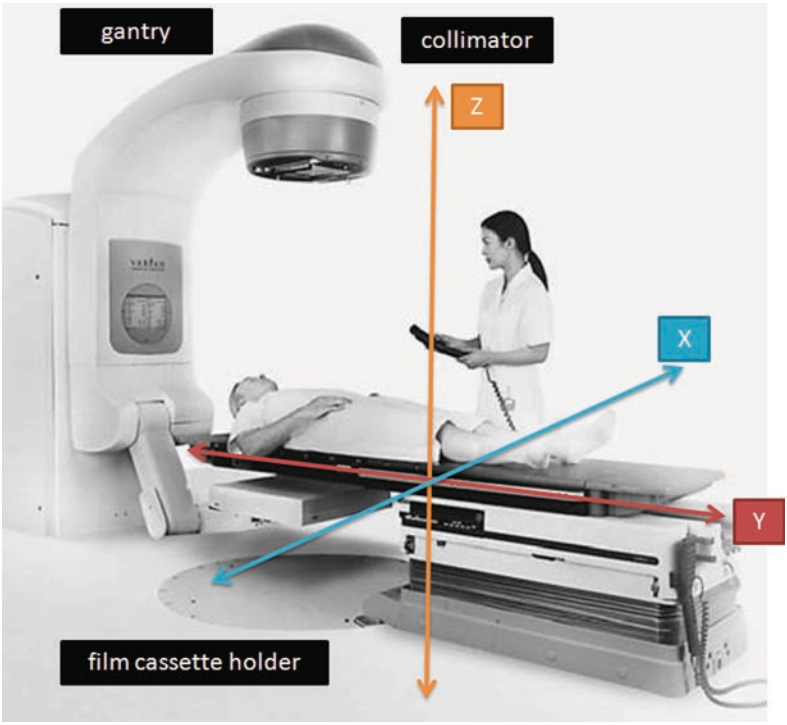


Fig. 3.7 A conventional simulator and its movement abilities [Levitt et al. 8, p 108, Fig. 6.1]

The simulation performed by a conventional simulator is a real-time simulation procedure, since it is done directly in the patient (Fig. 3.6). However, the simulation performed by a CT or MRI is a virtual simulation since the tumor is localized digitally.

Conventional Simulation Steps

Immobilization. The patient should be immobile during therapy. Movements cause changes in the treatment area and increase side effects, thus affecting treatment success. The patient should be positioned in the most comfortable, easily reproducible way that is suitable for the irradiated region of interest.

- Various types of apparatus are used for immobilization. The most frequently used apparatus is the thermoplastic mask (Fig. 3.8). Such a mask should not only be tight; there should be no space between the patient's skin and the mask. The mask should be checked during every setup procedure for tightness or looseness (due to edema or weight loss), and should be remade if necessary.

Patient positioning. The patient's treatment position should be recorded on both the patient's chart and the simulation film (e.g., supine, prone, hands up, hands on side) (Fig. 3.9). The gantry is adjusted according to the actual treatment machine's source–axis distance (SAD) before simulation. After the patient has been positioned on the couch, the desired SSD value (usually 80–100 cm) is achieved by adjusting the couch height. The SSD is reduced by half the thickness of the patient. Finally, the irradiation field is determined according to the chosen technique (fixed SSD or fixed SAD).

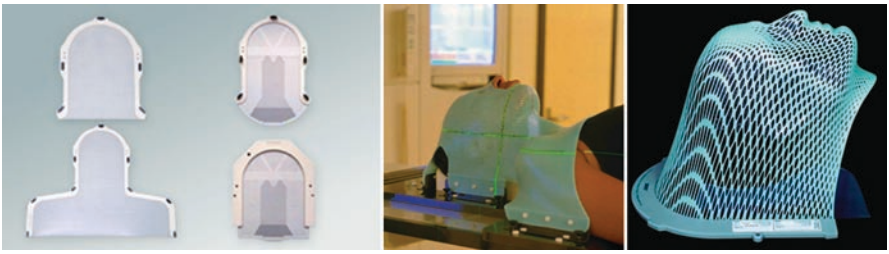


Fig. 3.8 Thermoplastic mask

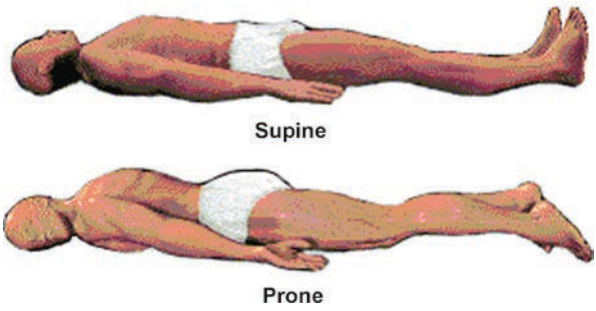


Fig. 3.9 Supine and prone positions

Imaging and tumor localization. The patient is placed on the simulator couch in the required position. The mask, base plate, T-arm, breast board, knee support or any other similar immobilization device is positioned accurately. The probable radiotherapy fields are determined and SSDs are calculated according to patient thickness. Gantry angles, field sizes and collimator angles are arranged by the simulator software under intermittent X-ray scopy (Fig. 3.10).

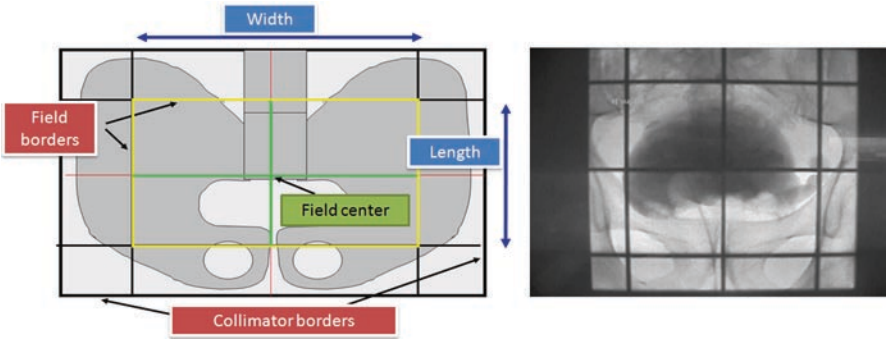


Fig. 3.10 Treatment field in a conventional simulator, and a simulation film

Any scar, palpable mass and drain site is marked with flexible wires; lead markers should be placed in lateral epicanthal regions for head and neck irradiation. These markings are easily seen during the simulation procedure.

Oral or IV contrast material can be used if required. Therefore, the contrast material should be prescribed before simulation; first aid equipment and drugs (e.g., adrenaline, atropine) should be available in the simulator room.

- An oral solution containing barium is generally used in gastrointestinal irradiation
- IV nonionic radioopaque materials are used for the imaging of the kidneys and bladder
- Radioopaque rectal and vaginal applicators or tamponades with contrast material can be used in the pelvic region

Treatment fields and block regions are marked on the patient's mask or skin after determining the radiotherapy fields. Simulation radiographs are then taken, and protected areas are marked on this film, which is sent to the block-cutting room. Focalized blocks are then fabricated. The patient is sent home at this point since block fabrication is a lengthy procedure. If no block is used, or if standard blocks are used, the patient's chart is sent to the physics room for dose calculations, and the patient can be treated on the same day.

If there is no block-cutting unit, protected areas are determined by wires, and these wires are verified in the simulation film. These areas are spared by standard blocks.

- If focalized blocks are used, the blocks can be checked on X-ray scopy by special trays mounted on the simulator's gantry. Minor errors can be corrected, but the blocks should be refabricated when there are major errors.
- Breast contours are observed by dosimetrists or radiation physicists in conventional breast simulations and then used for treatment planning, wedge and dose calculations.
- The daily dose fraction and the total dose are determined, and the patient's chart is sent to the medical physics room for dose calculations after all of these procedures. Schedules are arranged for the treatment machine.

Parameters That Should Be Written on the Simulation Film

Patient name
Simulation date
Field size
Gantry angle
Collimator angle
SSD
SAD
Depth
Magnification factor
Physician name
Technician name
Patient position
Right and left signs

Patient data and all other data associated with the disease, as well as all parameters related to the simulation, should be recorded on the treatment chart. The treatment fields should also be presented graphically along with the date, since these data may be needed for possible future irradiation.

CT Simulation (Fig. 3.11)

The mask and other required equipment are made on the day of CT simulation by the radiotherapist, under the supervision of the radiation oncologist, for the patient who is to receive conformal radiotherapy (Fig. 3.12).

The patient is sent to the nurse for an IV route before CT simulation if an IV contrast material is to be used. Then the patient is positioned on the CT couch, and the mask, knee support, alpha cradle, or any other similar device is fitted on the CT couch if required.

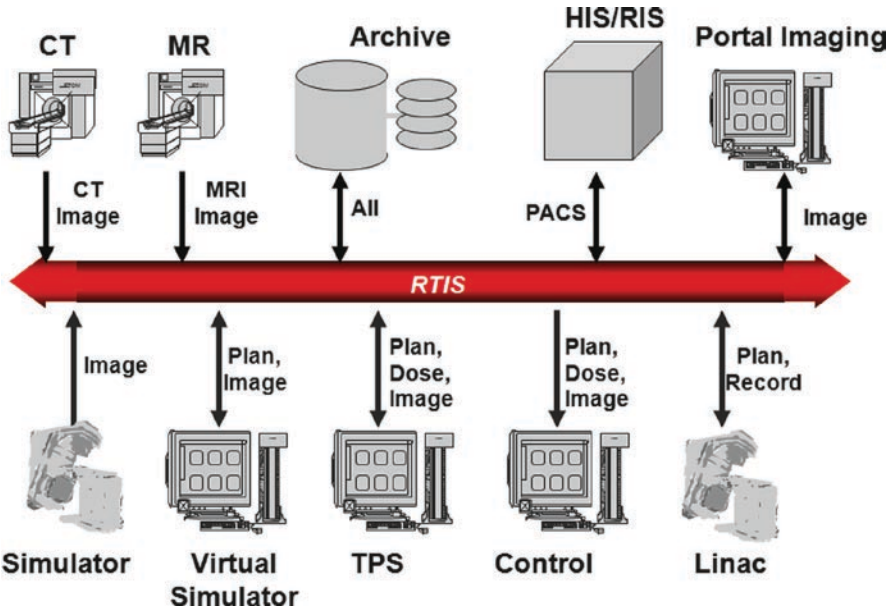


Fig. 3.11 CT simulation and 3D-conformal RT steps

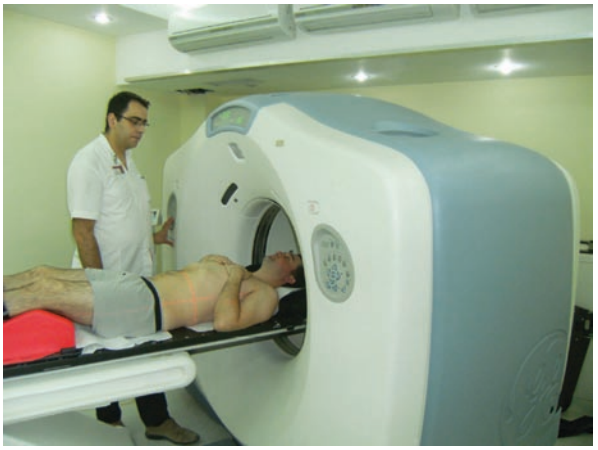


Fig. 3.12 Patient on a CT simulator couch

The lasers are turned on and they are positioned at the midline according to the region of interest.
Reference points are determined by radioopaque markers located at the cross-sections of the lasers (Fig. 3.13).
Reference points are predetermined locations for each region of the body. There are three reference points: one is craniocaudal and the others are on the right and left lateral sides.

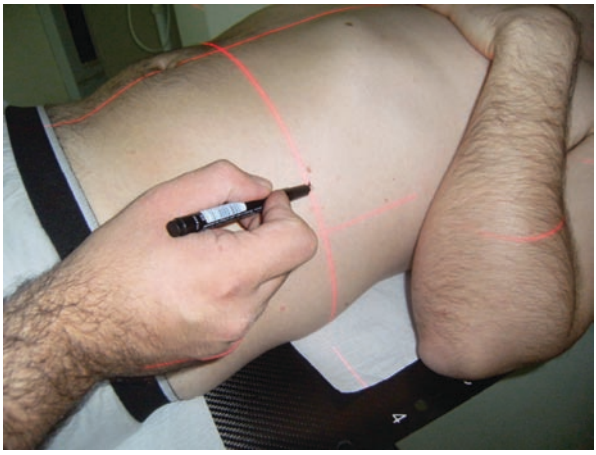


Fig. 3.13 Determination of reference points

Contrast material is given intravenously by the nurse, if required. Adequate measures should be taken for any possible anaphylactic reactions.

Any required adjustments are performed by the CT technician in the CT command room (Fig. 3.14). The region of interest (that for which serial CT slices are to be taken) is determined by the radiation oncologist. The slice thickness is also determined. All of these data are transferred to the CT computer. After the region of interest has been verified on screen, serial slices are taken.

These slices are sent online to the treatment planning room via the network (a radiotherapy information system utilizing PACS) (Fig. 3.15).

The patient should then rest for 20 min after CT to check for any possible adverse reactions. After this, they can be sent home.

- If no mask is used, particularly in the case of body simulations, reference points should be permanently tattooed on, otherwise they will easily disappear.

Fig. 3.14 CT command room

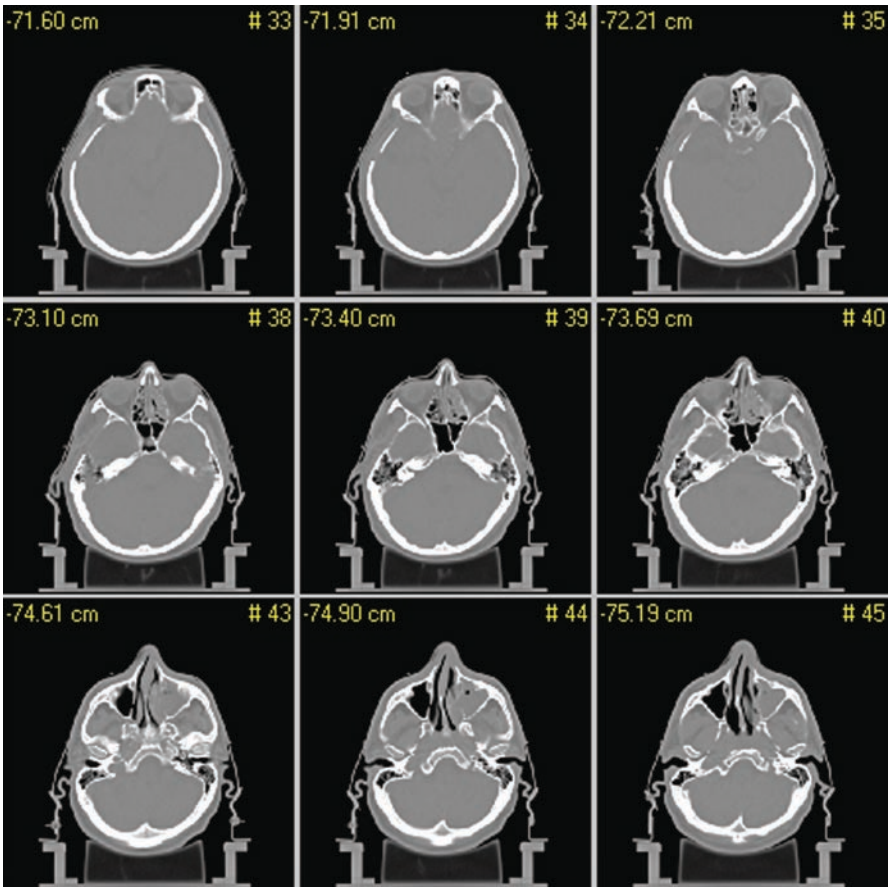


Fig. 3.15 Acquired serial CT slices

A virtual digital simulation is performed after the CT slices have been transferred to the network.

The acquired CT slices should be transferred to the treatment planning computer from the network for treatment planning.

The radiation oncologist then performs contouring on the acquired CT slices (Fig. 3.16). External body contours are usually delineated automatically. The radiation oncologist then contours the GTV, CTV, PTV, and the organs at risk.

Fig. 3.16 Contouring in serial CT slices

The slice with the reference points determined during CT simulation is recorded as the reference slice.

Contours are carefully checked and recorded, and the planning phase then begins.

Radiotherapy portals are determined during the first stage of planning according to the PTV (Fig. 3.17). Beams are placed according to the PTV using the beam's eye view (Fig. 3.18).

(continued)

(continued)

Delineation of the multileaf collimator (MLC) or the blocks is performed, and critical structures are spared. The penumbral region should be taken into account during MLC or block placing.

Data on the energy, fraction number and dose, and the treatment machine are entered into the planning computer. The treatment planning system (TPS) starts its calculations, and the final dose distribution and dose–volume histograms are formed.

The doses for the target and the organs at risk are evaluated with the DVH, and the isodoses are carefully checked in each slice. The reference isodose or isocenter is determined for the dose prescription, and the final treatment plan should be verified by the radiation oncologist.

The final verified treatment plan is sent online to the treatment machine via the network, treatment parameters are recorded on the patient's chart, and isodose curves and DVH printouts are also attached to the chart (Fig. 3.19).

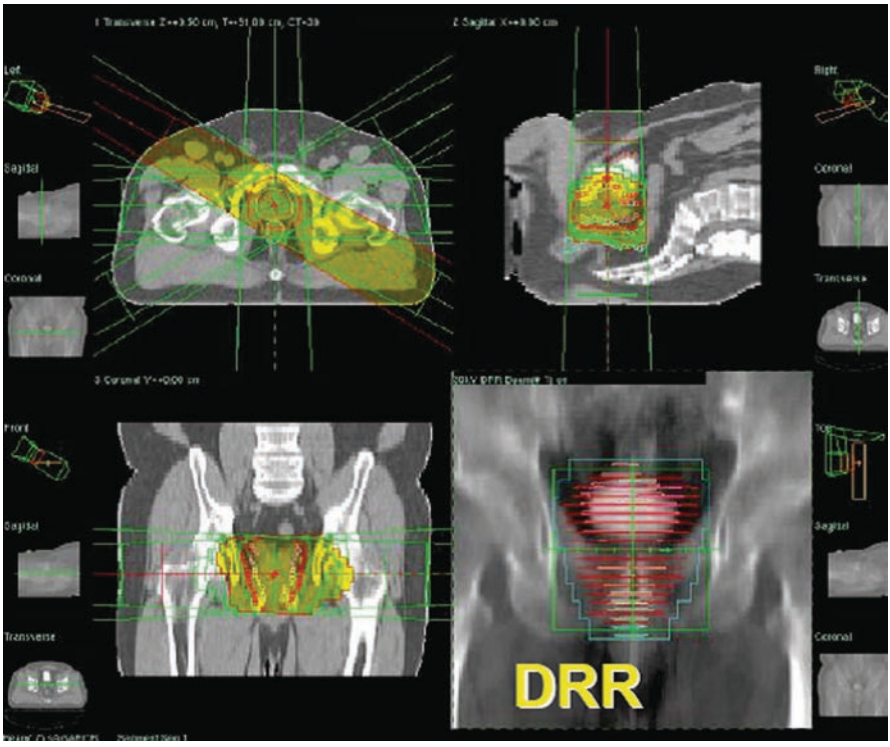


Fig. 3.17 Anterior radiotherapy field of a prostate cancer case

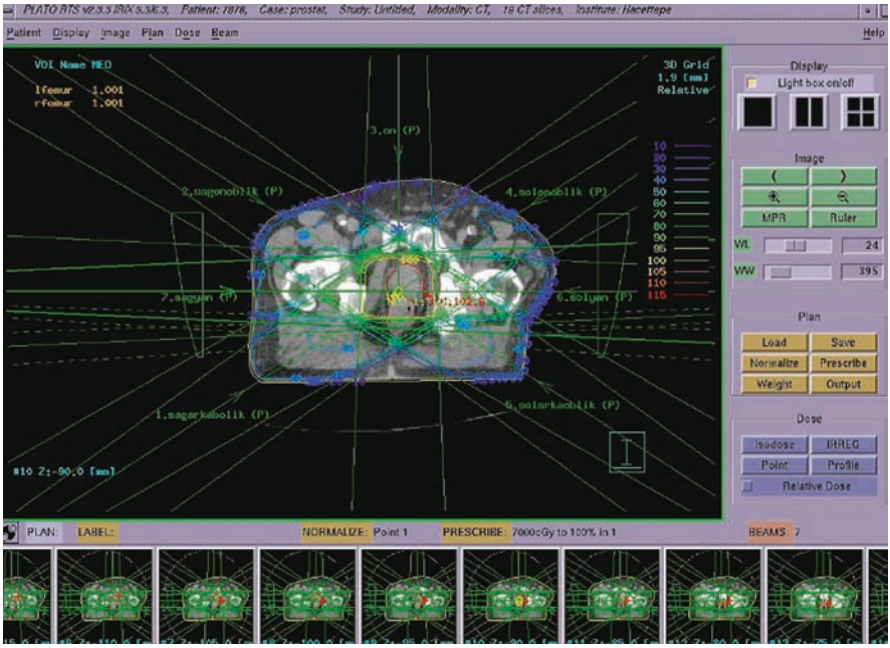


Fig. 3.18 Determination of beams

3.2.2 Treatment Planning

Conventional Planning

The energy is selected according to tumor depth and the surrounding normal tissues after determining the radiotherapy fields through simulation. High energies are selected for deeply seated tumors, while lower energies or electron beams are selected for superficially located tumors.

Therapies Utilizing Megavoltage Energy

Energy is selected according to target depth.

- High-energy X-rays are preferred for thick regions like the thorax and abdomen.
- Co-60 can be used for thin regions like the head and neck, or extremities.
- Target volume, organs at risk, and depth are the main factors in energy selection.

Therapies Utilizing Electron Energy

These are preferred for superficial tumors. The target volume should be the 80–95% isodose region of the selected energy, depending on the distance from the skin and underlying tissues.

- Deeply seated normal tissues are spared in electron therapies.
- The depth of the 80% isodose corresponds to one-third of the electron energy (E/3).
- Bolus can be used to increase the superficial dose if required.

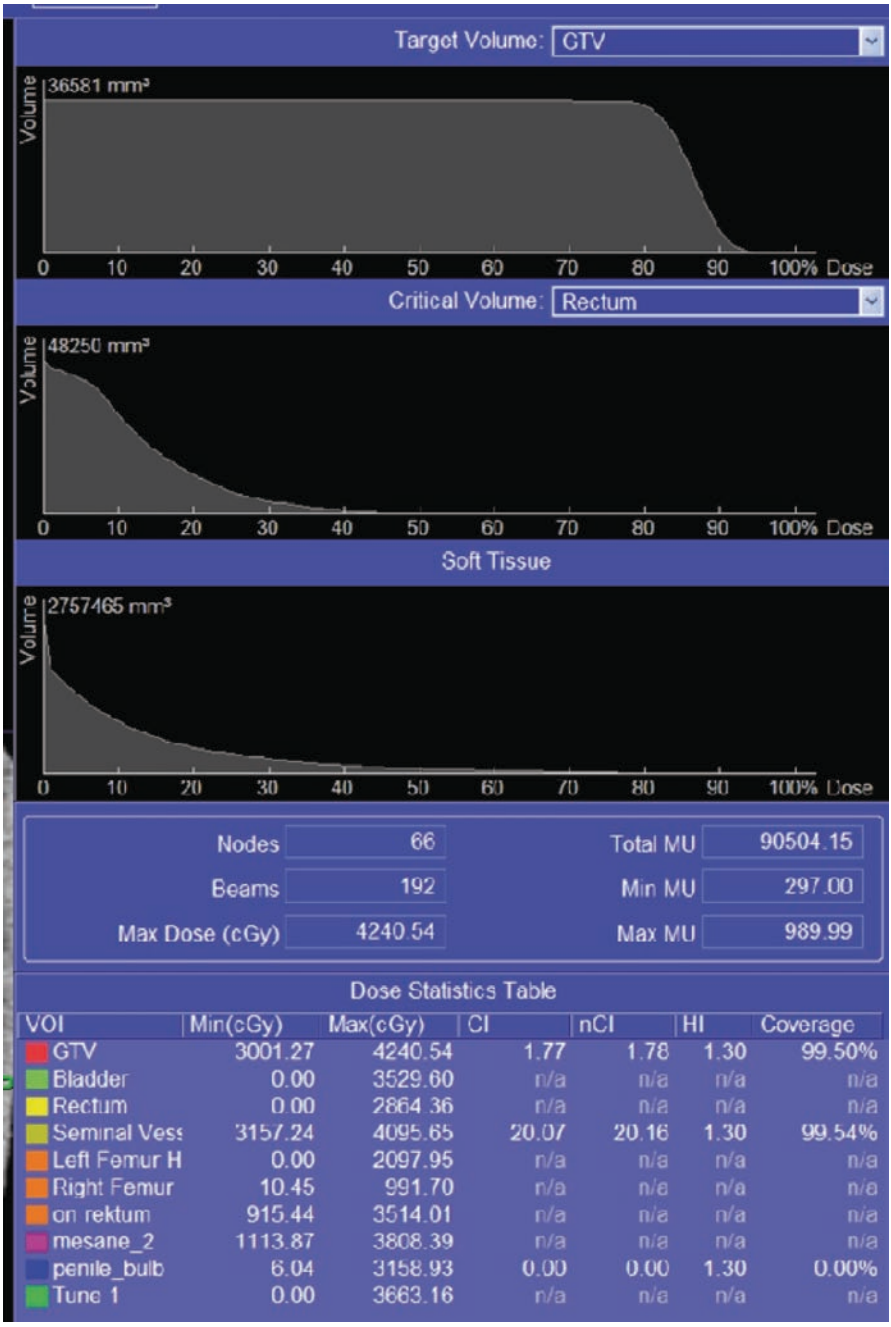


Fig. 3.19 Dose–volume histogram

Conformal Planning

The basic idea here is quite different from that of conventional planning. The treatment volume is determined virtually after contouring the target volume and the organs at risk in serial CT slices. Blocks or the MLC and isodoses can be seen and selected digitally in the TPS.

3.2.3 Target Volume Definitions

Successful radiotherapy treatment depends on determining the optimal technique for the target volume and surrounding normal tissues as well as the accurate application of this technique. Therefore, cells that form tumors are destroyed while causing minimal damage to the surrounding normal critical structures [2, 3].

The use of a common terminology is very important, since it allows procedures to be understood as well as comparisons to be made between therapeutic results after planning and between records at different institutions. The International Commission on Radiation Units and Measurements (ICRU) has published many reports that are used to determine treatment parameters and define target volumes so that radiotherapy can be accurately planned. These reports include ICRU 50 [4] and 62 [5] on photon energies of external treatments, ICRU 71 [7] on electron energies. The ICRU also published ICRU 78 on proton therapy in 2007.

The ICRU 50 and 62 reports define the target volumes and organs at risk. Accurate volume definition plays a very important role in radiotherapy.

The GTV and CTV are defined before radiotherapy planning according to ICRU 62. The PTV is then formed by adding IM and SM. Organs at risk are defined. TV and IV are then determined by taking into account the PRV.

The definitions in the ICRU 62 report are for photon beams. The ICRU published report 71 in 2004 for electron beams, which have a completely different dose distribution than photon beams [7].

Volume Definitions According to ICRU 50 (Fig. 3.20) [4]

The *gross tumor volume* (GTV) is the macroscopic volume of the tumor. The GTV defines the tumor volume determined by clinical exam and imaging modalities (visible, palpable).

- Visible or palpable tumor volume, clinical volume

The *clinical target volume* (CTV) encompasses the possible regions into which the microscopic disease may extend, or regions with a high risk of involvement based on clinical experience (invisible tumor).

- Subclinical volume and clinical volume

The *planning target volume* (PTV) defines the volume formed when the CTV is extended due to physiological organ movements or technical reasons.

- Physiological movements like respiration, bladder, and rectum fullness
- Technical reasons like patient movement, mask movement, or couch movement

The *treatment volume* (TV) is the volume, including the reference isodose, that has the minimum probability of incurring complications.
The *irradiated volume* (IV) is the volume that receives a significant dose, based on normal tissue tolerance doses.

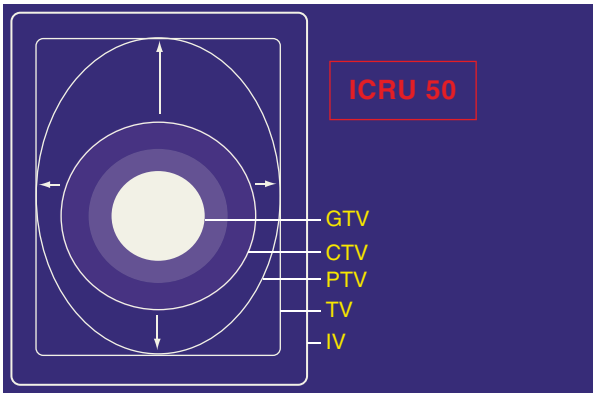


Fig. 3.20 Treatment volumes according to the ICRU-50 report [5]

Volume Definitions According to ICRU 62 (Fig. 3.21) [5]

In addition to the volumes defined by the ICRU 50 report, two new volumes termed the internal target volume (ITV) and the planning organs at risk volume (PRV) were added. Internal margin (IM), setup margin (SM), organ at risk (OAR), and conformity index (CI) were also defined.
The *internal margin* (IM) defines physiological organ movements.

- Respiration, swallowing, bladder fullness, lung movements, cardiac movement, and intestinal movement

The *setup margin* (SM) defines movements relating to the treatment and technique, and daily changes in setup position.

- Patient movement, treatment machine movement, setup errors

An OAR is an organ that may remain in the treatment field, and can cause changes to treatment plans and doses (spinal cord, heart, lungs, kidney, eye, etc.).
The *internal target volume* (ITV) is the combined volume of the CTV and IM.
The *planning organ at risk volume* (PRV) defines the volume of the OAR that may reside in the PTV during treatment.

CI = TV/PTV.

- The TV should include PTV (CI ratio)
- This is necessary for dose homogeneity within the PTV

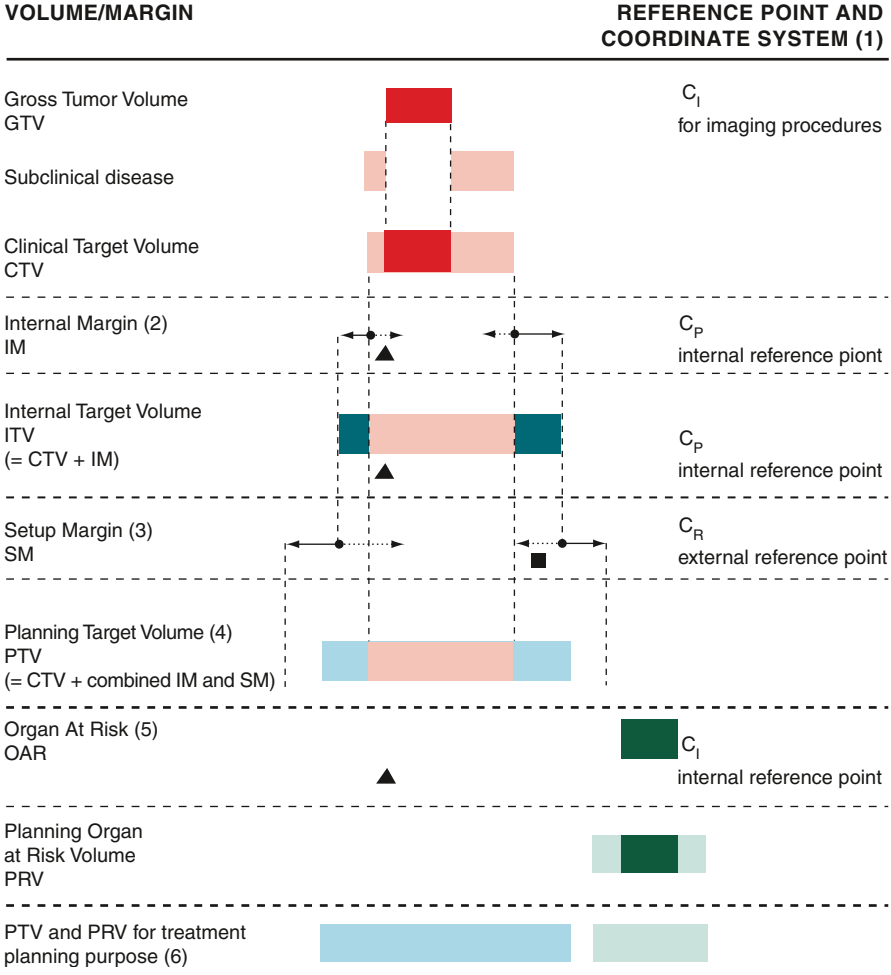


Fig. 3.21 Treatment volumes according to the ICRU-62 report

The *ICRU reference point and dose* [5] is a point outside the rapid dose change region that determines the PTV; it is easy to define and is dose-definable physically.

- It is a point on the central axis or close to it.
- It is defined separately for each treated region.

D_{max} is the maximum dose point within the PTV and the organ at risk.
D_{min} is the minimum dose point within the PTV.
Hot spots are high-dose regions in the treated volume.

- These are points that receive more than 100% of the total dose.
- They are acceptable in the GTV or CTV, but are unacceptable in organs at risk, and require technical correction.

The dose distribution should be homogeneous within the PTV, and an isodose heterogeneity of −5 to 7.5% is acceptable.

Uncertainties in the Volume Definitions in ICRU 62 [6]

The most important uncertainty is in the delineation of the CTV. The CTV is not just the region that has a high risk of the tumor spreading to it, because the whole body is at risk. Therefore, the CTV is the region that has a high risk of bearing tumor cells and that can be included within a reasonable radiotherapy field. The data used to determine CTV borders are generally based on weak and anecdotal information. Therefore, CTV is practically just an automatic enlargement of the GTV to a certain margin, and this approach is too weak to define the CTV.

The PTV defines a physical volume, while the GTV and CTV define biological volumes [6].

The PTV does not contain information about the radiation beam penumbra and thus does not provide any information on the actual treatment field size either. Therefore, it is very important to enlarge the treatment field to include a beam penumbra that is larger than the PTV.

The PTV is not useful for defining the field size since the relationship of the penumbra to the field size is weak for charged particles like protons.

ICRU 71 [7]

This report is similar to reports 50 and 62 in terms of general volume definitions.

- It recommends that the point of D_{max} dose of electron energy selected within PTV at ICRU reference point is determined at D_{max} of the selected electron energy for treatment.
- The changes in OAR and PRV with energy and patient movement in electron therapies are explained with examples.
- It provides information about some special electron therapy techniques (total skin irradiation, intraoperative RT).

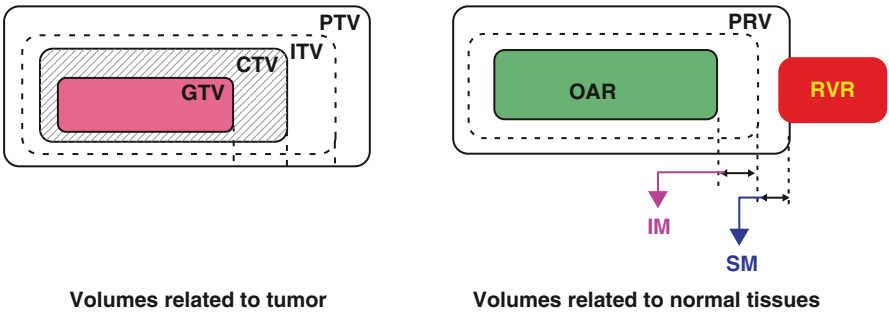


Fig. 3.22 Treatment volumes according to the ICRU-78 report

ICRU 78 (Fig. 3.22) [6, 7]

This report on proton therapies was published in 2007.

A new volume called the remaining volume at risk (RVR) was added to the volume definitions.

- RVR is examined in two parts: the region of the PRV and OAR included within the imaged field, and the region of the PRV and OAR remaining outside of the PTV.
- The dose received by the RVR is important when estimating late side effects (particularly secondary malignancies).
- It specifies that RVR should always be delineated [6].
- It recommends that OARs should be delineated during planning [6].

Other concepts that are pointed out are:
Volume of interest. This is any volume that needs to be defined. It can be generically used to define special volumes such as the PTV and OAR.
Surface of interest. This is a flat or curved plane or a particular surface.
Point of interest. This is any point in space.
The IAEA report in 2000 considers proton dosimetry, and the importance of the value of *w*, as measured in an ion chamber, is mentioned [6].
The definition of the RBE-weighted dose should be mentioned in proton therapy, and it is shown that this dose can be found by multiplying the total delivered dose (according to the photon energy of Co-60) by 1.1. This dose is called the bioeffective dose. It was mentioned that the bioeffective dose can change with depth, dose and fraction dose.
The old term for the RBE-weighted dose was the "cobalt gray equivalent (CGE)." However, the CGE is not recommended, since it is not given in SI units (Fig. 3.23) [6].

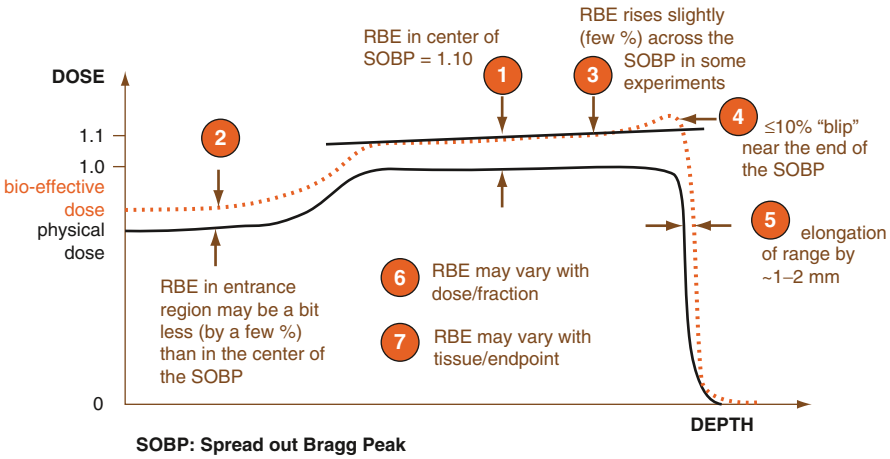


Fig. 3.23 Spread out Bragg Peak [6]

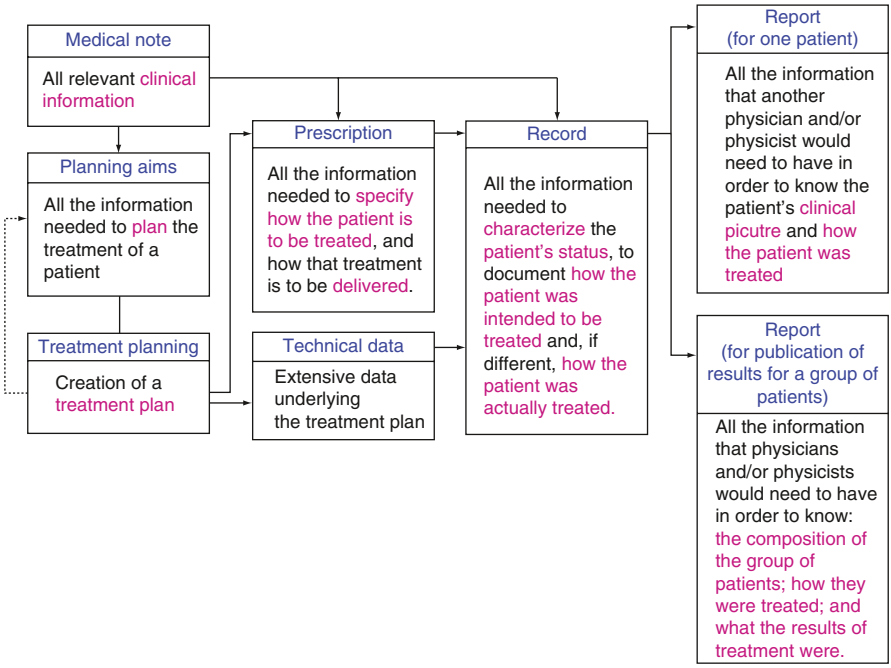


Fig. 3.24 The common algorithm for photon and proton therapies according to the ICRU-78 report [6]

- The CTV can be used in proton therapy beam design (Fig. 3.24) [6].
- The CTV can be used when generating the PTV, but it can vary [6].
- The PTV can be used for both proton therapy and photon therapy, thus enabling uniformity of reporting within institutions (Table 3.1) [6].

Table 3.1 Similarities and differences between proton therapies and photon therapies according to ICRU 78 [6]

Imaging modalities	Same or different?
GTV, CTV delineation	Same
PTV delineation	Different
Electron densities of tissues	Different
Treatment planning tools	Same
Treatment planning design	Same
Weights of planned beams	Different
Calculations of field irregularities	Quite different
Selection of plan	Same
Final prescription	Same
Simulation of plan	Same
Delivery of treatment and corrections	Different
Plan check during treatment	Same
Documentation and reporting	Same
Follow-up after treatment	Same

3.2.4 Setup and Treatment

The radiation oncologist should attend the first patient treatment (i.e., during setup) and see the patient at regular intervals during radiotherapy. This is true of both conventional and advanced radiotherapies. The applicability of a well-designed therapy plan requires meticulous review of the physician.

Port films are used to control of actual treated fields if they are exactly the same as the planned ones. These films are regularly taken during therapy when the patient is on the treatment couch and compared with the simulation films (Fig. 3.25). The patient's position is then adjusted accordingly.

Digitally reconstructed radiographies created by the TPS are compared with images taken by an electronic portal imaging device in more developed techniques (e.g., conformal RT, IMRT) (Fig. 3.26).

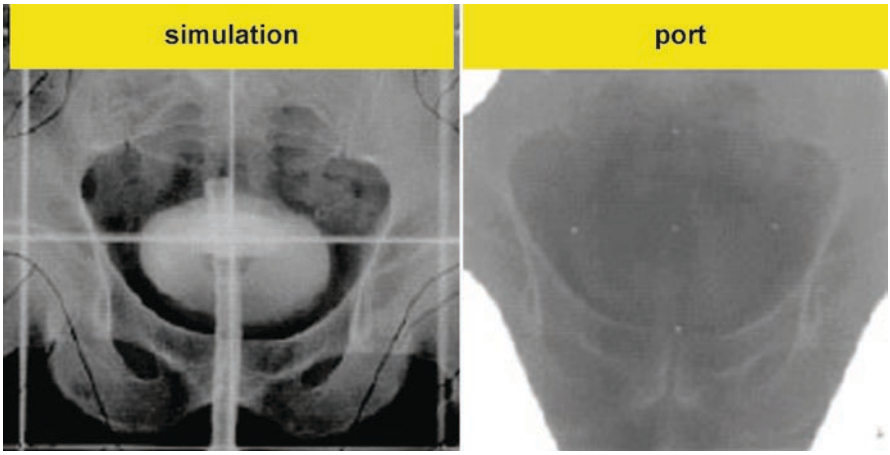


Fig. 3.25 Simulation and port films

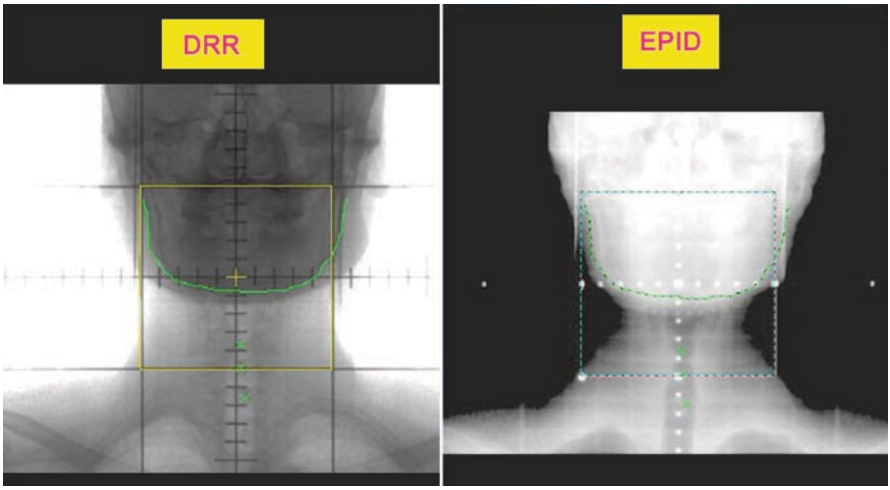


Fig. 3.26 Imaging of DRR and EPID

3.2.5 Quality Assurance

Quality assurance (QA) is absolutely essential in radiotherapy (Fig. 3.27). QA includes all aspects of the therapy, from recording the patient's data to follow-up procedures after treatment. A problem at any stage of this overall procedure affects all functions. Therefore, control mechanisms should be standardized and continuously monitored if they are to be successful.

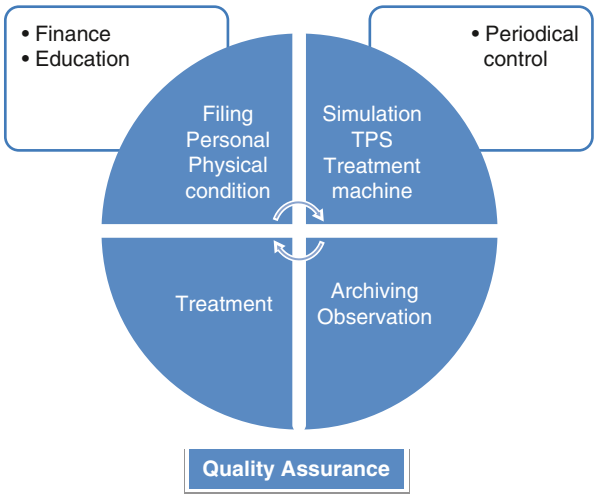


Fig. 3.27 Quality assurance and its components

Single Treatment Fields (Fig. 3.28). These are generally used for superficially located tumors (e.g., skin cancers), superficial lymphatic regions (e.g., supraclavicular lymphatics), metastatic nodules, and vertebral metastases.

Advantages include the fact that treatment planning is not usually required, dose calculations are rapid and easy, and setup is easy.

Factors determining the dose include subcutaneous tissue, heterogeneity in tumor volume, and normal tissues under the tumor.

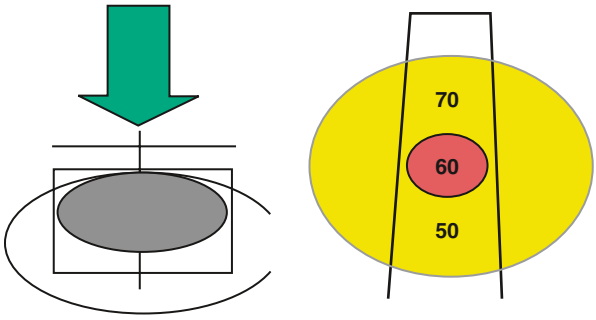


Fig. 3.28 Single RT field and change in isodose

Multiple Treatment Fields (Fig. 3.29). These are used for deeply seated tumors or large tumors to provide a homogeneous dose distribution and to spare normal tissues.

Factors that determine the dose include the size of the irradiated volume, the treatment machine, the cross-section of the treatment field, and the selected energy.

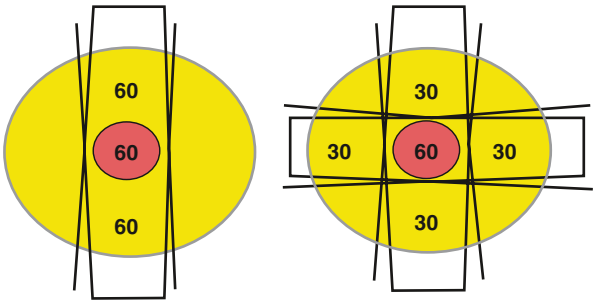


Fig. 3.29 Multiple RT fields and change in isodose

Special multiple treatment field examples include *tangential beams*, where parallel opposed tangential fields are used for convex-shaped regions such as the chest wall (Fig. 3.30), and *oblique fields (double-wedge technique)*, where nonparallel and nonopposed fields are used for convex-shaped regions such as parotid gland tumors (Fig. 3.31).

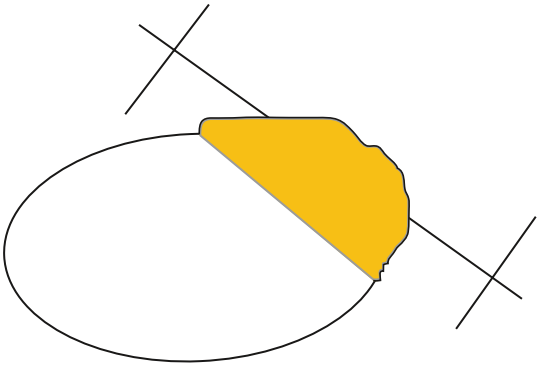


Fig. 3.30 Tangential fields

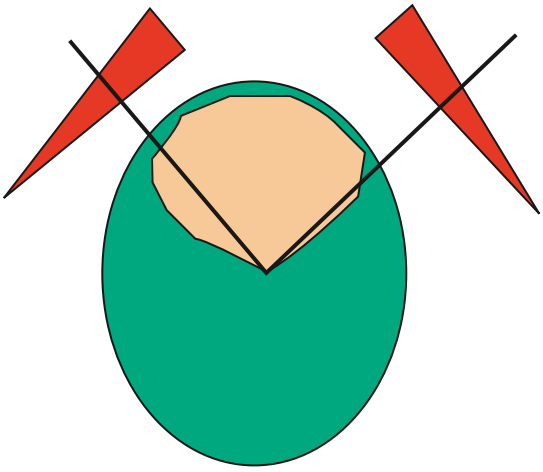


Fig. 3.31 Oblique fields (double-wedge technique)

3.2.6 Treatment Fields in Radiotherapy

Treatment fields in radiotherapy and beams are generally classified into two groups: single and multiple fields.

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Central Nervous System Tumors

4

Murat Beyzadeoglu, Gokhan Ozyigit, and Cuneyt Ebruli

CNS tumors constitute 2% of all cancers in the USA, and are observed in 4–5 in 100,000. A slight male predominance is seen, and they have a bimodal distribution according to age (a peak at 15–34 and another at 75–85 years of age). CNS tumors exhibit different behaviors according to age, histology, and location [1].

Tentorium cerebelli. This is an extension of the dura mater that covers the top of the cerebellum (Fig. 4.1). The top portion is called the supratentorium, and that below is known as the infratentorium.

- Supratentorial location is frequent in adults.
- Infratentorial location is frequent in children.

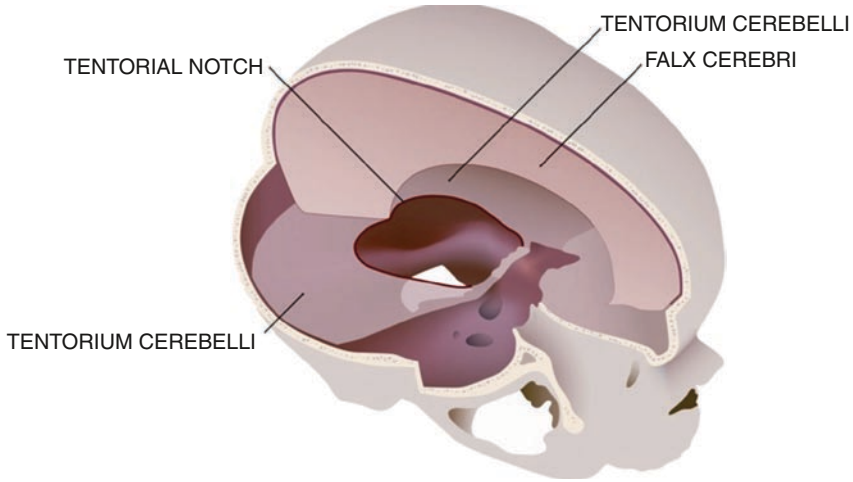

Fig. 4.1 Tentorium cerebelli

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4.1 Anatomy

Brain (Fig. 4.2) [2]

- Embryologically, the brain consists of the prosencephalon (forebrain), the mesencephalon (midbrain), and the rhombencephalon (hind brain).
- The prosencephelon forms important parts of brain including the two hemispheres (telencephalon) and the diencephalon (interbrain) during the later stages of embryonic life.
- White matter is located inside the structure, while gray matter surrounds the white matter like a shell.
- The shell of gray matter is called the cerebral cortex. There are important functional centers at particular positions in the cerebral cortex.
- The white matter of the brain does not contain any neuronal cells. It consists solely of neuronal pathways.
- The part that links the two hemispheres of the brain is the interbrain (diencephalon).
- The midbrain (mesencephalon) is the smallest part of the brain. It acts as a connection between the spinal cord and the neuronal pathways of the brain. It also contains important and vital functional cranial nerves (e.g., the oculomotor nerve or N. oculomotorius, and the trochlear nerve or N. trochlearis) and nuclei (e.g., the nucleus ruber and the substantia nigra).
- The hindbrain (rhombencephalon) consists of three important parts: the pons, bulbus, and cerebellum. An important brain cavity, the fourth ventricle, is located between these three parts. The pons and the bulbus (also known as the medulla oblongata or simply "medulla") contain important start and end nuclei for some cranial nerves.

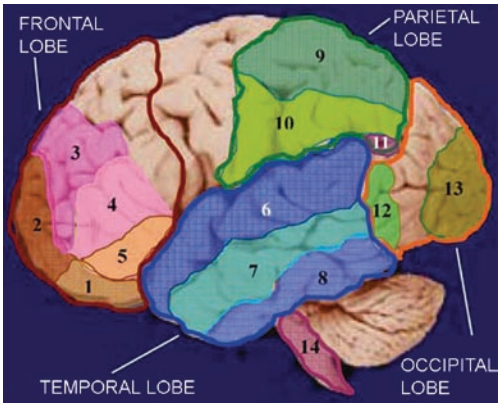

Fig. 4.2 Brain lobes

Brain and spinal cord is covered by three membranes, called meninges: the dura mater, pia mater, and arachnoid mater (Fig. 4.3) [2].

- There is a cavity filled with fluid between the pia mater and arachnoid mater. This fluid protects the brain from excessive pressure. It also protects against external mechanical trauma.
- The dura mater and pia mater are very sensitive to pain.
- The neuronal network of the arachnoid mater is very poorly developed.

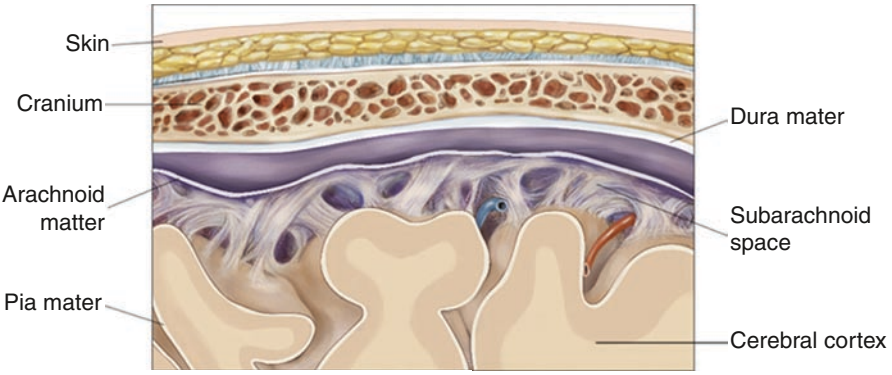

Fig. 4.3 Brain meninges and subarachnoid space

Brain Ventricles [2]

- The *first and second ventricles* lie within the hemispheres of the brain (telencephalon).
- The *third ventricle* is located in the interbrain (diencephalon).
- The *fourth ventricle* is the space between the pons, bulbus, and cerebellum. Its base, which is formed by the pons and bulbus, is rhomboidal in shape, so it is called the rhomboid fossa.

Cerebrospinal Fluid (CSF) [2]
There is a vascular network in the ventricles of the brain that is called the choroid plexus, which secretes the CSF found in the ventricles. Brain ventricles normally produce 300–400 mL of CSF daily. In addition, CSF is found in the subarachnoid space located between the arachnoid mater and pia mater.

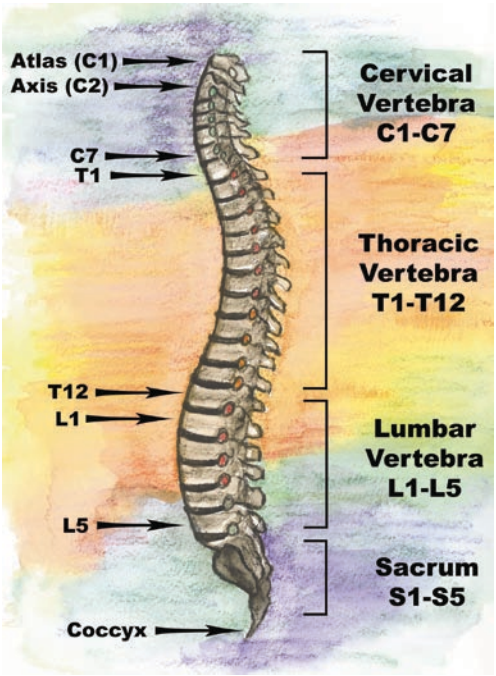

Fig. 4.4 Sections of spinal cord

Spinal Cord (Fig. 4.4) [3]

The spinal cord runs through the vertebral canal between the top portion of the atlas and the intervertebral disc of L1–2 in adults.

- It may extend to the L3 vertebral body in small children.
- It is 45 cm long, 30 g in weight, and 1 cm in diameter.
- The spinal cord is not a straight pipe; it exhibits enlargements in two places.
- The first enlargement is between the C4 and T1 segments.
- The second enlargement is between the L1 and S3 segments.
- The spinal cord gets thinner and ends at the intervertebral disc of the L1 and L2 vertebra. This end region of the spinal cord is called the conus medullaris. A bond originating from the conus medullaris connects the spinal cord to the tip of the coccyx. This bond known as the filum terminale, and is approximately 20 cm in length.

4.2 General Presentation and Pathology

Brain Tumors [1]
Symptoms and findings depend on tumor histology, location, and age. Brain tumors cause neurological disorders by either infiltrating normal CNS structures or obstructing CSF pathways and subsequently increasing intracranial pressure. This increase in intracranial pressure results in the early symptoms of brain tumors: headaches, vomiting, and lethargy.

- Headaches are frequently seen, and they occur more frequently in the morning.
- Papilledema is present in 25% of cases.
- Endocrine tumors have hyperfunctional or hypofunctional findings.
- Tumors located in the motor area generally cause hemiparesis or hemiplegia, while tumors of the cerebellum cause balance and coordination disorders.
- Frontal tumors cause personality and memory disorders.
- Infratentorial tumors cause obstructive hydrocephalus, cerebellar dysfunctions, and cranial nerve disorders.
- Hypophyseal tumors compress the optic chiasm and cause visual disorders.

Spinal Cord Tumors [1]
Pain is the earliest and most frequently observed symptom. Pain occurs in 80% of cases, while motor weakness, sphincter problems, and sensory disorders are seen in 10% of cases. Pain has a tendency to increase with movement and at night. Neurological deficits are generally seen during the terminal periods of the disease and with late diagnosis.

Sixty percent of all primary brain tumors are glial tumors, and two-thirds of these are clinically aggressive, high-grade tumors (Fig. 4.5) [1].

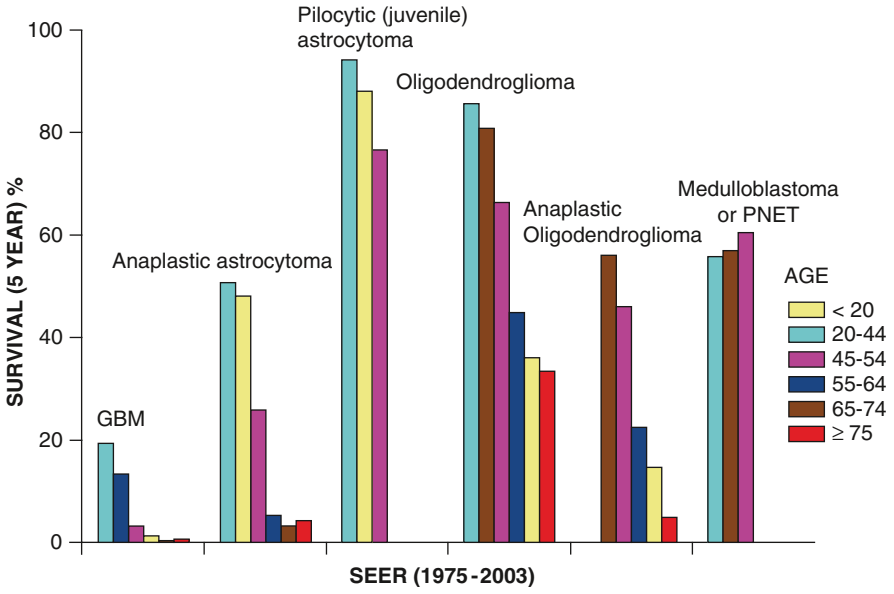

Fig. 4.5 Survival distributions for brain tumors according to SEER data

The WHO recently modified their classification of CNS tumors (Tables 4.1–4.4).

Table 4.1 Neuroepithelial brain tumors (WHO 2007) [4]

Neuroepithelial tumors	Subtypes
Astrocytic tumors	Pilocytic astrocytoma
	Polymyxoid astrocytoma
	Subependymal giant cell astrocytoma
	Pleomorphic xanthoastrocytoma
	Diffuse astrocytoma
	Fibrillary astrocytoma
	Gemistocytic astrocytoma
	Protoplasmic astrocytoma
	Anaplastic astrocytoma
	Glioblastoma
	Giant cell glioblastoma
	Gliosarcoma
	Gliomatosis cerebri
Oligodendroglial tumors	Oligodendroglioma
	Anaplastic oligodendroglioma
Oligoastrocytic tumors	Oligoastrocytoma
	Anaplastic oligoastrocytoma
Neuronal and mixed neuronal–glial tumors	Cerebellar dysplastic gangliocytoma
	Lhermitte–Duclos
	Desmoplastic infantile
	Astrocytoma/ganglioglioma
	Dysembryoplastic neuroepithelial tumor
	Gangliocytoma
	Anaplastic ganglioglioma
	Central neurocytoma
	Extraventricular neurocytoma
	Cerebellar liponeurocytoma

Table 4.1 (continued)

Neuroepithelial tumors	Subtypes
	Papillary glioneuronal tumor
	Rosette-forming glioneuronal tumor of the fourth ventricle
	Paraganglioma
Ependymal tumors	Subependymoma
	Myxopapillary ependymoma
	Ependymoma
	Cellular
	Papillary
	Clear cell
	Tanycytic
Choroid plexus tumors	Choroid plexus papilloma
	Atypical choroid plexus papilloma
	Choroid plexus carcinoma
Pineal region tumors	Pineocytoma
	Moderately differentiated parenchymal tumor
	Pineoblastoma
	Pineal region papillary tumor
Embryonal tumors	Medulloblastoma
	Desmoplastic/nodular medulloblastoma
	Medulloblastoma with extensive nodularity
	Anaplastic medulloblastoma
	Giant cell medulloblastoma
	Primitive neuroectodermal tumor
	Neuroblastoma
	Ganglioneuroblastoma
	Medulloepithelioma
	Ependymoblastoma
	Atypical teratoid/rhabdoid tumor

Table 4.2 Meningeal tumors (WHO 2007) [4]

Meningeal tumors	Subtypes
Meningothelial cell tumors	Meningioma Meningothelial Fibrous (fibroblastic) Transitional (mixed) Psammomatous Angiomatous Microcytic Secretory Lymphoplasmacyte-rich Metaplastic Choroid Clear cell Atypical Papillary Rhabdoid Anaplastic (malignant)
Primary melanocytic lesions	Diffuse melanocytosis Melanocytoma Malignant melanoma Meningeal melanomatosis
Mesenchymal tumors	Lipoma Angiolipoma Hibernoma Liposarcoma Solitary fibrous tumor Fibrosarcoma Malignant fibrous histiocytoma Leiomyoma Leiomyosarcoma Rhabdomyoma Rhabdomyosarcoma Chondroma Chondrosarcoma Osteoma Osteosarcoma Osteochondroma Hemangioma Epithelioid hemangioendothelioma Hemangiopericytoma Anaplastic hemangiopericytoma Angiosarcoma Kaposi's sarcoma Ewing sarcoma–PNET
Other tumors related to meningeal regions	Hemangioblastoma

Glial tumors originate either from astrocytes or oligodendroglial cells.

Kernohan Grading System

- *Grade I–II*: low-grade tumors
- *Grade III–IV*: high-grade tumors

Table 4.3 Other neoplasms of the central nervous system (WHO 2007) [4]

Other neoplasms	Subtypes
Cranial and paraspinal tumors	Other neuroepithelial tumors Astroblastoma Third-ventricle choroid glioma Perineurioma Malignant perineurioma Malignant peripheral nerve sheath tumor (MPNST) Epithelioid MPNST Mesenchymal differentiated MPNST Melanotic MPNST Glandular differentiated MPNST
Lymphoma and hematopoietic tumors	Malignant lymphoma Plasmocytoma Granulocytic sarcoma
Suprasellar region tumors	Craniopharyngioma Adenomatous Papillary Granular cell tumor Pituicytoma Adenohypophysis spindle cell oncocytoma
Germ cell tumors	Germinoma Embryonal carcinoma Yolk sac tumor Choriocarcinoma Teratoma Mature Immature Malignant transformated teratoma Mixed germ cell tumor
Metastatic tumors	–

Table 4.4 High-grade (grade III–IV) brain tumors according to WHO 2007 [4]

	Grade III	Grade IV
Astrocytic	Anaplastic astrocytoma	Glioblastoma Giant cell glioblastoma Gliosarcoma
Oligodendroglial	Anaplastic oligodendroglioma	–
Oligoastrocytic	Anaplastic oligoastrocytoma	–
Ependymal	Anaplastic ependymoma	–
Choroid plexus tumors	Choroid plexus carcinoma	–
Neuronal and mixed neuronal–glial tumors	Anaplastic ganglioglioma	–
Pineal tumors	Papillary tumor of pineal region Moderately differentiated parenchymal pineal tumor	Pineoblastoma
Embryonal tumors	–	Medulloblastoma PNET Atypical teratoid/rhabdoid tumor
Cranial and paraspinal nerve tumors	Perineurioma Malign peripheral nerve sheath tumor (MPNST)	MPNST
Meningeal tumors	Anaplastic (malignant) meningioma Anaplastic hemangiopericytoma	

New WHO (2007) Classification of Brain Tumors [4]

- Angiocentric glioma (Grade I)
- Atypical choroid plexus papilloma (Grade II)
- Extraventricular neurocytoma (Grade II)
- Papillary glioneuronal tumor (Grade I)
- Rosette-forming glioneuronal tumor of the fourth ventricle (Grade I)
- Papillary tumor of the pineal region (Grade II–III)
- Pituicytoma (Grade I)
- Adenohypophyseal spindle cell oncocytoma (Grade II)

Survival Estimates According to the WHO 2007 Classification [4]

- Grade II: >5 years
- Grade III: 2–3 years
- Grade IV: fatal if untreated; survival depends on treatment regimen

For example, medulloblastomas and germinomas are rapidly fatal if untreated, but 5-year survival is 60–80% of a state-of-the-art combined radiotherapy and chemotherapy regimen is applied.

Spinal Cord Tumors [5]
Spinal tumors are classified as either extradural, intradural extramedullary, or intradural intramedullary. Among all spinal tumors, 55% are extradural, 40% are intradural extramedullary, and 5% are intradural intramedullary.

Extradural spinal tumors

- Metastatic extradural tumors
- Primary extradural tumors

Intradural extramedullary spinal tumors

- Meningioma
- Schwannoma/neurofibroma

Intradural intramedullary spinal tumors

- Astrocytoma
- Ependymoma

Other

- Hemangioblastoma

4.3 Staging

CNS tumors have no TNM designation, and no stage grouping applies. Although there was an old AJCC staging system in brain tumors, it is not used in practice [6]. Therefore, AJCC did not recommend any staging system for CNS tumors.

Supratentorial tumors
T1: unilateral, <5 cm
T2: unilateral, ≥5 cm
T3: ventricular system extension
T4: extension beyond midline, contralateral hemisphere invasion, or infratentorial extension

Infratentorial tumors

T1: unilateral, <3 cm
T2: unilateral, ≥3 cm
T3: ventricular system extension
T4: extension beyond midline, contralateral hemisphere invasion, or supratentorial extension
Stage IA: G1 T1 M0; Stage I B: G1 T2 M0/G1 T3 M0
Stage IIA: G2 T1 M0; Stage IIB: G2 T2 M0/G2 T3 M0
Stage IIIA: G3 T1 M0; Stage IIIB: G3 T2 M0/G3 T3 M0
Stage IV: G1, 2, 3 T4 M0/G4 with any T M0/any G with any T M1
(G: grade)

(No lymph node → no lymphatic spread → no nodal staging!)

CT and MRI Are Useful in Diagnosis [7, 8]

- High-grade gliomas are seen as mass lesions surrounded by edema with enhanced contrast.
- Malignant gliomas are multifocal in 5%.
- Low-grade gliomas usually do not take contrast; they diffusely infiltrate brain tissue.
- Low-grade gliomas are best visualized in T2-weighted MRI sequences.

Open biopsy, endoscopic biopsy, and stereotactic biopsy can be used for histopathological diagnosis. In addition, open or closed surgery enables both diagnosis and treatment.

4.4 Treatment Algorithm

Adult Low-Grade Astrocytoma/Oligodendroglioma [9]

Primary brain tumor (+) in MRI

Gross total resectability (GTR) probability (+)
GTR → diagnosis: low grade astrocytoma/oligodendroglioma
Less than 45 years → surveillance or RT
Less than or equal to 45 years → surveillance
GTR probability (−)
Stereotactic biopsy (Bx)/open Bx/subtotal resection (STR)

- Diagnosis: low-grade astrocytoma/oligodendroglioma

Intractable or progressive neurological symptoms
RT
Stable or symptoms under control
Surveillance or RT

If there is recurrence

Previous RT (+)
Resectable → surgery → chemotherapy (CT) → progression →
± Reirradiation (if there is a 2-year interval from previous radiotherapy or the lesion is outside of the previous RT portal)
Unresectable → CT → progression →

± Reirradiation (if there is a 2-year interval from previous radiotherapy or the lesion is outside of the previous RT portal)
Previous RT (−)
Resectable → surgery ± RT
Unresectable → RT ± CT

Adult Intracranial Ependymoma [9]

(Except subependymoma and myxopapillary ependymoma)
Primary brain tumor in contrast MRI/CT (+)
Gross total resection probability (+)

GTR → diagnosis: ependymoma
Postoperative GTR (+), spinal MRI (−) ± CSF (−)

- Localized field RT or surveillance

Postoperative subtotal resection (STR) (+), spinal MRI (−) ± CSF (−)

- Localized field RT

Postoperative GTR or STR (+), spinal MRI (+), or CSF (+)

- Craniospinal RT

GTR → diagnosis: anaplastic ependymoma
Postoperative GTR or STR (+), spinal MRI (−) ± CSF (−)

- Localized-field RT
- Postoperative GTR or STR (+), spinal MRI (+), or CSF (+)

Craniospinal RT

Gross total resection probability (−)
Stereotactic Bx/open Bx/STR

- Diagnosis: ependymoma/anaplastic ependymoma
- Spinal MRI (−) ± CSF (−)
- Localized-field RT
- Spinal MRI (+) or CSF (+)
- Craniospinal RT

If there is recurrence
(Brain or spinal)

Resectable
Previous RT (−) → surgery + RT → progression → CT/RT/best supportive care
Previous RT (+) → surgery → progression → CT/reirradiation/best supportive care
Unresectable
Previous RT (−) → RT → progression → CT/RT/best supportive care
Previous RT (+) → CT/reirradiation/best supportive care

Anaplastic Astrocytoma, Anaplastic Oligodendroglioma, GBM [9]

High-grade brain tumor (+) in MRI
GTR probability (+)

- GTR

Diagnosis: anaplastic oligodendroglioma

- RT ± CT
- Then

<70 years, KPS>60 → ±CT
>70 years, KPS<60 → surveillance
Diagnosis: GBM/anaplastic astrocytoma

- Concurrent RT + temozolomide (75 mg/m^2)
- Then adjuvant temozolomide (150 mg/m^2)

GTR probability (−)

- Stereotaxic Bx/open Bx/STR

Diagnosis: anaplastic oligodendroglioma

- RT ± CT
- Then

<70 years, KPS >60 → ±CT
>70 years, KPS <60 → surveillance
Diagnosis: GBM/anaplastic astrocytoma

- Concurrent RT + temozolomide
- Then adjuvant temozolomide

If there is recurrence
Diffuse/multiple recurrences
If KPS is low, best supportive care
CT
Surgery for symptomatic large lesions

- If response (−), best supportive care

Local recurrence
Resectable
Surgery → then ±CT ± reirradiation
Unresectable
CT ± reirradiation

- If response (−), best supportive care

4.5 Radiotherapy

4.5.1 External Radiotherapy

Accessory equipment: thermoplastic mask (Fig. 4.6), special RT headrest (Fig. 4.7).

- *Patient position*: supine for brain tumor, prone for spinal tumor

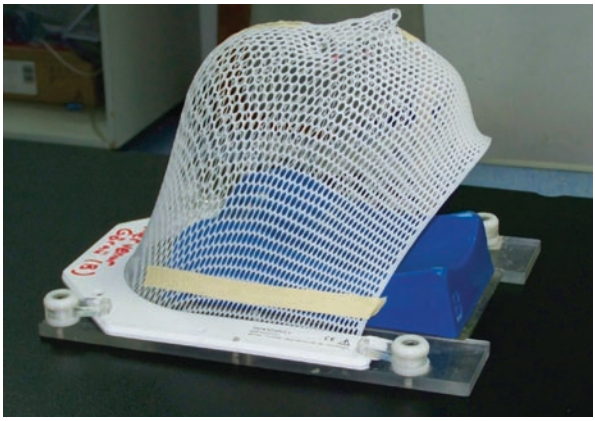

Fig. 4.6 Thermoplastic mask

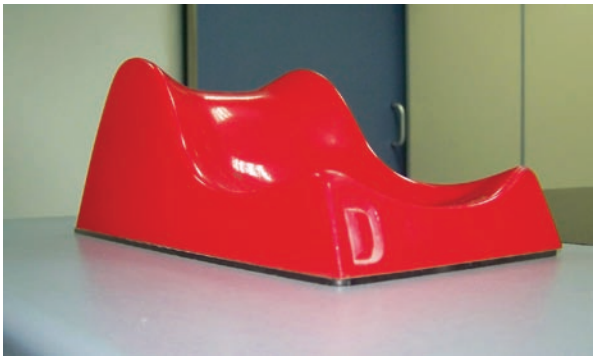

Fig. 4.7 Special RT cushion for head and neck area

Conventional Simulation

The tumor is located in simulation films by CT and MRI of the patient (preoperative imaging modalities if the patient is operated on).

Brain Tumors

Whole-brain RT (Fig. 4.8)

- Superior: skin fall off
- Anterior: skin fall off
- Posterior: skin fall off
- Inferior: cranial base

In the case of prophylactic cranial irradiation (PCI), the inferior border is the bottom of the C2 vertebra → helmet field.

Helmet field (Fig. 4.9). Anterior border is 2 cm posterior to lens; inferior border is the bottom of the C2 vertebra and 0.5 cm inferior to the cribriform plate in PCI (helmet type → similar to a German helmet in World War II).

CSF circulates around the optic nerve. Therefore, the orbital apex should be included in the helmet field. Corpus vertebrae C1 and C2 should not be spared due to a high risk of recurrence.

Local brain RT (Fig. 4.10)

- After tumor is located, 1–3 cm margin is given.
- For boost: tumor + 1 cm.

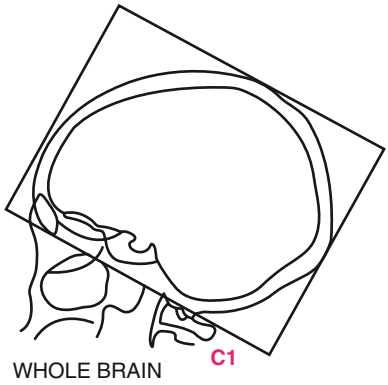

Fig. 4.8 Illustration of whole-cranium RT field

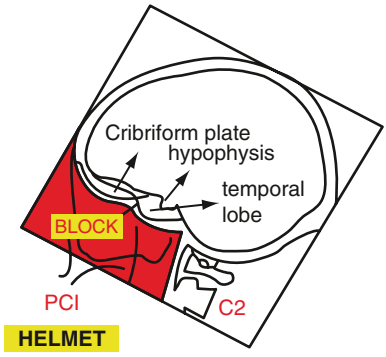

Fig. 4.9 Illustration of helmet-type whole-cranium RT field

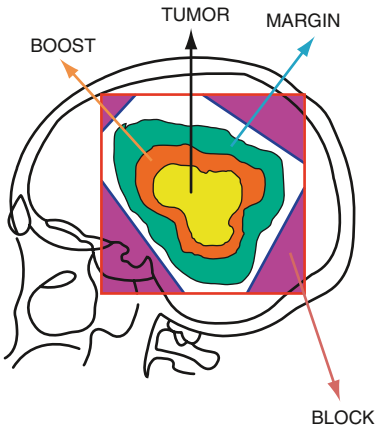

Fig. 4.10 An illustration of local RT field for brain tumor

Conformal Planning [10]

GTV → contrast enhanced field in T1 MRI/CT
Low-grade tumors

- CTV = GTV + 1.5 cm
- (If tumor is benign CTV = GTV)
- PTV = CTV + 0.5 cm

High-grade tumors

- Local cranial field
- CTV1 = GTV + 2.5 cm (or high-intensity field in T2 MRI, edema field)
- PTV1 = CTV1 + 0.5 cm
- Boost field
- CTV2 = GTV + 1 cm
- PTV2 = CTV2 + 0.5 cm

Contrast material: 50–70 cc IV bolus should be given in CT simulator.

Technique

Conventional planning → two lateral fields are used.

Conformal planning → varies according to tumor localization, but generally more than two fields are used.

Dose

- Low-grade tumor

Phase I → 40 Gy
Phase II → 54 Gy

(*continued*)

(continued)

- High-grade tumor

Phase I → 40 Gy
Phase II →60 Gy
Energy → Co-60, 4–18 MV photon energies

4.5.2 Craniospinal RT

The aim is to irradiate all of the subarachnoid space [10, 11]. The patient is simulated in the prone position and with a thermoplastic head and neck mask (anesthesia may be required in children) (Fig. 4.11).

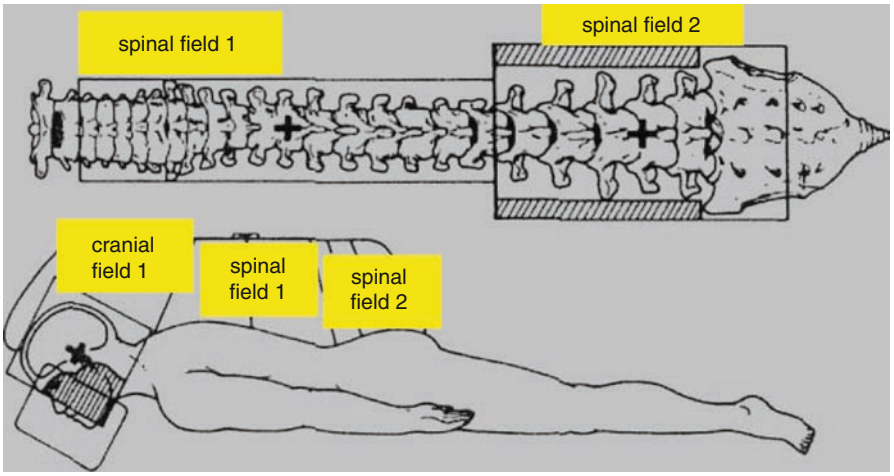

Fig. 4.11 Craniospinal irradiation technique

Cranial field

- Two lateral fields are simulated.
- Inferior border of the field includes cervical vertebrae as much as possible.
- Oral cavity, neck outside spinal cord, nasopharynx is protected.

Spinal field

- Two separate single fields (single field in children).
- The superior border starts from the inferior border of cranial field.

- Second field ends at the S2 vertebra.
- Field widths vary between 4 and 6 cm.

A gap calculation is needed in order to find the space required between the cranial and spinal fields (Fig. 4.12).

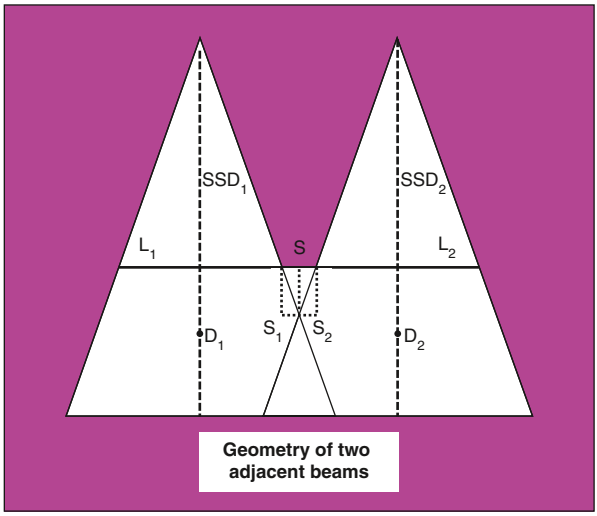

Fig. 4.12 Gap calculation for abutting fields

Gap Calculation [10]

$$S1 = 1/2L1\left(\frac{D1}{SSD1}\right) \tag{4.1}$$

$$S2 = 1/2L2\left(\frac{D2}{SSD2}\right) \tag{4.2}$$

$$S = S1 + S2 \tag{4.3}$$

$L1$, $L2$ = length of each field
$D1$, $D2$ = depth of each field
S = gap length

Collimator angle for cranial field (Fig. 4.13) [10]:

$$\tan^{-1}\theta = \frac{\text{Spinal field length}}{2 \times SSD} \tag{4.4}$$

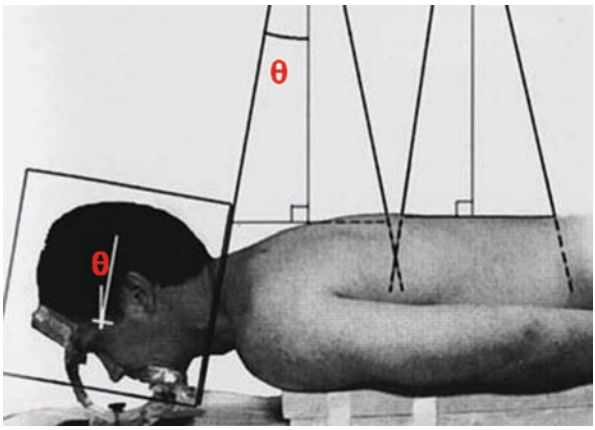

Fig. 4.13 Collimator angle (θ) for cranial field (from [12], reproduced with the permission from Springer Science and Business Media)

Craniospinal simulation for conformal treatments [10, 11]

CTV_1: whole brain
CTV_{1B}: boost field (posterior fossa for medulloblastoma)
$CTV_{cervical}$: the first spinal field
CTV_1: the second spinal field
0.5 cm is added to the CTV for PTV

Dose in craniospinal irradiation [10, 11, 13]

- Whole brain and spinal field
  1.8 Gy daily fraction dose, total 30–36 Gy
- Posterior fossa boost dose in medulloblastoma
  1.8 Gy daily fraction dose; total 18 Gy posterior fossa boost dose (making the total posterior fossa dose 54 Gy)

Energy in craniospinal irradiation [10, 11, 13]

- Cranial field
  Co-60, 6 MV photon energies
- Spinal field
  Adult → Co-60, 6 MV photon energies
  Children → 15–21 MeV electrons

Radiotherapy in Spinal Tumors [11]

- Primary treatment is surgery.
- Primary tumors are generally low-grade glial tumors, but metastatic tumors are more frequent.
- Postoperative radiotherapy may be beneficial for subtotally resected low-grade tumors, but radiotherapy is indicated in all high-grade tumors.
- Single field in prone position.
- Superior and inferior borders are one corpus vertebrae corpus from the location of the lesion.
- A suitable energy is selected according to field depth (generally photon energies).
- 1.8–2 Gy daily fractions to a total of 45–50 Gy.
- Metastatic spinal tumors: 30 Gy in ten fractions of palliative RT.

4.5.3 Symptomatic Treatments and Special Therapies

Symptoms of increased intracranial pressure and spinal cord compression

16 mg/day dexamethasone is started and continued throughout radiotherapy; the dose is tapered and stopped after RT (an antiulcer medication should always be given with steroids).

- The dose can be increased to 32 mg in the case of spinal cord compression.

Epileptic seizures or prophylaxis for them

Phenytoin sodium 100 mg 2 × 1 (the dose is adjusted according to blood level).
Carbamazepine 200 mg 1 × 1 (the dose is adjusted according to blood level).
Valproate sodium 200 mg 1 × 1 (the dose is adjusted according to blood level).

Temozolomide Concurrent with RT [16]

Indicated in high-grade glial tumors
GBM, anaplastic astrocytoma
Seventy-five milligrams per square meter per day P.O. during radiotherapy
Complete blood count should be examined weekly

Temozolomide After RT (Adjuvant)

Indicated in high-grade glial tumors
GBM, anaplastic astrocytoma
One hundred and fifty milligrams to 200 mg per square meter once every 28 days/for 5 days, P.O. after radiotherapy
Complete blood count should be examined before each cycle

4.5.4 Side Effects Due to CNS Radiotherapy

Critical organs in the CNS and their radiation tolerance doses are summarized in Tables 4.5 and 4.6.

Table 4 5 TD 5/5 radiotherapy doses for the entire organ in CNS tumors

Organ	Single fraction (Gy)	Fractionated dose (Gy)
Brain	15–25	60–70
Lens	2–10	6–12
Skin	15–20	30–40
Spinal cord	8–10	50–60
VCTS	10–20	50–60
Mucosa	5–20	65–77
Peripheral nerve	15–20	65–77
Muscle	>30	>70
Bone–cartilage	>30	>70
Thyroid	–	30–40

VCTS, vasculoconnective tissue systems
Modified from [14]

Table 4.6 Normal tissue tolerance doses in CNS radiotherapy

Organ	TD5/5			TD50/5			End-point
	1/3	2/3	3/3	1/3	2/3	3/3	
Brain	60	50	45	75	65	60	Necrosis, infarction
Brain stem	60	53	50	–	–	65	Necrosis, infarction
Spinal cord	5 cm	10 cm	20 cm	5 cm	10 cm	20 cm	Myelitis
	50	50	47	70	70	–	Necrosis

Adapted from [15]

Skin. In the early period: hyperemia, dry squamation, wet squamation, and ulceration. In the late period: telangiectasia, fibrosis, tissue necrosis, and achromia.
Hair. Alopecia starts on the seventh day (temporary at 7 Gy, permanent at >7 Gy).
Mucosa. Erythema, edema, patchy mucositis, and confluent mucositis (mucositis starts at >3 Gy).
Eye. In the early period: conjunctivitis, decreased teardrops, infection. In the late period: necrosis in retina, dry eye, cataract. Optic nerve and optic chiasma damage at >50 Gy, total blindness at >70 Gy.

CNS. Acute side effects depend on edema and dose. Late effects: transient demyelination (somnolence syndrome) and brain necrosis 2–3 years after high dose of radiation.
Spinal cord (L'Hermitte's sign). Transient demyelination in the spinal cord. Patient feels a sensation like an electrical shock starting from the arms and spreading throughout the body during head flexion. This appears after 8 weeks of radiotherapy, and heals spontaneously. Myelitis may occur when tolerance doses are exceeded in the spinal cord.

4.6 Selected Publications

Low - grade glial tumors

Adjuvant RT dose
EORTC 22844 → randomized phase III. 343 cases. Ages 16–65. Histology: astrocytoma (except totally resected pilocytic astrocytoma), oligodendroglioma, mixed oligoastrocytoma. Randomized after surgery to 45 vs. 59.4 Gy. RT field was contrast-enhanced area + 2 cm until 45 Gy, contrast-enhanced area + 1 cm between 45 and 54 Gy, and only the contrast-enhanced area between 54 and 59.4 Gy. Median follow-up was 6.2 years.

- Five-year OS: low dose 58% vs. high dose 9%; 5-year PFS: low dose 47% vs. high dose 50%. No significant difference.
- Conclusion: 45 Gy is adequate.

Karim AB et al (1996) A randomized trial on dose-response in radiation therapy of low-grade cerebral glioma: European Organization for Research and Treatment of Cancer (EORTC) Study 22844. Int J Radiat Oncol Biol Phys 36(3):549–556

Intergroup NCCTG/RTOG/ECOG → randomized. 203 cases. Ages >18. Histology: astrocytoma (except totally resected pilocytic astrocytoma), oligodendroglioma, mixed oligoastrocytoma. Randomized after surgery to 50.4 vs. 64.8 Gy. RT field was contrast-enhanced area + 2 cm until 50.4 Gy and contrast-enhanced area + 1 cm between 50.4 and 64.8 Gy.

- Five-year OS: low dose 72% vs. high dose 65%; 5-year PFS: low dose 58% vs. high dose 52%. No significant difference.
- Toxicity was greater in the high-dose arm (5 vs. 2.5%).
- Conclusion: high dose is unnecessary and is more toxic.

Shaw E et al (2002) Prospective randomized trial of low- vs. high-dose radiation therapy in adults with supratentorial low-grade glioma: initial report of a North Central Cancer Treatment Group/Radiation Therapy Oncology Group/Eastern Cooperative Oncology Group study. J Clin Oncol 20(9):2267–2276

Radiotherapy timing

EORTC 22845 → randomized. 314 cases. Ages 16–65. Supratentorial low-grade astrocytoma (except for totally resected pilocytic astrocytoma, optic nerve glioma, brain stem glioma, third ventricle glioma and infratentorial glioma), oligodendroglioma, and mixed oligoastrocytoma. Randomized after surgery to early radiotherapy 50.4 Gy vs. late radiotherapy 50.4 Gy. RT field was contrast-enhanced area + 2 cm until 45 Gy and contrast-enhanced area + 1 cm between 45 and 50.4 Gy. Contrast CT was performed every 4 months until progression.

- Median PFS: 5.3 years in early RT arm; 3.4 years in late RT arm.
- Five-year PFS: 55% in early RT arm; 35% in late RT arm (significant).
- Median OS: 7.4 years in early RT arm; 7.2 years in late RT arm (not significant).
- One-year epilepsy control: 41% in early RT arm; 25% in late RT arm (significant).
- No difference in terms of toxicities.
- Conclusion: early RT increases PFS and controls epileptic seizures, but has no effect on OS.

van den Bent MJ et al (2005) Long-term efficacy of early vs. delayed radiotherapy for low-grade astrocytoma and oligodendroglioma in adults: the EORTC 22845 randomized trial. Lancet 366(9490)985–990

Grade III glial tumors

EORTC 26591 → randomized phase III. 368 cases. Histologically confirmed anaplastic oligodendroglioma and anaplastic oligoastrocytoma (>25% included oligodendroglial elements). Median age 49. Randomized after surgery and postoperative RT (45 + 14.4 Gy = 59.4 Gy) to surveillance and six cycles of a PCV (procarbazine 60, lomustine 110, vincristine 1.4 mg/m^2) chemotherapy regimen.

- Conclusion: adjuvant PCV increases PFS but has no effect on OS.

van den Bent MJ et al (2006) Adjuvant procarbazine, lomustine, and vincristine improve progression-free survival but not overall survival in newly diagnosed anaplastic oligodendrogliomas and oligoastrocytomas: a randomized European Organisation for Research and Treatment of Cancer phase III trial. J Clin Oncol 24(18):2715–2722

High Grade (III–IV) glial tumors

RT vs. best supportive care

2002 Review → it was demonstrated in six randomized trials that postoperative RT was superior to best supportive care in terms of OS.

- Relative risk was 0.81 in postoperative RT.

Laperriere N (2002) Radiotherapy for newly diagnosed malignant glioma in adults: a systematic review. Radiother Oncol 64(3):259–273

SGSG, 1981 → randomized. 118 cases of Grade III/IV histology. Randomized after surgery to (1) 45 Gy whole-brain RT + bleomycin, (2) 45 Gy whole-brain RT, and (3) best supportive care.

- Median OS: 10.8 months in 45 Gy whole-brain RT + bleomycin arm vs. 10.8 months in whole-brain RT arm and 5.2 months in best supportive care arm
- RT is dramatically superior to best supportive care
- No effect of bleomycin

Kristiansen K (1981) Combined modality therapy of operated astrocytomas grade III and IV. Confirmation of the value of postoperative irradiation and lack of potentiation of bleomycin on survival time: a prospective multicenter trial of the Scandinavian Glioblastoma Study Group. Cancer 47(4):649–652

RT dose

BTSG, 1979 → 420 cases.

- Median OS: 18 weeks in no RT arm, 28 weeks in 50 Gy RT arm, 36 weeks in 55 Gy RT arm, 42 weeks in 60 Gy RT arm

Conclusion: increasing the dose improves survival in malignant gliomas.

Walker MD (1979) An analysis of the dose–effect relationship in the radiotherapy of malignant gliomas. Int Radiat Oncol Biol Phys 5(10):1725–1731

RTOG 74-01/ECOG 1374, 1988 → 420 cases. Four arms: 60 Gy whole-brain RT; 60 Gy whole-brain RT + 10 Gy boost; 60 Gy + BCNU; 60 Gy + CCNU + dacarbazine.

- Median OS: 9.3 months in 60 Gy whole brain RT, 8.2 months in 60 Gy whole brain RT + 10 Gy boost
- Conclusion: no effect of increasing the dose beyond 60 Gy.

Nelson DF et al (1988) Combined modality approach to treatment of malignant gliomas—reevaluation of RTOG 7401/ECOG 1374 with long-term follow-up: a joint study of the Radiation Therapy Oncology Group and the Eastern Cooperative Oncology Group. NCI Monogr (6):279–284

RTOG 98-03 → phase I/II. 209 cases. Dose escalation with 3D-CRT: 66, 72, 78, 84 Gy (stratification was done according to tumor volume).

- PTV1: GTV + 15 + 3 mm (2 Gy/day until 46 Gy).
- PTV2: GTV + 3 mm (boost) 66, 72, 78, 84 Gy (2 Gy/day).
- Conclusion: dose escalation was possible; there was no dose-limiting toxicity.

Werner-Wasik M et al (2004) Phase I/II conformal three-dimensional radiation therapy dose escalation study in patients with supratentorial glioblastoma multiforme: report of the Radiation Therapy Oncology Group 98-03 Protocol. ASTRO 2004 Abstr 2769

Canada 2004 → randomized. 100 cases; >60 years. Two arms: 60 Gy/30 fractions, overall treatment time >6 weeks; 40 Gy/15 fractions, overall treatment time >3 weeks. Standard RTOG fields were used.

- Median OS: 5.1 months in the first arm, 5.6 months in the second arm (no significance).
- Corticosteroid requirements were less in the second arm.

- Conclusion: low-dose RT with a shorter overall treatment time can be used in older patients with malignant gliomas.

Roa W (2004) Abbreviated course of radiation therapy in older patients with glioblastoma multiforme: a prospective randomized clinical trial. J Clin Oncol 22(9):1583–1588

RT fields (whole brain vs. localized field)

Anderson (1991) → retrospective. 60 cases: GBM (39), AA (21), treated between 1982 and 1986. 53 cases with small RT field, 7 cases with whole brain.

- Conclusion: no significant difference between the two RT fields

Garden AS (1991) Outcome and patterns of failure following limited-volume irradiation for malignant astrocytomas. Radiother Oncol 20(2):99–110

BTCG 80-01, (1989) → randomized. 571 cases treated between 1982 and 1983. Randomized to two RT arms and three CT arms. RT arms: whole-brain 60.2 Gy and whole brain 43 + 17.2 Gy boost field.

- No difference in OS, but whole brain + boost field is more effective than whole brain.

Shapiro WR (1989) Randomized trial of three chemotherapy regimens and two radiotherapy regimens and two radiotherapy regimens in postoperative treatment of malignant glioma. Brain Tumor Cooperative Group Trial 8001. J Neurosurg 71(1):1–9

Fractionation

RTOG 83-02 → 786 cases. Phase I/II. AA + GBM. Dose escalation trial of combined hyperfractionation (HF; 1.2 Gy b.i.d. 64.8, 72, 76.8 and 81.6 Gy) RT with BCNU and combined accelerated HF (AHF; 1.6 Gy b.i.d. 48, 54.4 Gy) RT with BCNU.

- Median OS: 9.6 months in AHF, 11 months in HF (no difference in OS in terms of doses).
- OS was better in GBM cases receiving higher RT doses (76.8 and 81.6 Gy).

Werner-Wasik M et al (1996) Final report of a phase I/II trial of hyperfractionated and accelerated hyperfractionated radiation therapy with carmustine for adults with supratentorial malignant gliomas. Radiation Therapy Oncology Group Study 83-02. Cancer 77(8):1535–1543

Temozolomide

EORTC/NCI Canada 2005 → randomized. 573 GBM patients. Randomized to RT alone (60 Gy) vs. RT concurrent with daily temozolomide (75 mg/m^2, 7 days/week), then six cycles of adjuvant temozolomide (150–200 mg/m^2 for 5 days during each 28-day cycle). RT field: CTV = GTV + 2–3 cm. Median PFS 4 months, median OS 6.1 months.

- Median follow-up was 28 months. Median survival: 14.6 months in chemoradiotherapy (CRT) arm, 12.1 months in RT-alone arm (significant).
- Two-year OS: 26.5% in CRT arm vs. 10.4% in RT-alone arm.
- Mortality decreased 37% in CRT arm.
- Progression was 85% in CRT arm vs. 94% in RT-alone arm.

Conclusion: current standard therapy for GBM is RT + temozolomide.

Stupp R et al (2005) Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. N Engl J Med 352(10):987–996

4.7 Pearl Boxes

Good Prognostic Factors in Low-Grade Glial Tumors

- Young age
- Good performance status
- Oligodendroglial component
- Gross total resection

Oligodendrogliomas are chemosensitive → BCNU (carmustine), procarbazine, vincristine.

Prognostic Factors in High-Grade Tumors

Tumor- and patient-related factors

- Age
- KPS
- Histology
- Symptom duration
- Tumor localization
- Tumor size

Treatment-related factors

- Status of surgery extent
- Postoperative residue size
- Radiotherapy dose
- Chemotherapy usage

Tumors Capable of Subarachnoid Seeding via CSF

- Medulloblastoma
- Ependymoma (high grade)
- Pinealoblastoma
- Germ cell tumors

Bone marrow: 20% in cranium, 25% in spinal column, and 10% in spongy bone. Therefore, approximately 50% of the bone marrow is irradiated in craniospinal irradiation.

Posterior fossa syndrome. This syndrome may be observed after medulloblastoma surgery, and is characterized by mutism, dysphagia, and truncal ataxia lasting more than a month.

- This is not a contraindication for craniospinal RT of medulloblastoma.

The most frequently seen genetic mutation in brain tumors is p53 mutation (17p).

CNS radiotherapy actually acts on oligodendrocytes and glial cells. Although radiation affects neurons, this effect does not cause any actual CNS damage.

RT can be given to some brain tumors without any histopathological diagnosis, including:

- Optic glioma
- Diffuse pontine glioma
- Meningioma
- Choroidal melanoma

CNS Tumors That Can Metastasize Outside the CNS

- Glioblastoma
- Medulloblastoma
- Ependymoma
- Meningioma
- Hemangiopericytoma

The mean tumor doubling time is 39.5 days in malignant gliomas.

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Head and Neck Cancers

5

Gokhan Ozyigit, Murat Beyzadeoglu, and Cuneyt Ebruli

Head and neck cancers constitute approximately 10% of all cancers [1]. They are named according their location and subsite in the head or neck. Head and neck cancers are essentially seen in older patients (50–70 years), but they can also be seen in children, and they are more common in males than females. Certain types are more frequently observed in certain geographic regions (e.g., nasopharyngeal cancer in Far East Asia). Smoking and alcohol use have a very close association with head and neck cancers. Chewing tobacco and tobacco-like substances also increase the risk of oral cavity cancers [2].

Genetic tendency is another important risk factor. A previous history of head or neck cancer as well as a history of cancer in first-degree family members is also a risk factor. Head and neck cancers can be seen simultaneously or metachronously in multiple locations in the same person. Exposure to radiation, as well as to sun (ultraviolet radiation), is closely related to the risk of head and neck cancer [3]. Exposure to radiation can occur in various ways, such as through previous radiotherapy in the head and neck region, or radioactive contamination from nuclear reactor accidents (e.g., Chernobyl) or nuclear weapons (e.g., Hiroshima and Nagasaki).

Nutritional disorders and vitamin deficiencies are other risk factors. Bad nutritional habits and iron deficiency anemia in particularly women may cause these types of cancers [4]. Poor oral hygiene, use of inappropriate prostheses, chronic infections, gastroesophageal reflux, and particular viral infections (EBV, HPV) are additional risk factors [5].

The head and neck region has a rich lymphatic network (Table 5.1). This network is divided into sublevels for the purposes of neck dissection or neck radiotherapy (Fig. 5.1). Each site-specific cancer has also its specific route for lymph node metastasis (Fig. 5.2).

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Table 5.1 Head and neck lymphatics

Level	Lymphatics
Ia	Submental lymphatics
Ib	Submandibular lymphatics
II	Upper jugular lymph nodes
III	Mid-jugular lymph nodes
IV	Lower jugular lymph nodes (transverse cervical)
V	Spinal accessory chain lymph nodes (posterior triangle)
VI	Prelaryngeal, pretracheal, paratracheal lymph nodes

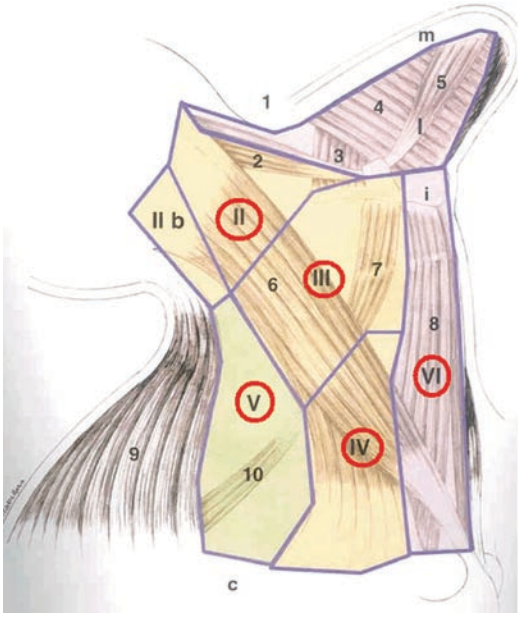


Fig. 5.1 Lymphatic levels of neck for head and neck cancers

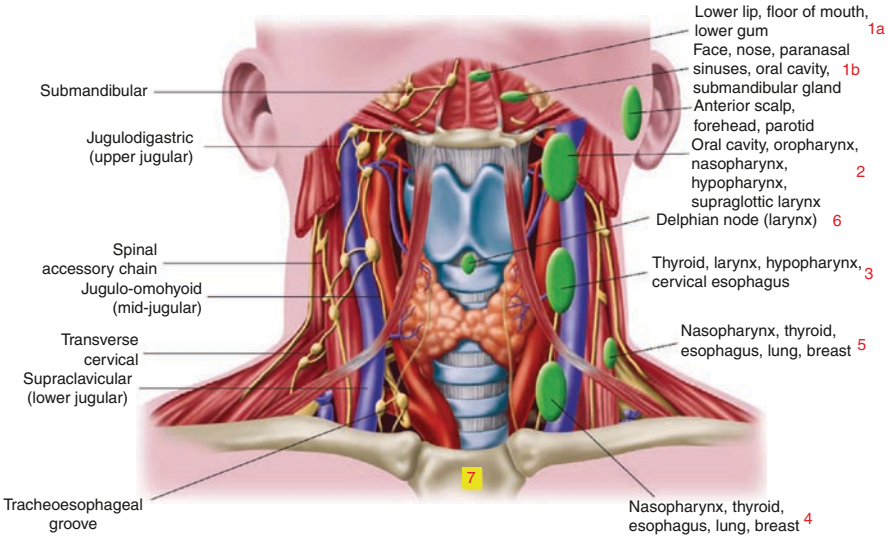


Fig. 5.2 Route of lymphatic involvement for head and neck cancers (from [6], p 18, Fig. 2.1, reproduced with the permission from Springer Science and Business Media)

Over 30% of all head–neck cancer cases show clinical lymph node positivity (Table 5.2) [9]:

- Pharyngeal wall cancer: 50%
- Pyriform sinus cancer: 49%
- Supraglottic laryngeal cancer: 39%

Head–neck cancers with clinical neck lymph node (−) but pathological lymph node (+) (Table 5.2) [9]:

- Pyriform sinus cancer: 59%
- Pharyngeal wall cancer: 37%
- Tongue cancer: 33%
- Supraglottic laryngeal cancer: 26%
- Floor of mouth cancer: 21%
- Glottic laryngeal cancer: 15%

Table 5.2 Lymphatic involvement ratios in various head–neck cancers (%) [8]

Region	Level I		Level II		Level III		Level IV		Level V		RPLN	
	N–	N+	N–	N+	N–	N+	N–	N+	N–	N+	N–	N+
Nasopharynx											40	86
Tongue	14	39	19	73	16	27	3	11	0	0	–	–
Base of tongue	4	19	30	89	22	22	7	10	0	18	0	6
Retromolar trigone	25	38	19	84	6	25	5	10	1	4	–	–
Tonsil	0	8	19	74	14	31	9	14	5	12	4	12
Pharyngeal wall	0	11	9	84	18	72	0	40	0	20	16	21
Pyriform sinus	0	2	15	77	8	57	0	23	0	22	0	9
Supraglottic larynx	6	2	18	70	18	48	9	17	2	16	0	4
Glottic larynx	0	9	21	42	29	71	7	24	7	2	–	

RPLN retropharyngeal lymph nodes

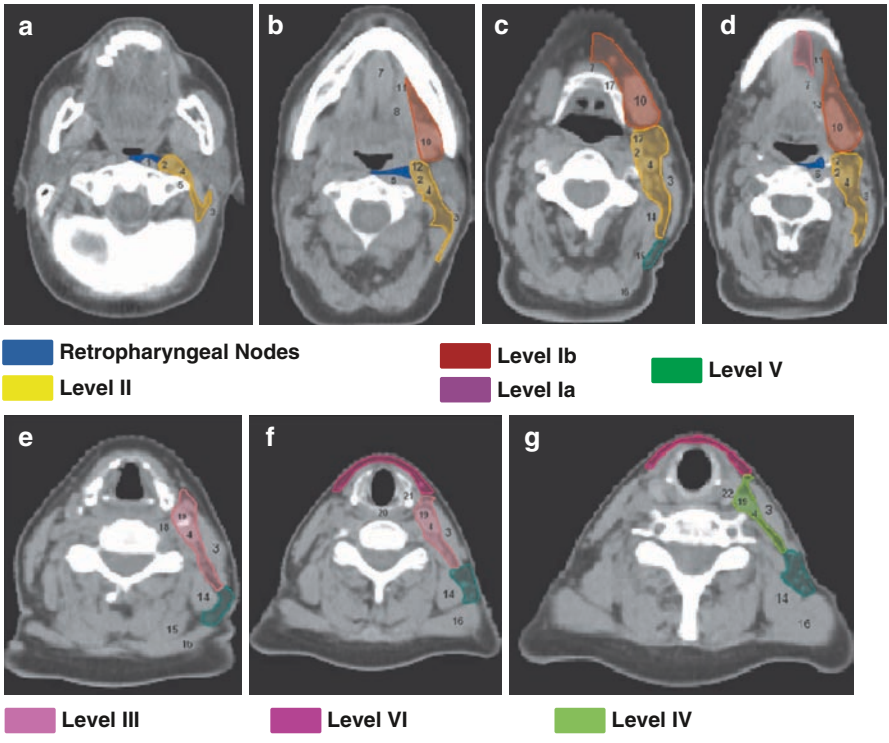


Fig. 5.3 Consensus guidelines for the delineation of N0 (elective) neck nodes [7]

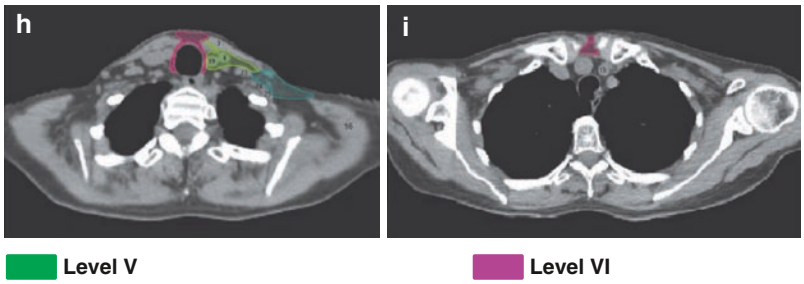


Fig. 5.3 (continued)

The RTOG/EORTC group has published a consensus document on the determination and delineation of N0 neck nodes for conformal radiotherapy of head and neck cancers (Fig. 5.3) [7].

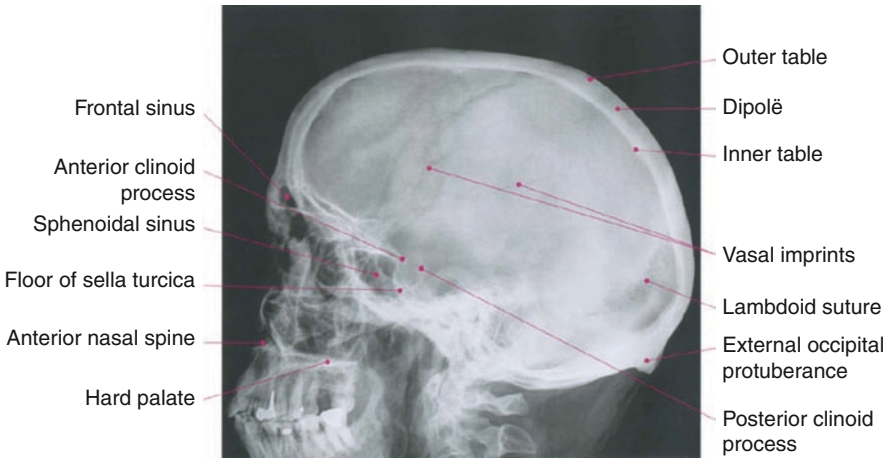


Fig. 5.4 Bony markers useful for the determination of conventional radiotherapy portals

One anterior and two lateral fields are usually used in conventional radiotherapy of head–neck cancers.

- Orthogonal planning.

Several bony markers are used to determine the radiotherapy portal in conventional planning (Fig. 5.4).

There is a risk of hot spots or cold spots in the abutment region between these fields. Two main methods are used to decrease this probability:

1. **Divergence adjustment technique**. This is based on couch rotation or changing the collimator angle.

(*continued*)

(continued)

- Divergence is prevented at the abutment of the lateral and anterior fields by modifying the couch rotation angle and/or collimator angle as the lateral fields are planned.
- The couch and/or collimator angle usually varies between 2 and 4° (Fig. 5.5).

$$\text{Collimator angle} = \text{arctangent}\frac{\text{SCF field length}}{2 \times \text{SSD}} \tag{5.1}$$

$$\text{Couch rotation angle} = \text{arctangent}\frac{\text{SCF field length}}{2 \times \text{SAD}} \tag{5.2}$$

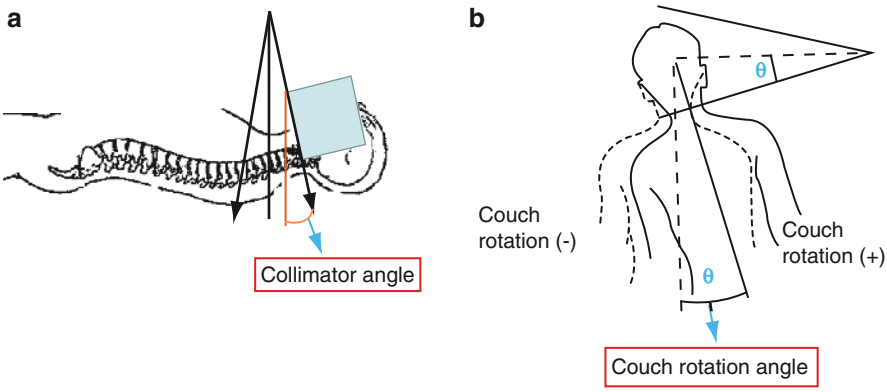


Fig. 5.5 Collimator and couch angles

2. **Half-block/asymmetrical collimator use** (Fig. 5.6).

- An asymmetrical collimator is a component of a linac that allows secondary collimators move independently of each other. Thus, asymmetrical fields can be created. The beam divergence problem is totally eliminated with this simple and easy-to-use technique.
- A half-block shuts out half of the beam from the center so that lateral beams and anterior supraclavicular fields do not abut.

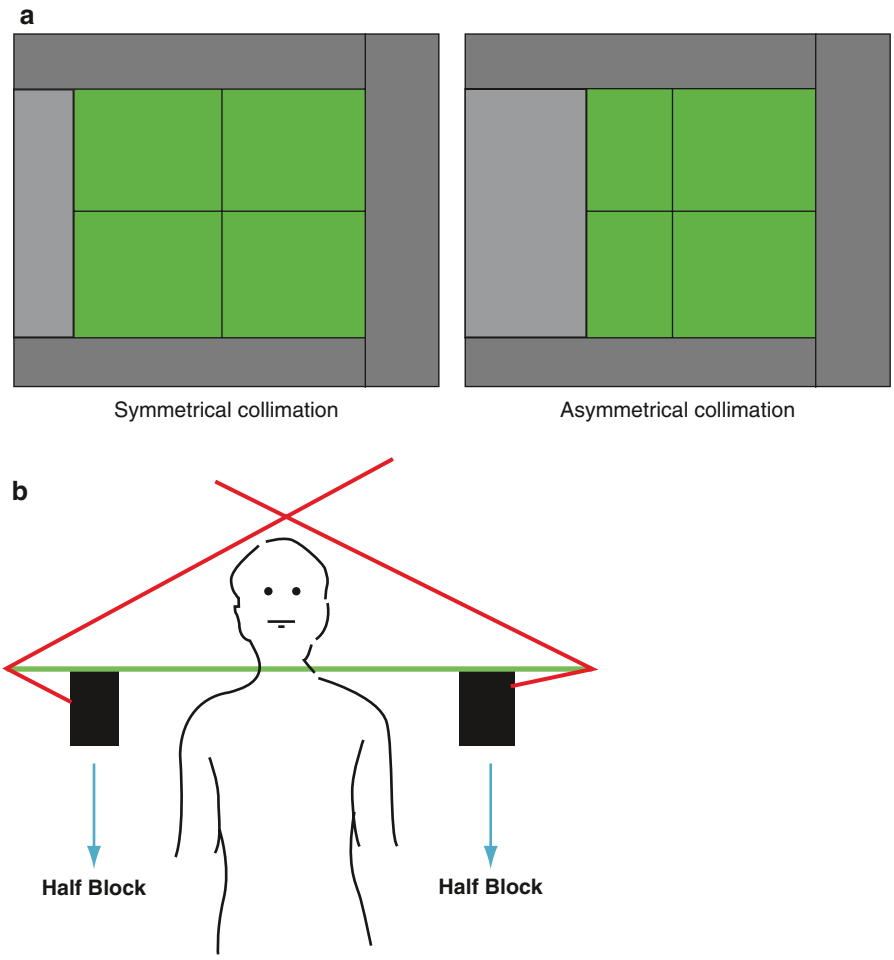


Fig. 5.6 (**a**) Asymmetrical collimation technique; (**b**) half-beam cutter

Practically, a 3–5 mm gap is left between the anterior and supraclavicular fields to prevent hot and cold spots. However, dose the distribution should be checked, since this gap interval may change according to photon energy.

- The utilization of such a gap on involved lymph nodes or stoma is not recommended.

5.1 Pharyngeal Cancers

The superior border of the pharynx is the cranial base (the base of the sphenoid sinus), and it extends inferiorly to the cricopharyngeal sphincter, becoming thinner as it goes down. It is located between the C1 and C6 vertebrae, and is 12–13 cm long in adults. It has a muscular structure, and is covered with mucosa [10].

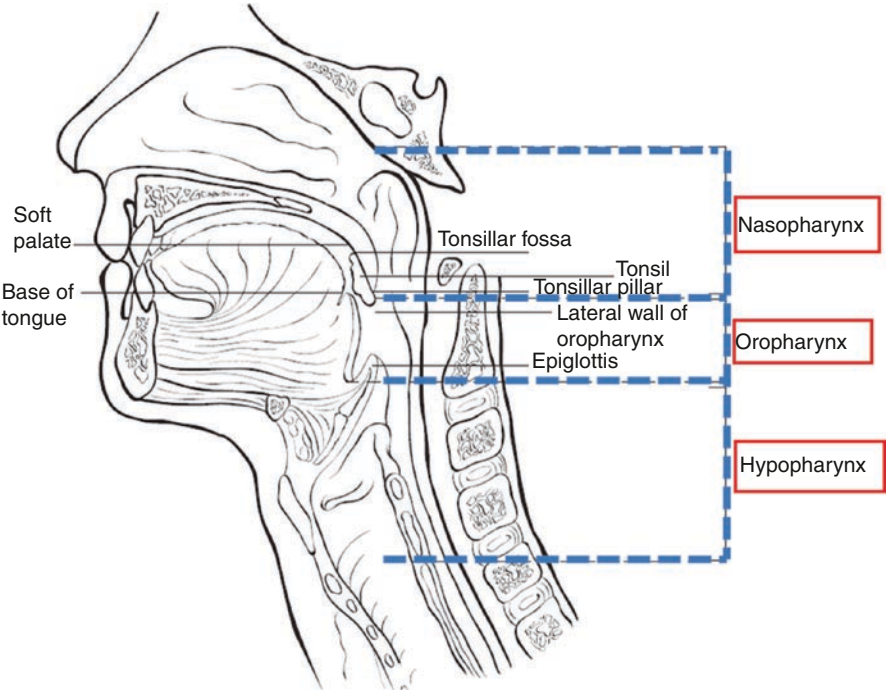


Fig. 5.7 Subsites of the pharyngeal region (from [11], p 28, Fig. 4.1, reproduced with the permission from the American Joint Committee on Cancer)

Subsites of the Pharyngeal Region (Fig. 5.7)

Superior part that is continuous with the nasal cavity: *nasopharynx* or *epipharynx.*
Middle part that is continuous with the oral cavity: *oropharynx* or *mesopharynx.*
Inferior part that is continuous with the larynx: *laryngopharynx* or *hypopharynx.*

5.1.1 Nasopharyngeal Cancer

The nasopharynx extends from the cranial base to the soft palate, and is continuous with the nasal cavity via the choanae anteriorly (Fig. 5.8).

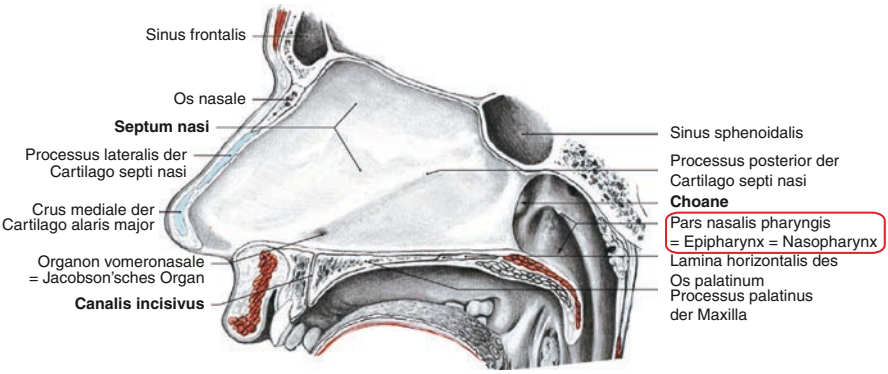


Fig. 5.8 Nasopharyngeal anatomy

Normal Anatomical Structures in the Nasopharynx [10]

Base of sphenoid sinus and cranial base superiorly
Nasal cavity and choanae superior–anteriorly
Pharyngeal side of soft palate inferior–anteriorly
Laterally: ostium of eustachian tubes, tubal tonsils (Gerlach tonsils)

5.1.1.1 Pathology

Recent studies have shown that the histological subtype of nasopharyngeal cancer is an important prognostic factor. The WHO classification is the most widely used histopathological classification system. This system essentially differentiates between tumors that do or do not produce keratin. Although the WHO classification is practical and simple, it does not give detailed information on the cell type and degree of anaplasia. Therefore, this system is considered inadequate to determine prognosis in regions where nasopharyngeal cancer is endemic. The use of Hsu's histopathological classification is recommended to compensate for these inadequacies. Another system is the Cologne system, which divides the nonkeratinized tumors into subgroups based on the presence of lymphoid infiltration, which is frequently seen together with nasopharyngeal cancers [12].

WHO Classification, 1978 [12]
WHO Type 1: keratinized squamous cell cancer.
WHO Type 2: nonkeratinized carcinoma.
WHO Type 3: undifferentiated carcinoma.

Cologne system, 1981

Nonkeratinized carcinoma	Lymphoid infiltration (+)
	Lymphoid infiltration (−)
Undifferentiated carcinoma	Lymphoid infiltration (+)
	Lymphoid infiltration (−)

Keratinized squamous cell carcinoma – WHO Type I: seen in older patients, less frequently associated with EBV, and has the best prognosis (represents 20% of all nasopharyngeal cancer cases).

Nonkeratinized tumors: includes most nasopharyngeal cancers.

- Nonkeratinized carcinoma – WHO Type II (30–40%)
- Undifferentiated carcinoma – WHO Type III (40–50%)

Undifferentiated carcinoma = lymphoepithelioma

5.1.1.2 General Presentation

Symptoms appear to be related to the localization and extent of the tumor. These symptoms can be grouped into four classes [13]:

1. Nasal and nasopharyngeal symptoms are seen as a result of nasopharyngeal localization and tumor extension into the nasal cavity anteriorly. These symptoms are nasal obstruction and nasal bleeding.
2. Otological symptoms are due to the entrance to an Eustachian tube becoming filled and obstructed. These are the symptoms and findings of serous otitis media: hearing loss, tinnitus, and otophonia.
3. Cervical symptoms are neck lymph node metastases that are the extension of the nasopharyngeal cancer into first the parapharyngeal and retropharyngeal lymph nodes and then the jugular and spinal accessory chain. Fifty percent of patients have bilateral while 80–90% have bilateral neck metastases at presentation. Neck mass is the first sign in 40% of cases.
4. Ophthalmoneurological symptoms are observed due to the extension of the tumor into the cranial base and then into the foramen lacerum, various other foramens and fissures, and the cranial nerves. Dry eye due to the invasion of the greater superficial petrosal nerve; hypo- or hyperesthesia in the face due to the invasion of the trigeminal nerve;

and ophthalmoplegia and diplopia due to extension into the cavernous sinus and superior orbital fissure, resulting in III, IV, and VI cranial nerve invasion, are all important findings. Parapharyngeal lymphatic involvement or extensive invasion of the lower cranial nerves (IX, X, XI, and XII) causes nasolali, aspiration, stridor, shoulder pain, motor weakness, and speaking disorders. Horner's syndrome may develop as a result of invasion of the cervical sympathetic chain located around large vessels.

5.1.1.3 Staging

T staging (Fig. 5.9) [14]

TX: Primary tumor cannot be assessed
T0: No evidence of primary tumor
Tis: Carcinoma *in situ*
T1: Tumor confined to the nasopharynx, or extends to the oropharynx and/or nasal cavity without parapharyngeal extension*
T2: Tumor with parapharyngeal extension*
T3: Tumor invades bony structures and/or paranasal sinuses
T4: Tumor with intracranial extension and/or involvement of cranial nerves, infratemporal fossa, hypopharynx, orbit, or masticator space
*Parapharyngeal extension denotes posterolateral infiltration of tumor

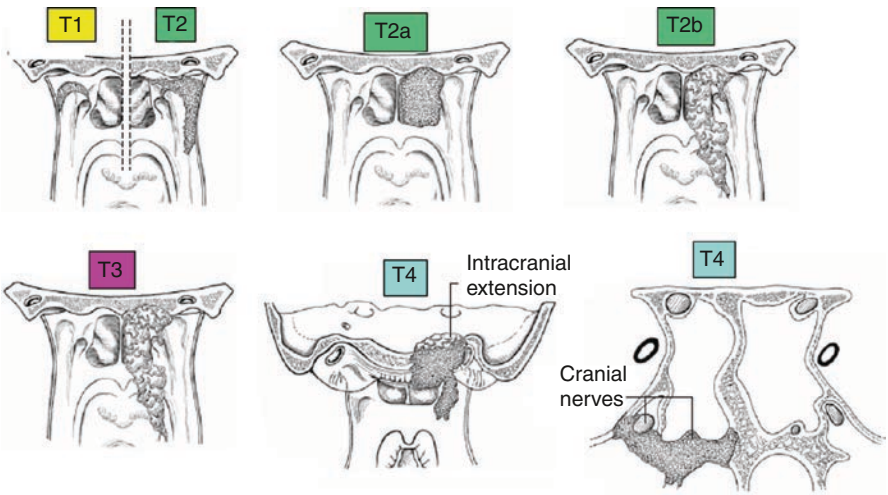


Fig. 5.9 T staging for nasopharyngeal cancers (from [11], reproduced with the permission from the American Joint Committee on Cancer)

N Staging (Fig. 5.10)

N0: No regional lymph node metastasis
N1: Unilateral metastasis in lymph node(s), not more than 6 cm in greatest dimension, above the supraclavicular fossa, retropharyngeal lymph nodes, 6 cm or less in greatest dimension (Midline nodes are considered ipsilateral nodes)
N2: Bilateral metastasis in lymph node(s), not more than 6 cm in greatest dimension, above the supraclavicular fossa
N3: Metastasis in a lymph node(s) larger than 6 cm and/or to supraclavicular fossa
N3a: Larger than 6 cm
N3b: Extension to the supraclavicular fossa

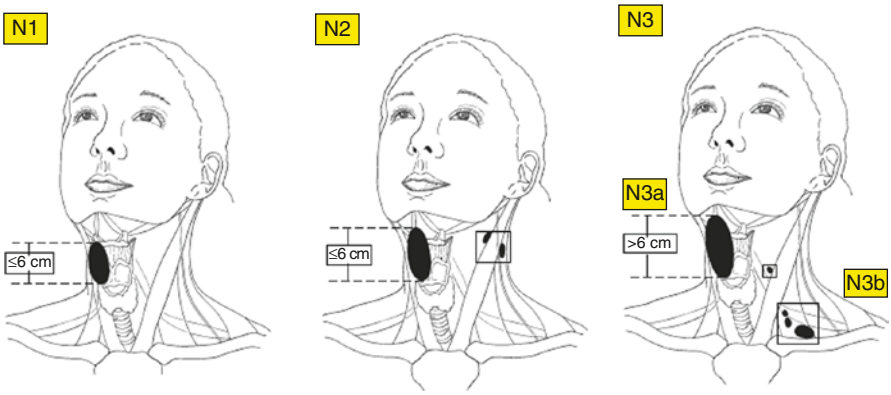


Fig. 5.10 N staging for nasopharyngeal cancers (from [11], reproduced with the permission from the American Joint Committee on Cancer)

AJCC Stage Groups

Stage 0: TisN0M0
Stage I: T1N0M0
Stage II: T1N1M0, T2N0M0 T2N1M0,
Stage III: T1N2M0, T2N2M0, T3N0M0, T3N1M0, T3N2M0
Stage IVA: T4N0M0, T4N1M0, T4N2M0
Stage IVB: Any T, N3M0
Stage IVC: Any T, Any N, M1

Gadolinium MRI is superior to CT in the differentiation of tumor and normal tissue. Its disadvantage is its high artifact ratio.

The most important prognostic factor in nasopharyngeal cancer is nodal status (N) followed by T stage (Fig. 5.11) [15]:

N0 → 17% distant metastasis (+).

N3 → 78% distant metastasis (+).

Distant metastasis is very rare, and the most frequent sites of distant metastasis are the lungs, bones and liver.

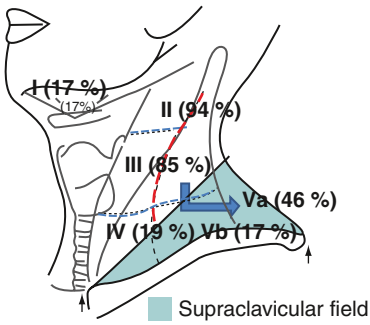


Fig. 5.11 Neck node metastasis ratio for nasopharyngeal cancers

Five-year survival in nasopharyngeal cancer is 35–50%.
Stage I–II → 70–80%, relapse-free survival (RFS) 75–90%
Stage III–IV → 10–40%, RFS ~50%

5.1.1.4 Treatment Algorithm

The treatment algorithm for nasopharyngeal cancers is summarized in Fig. 5.12 [16].

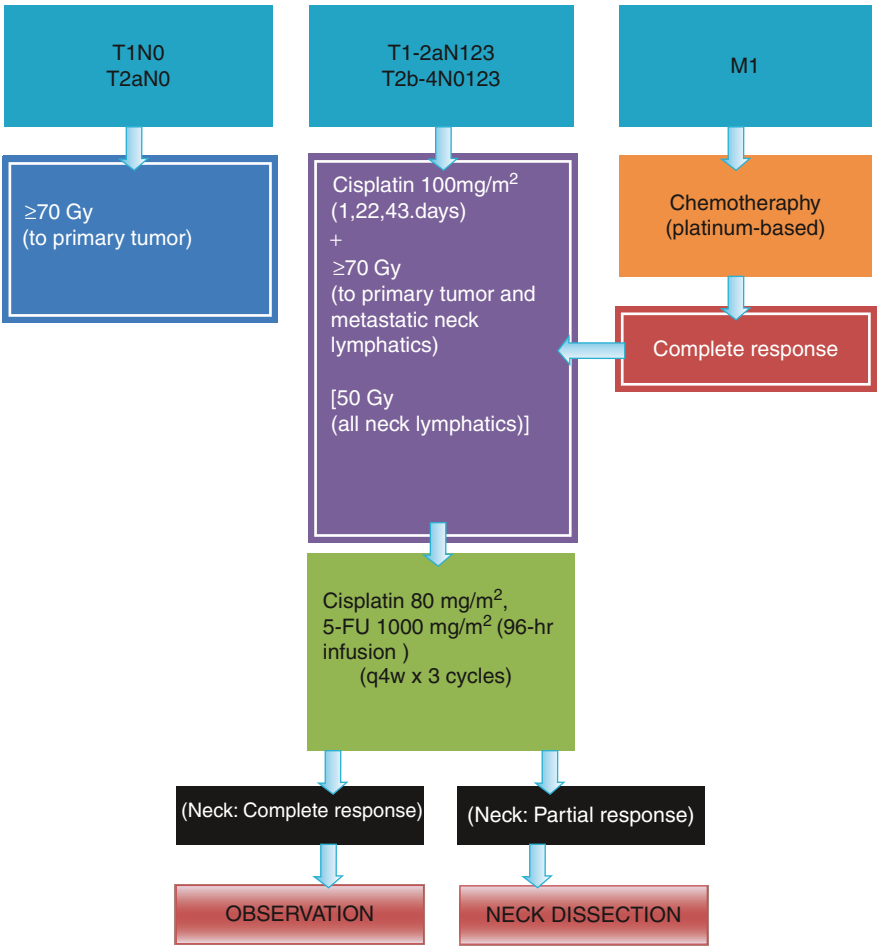


Fig. 5.12 Treatment algorithm for nasopharyngeal cancers [16]

Surgery does not play a major role in the management of nasopharyngeal cancer, except when diagnostic biopsies and neck dissections are performed in certain circumstances.

5.1.1.5 Radiotherapy

Conventional orthogonal irradiation (two lateral fields, one anterior supraclavicular field) (Fig. 5.13).

Borders of lateral fields (primary tumor + upper neck).
Superior: cranial base including sphenoid sinus.
Inferior: true vocal cords (to spare larynx).
Posterior: spinous processes of vertebrae.
Anterior: 2–3 cm margin to tumor including pterygoid plate and posterior one-third of maxillary sinus.

- If supraclavicular LN (+),the upper mediastinal lymph nodes are covered by the anterior field by lowering the inferior border.

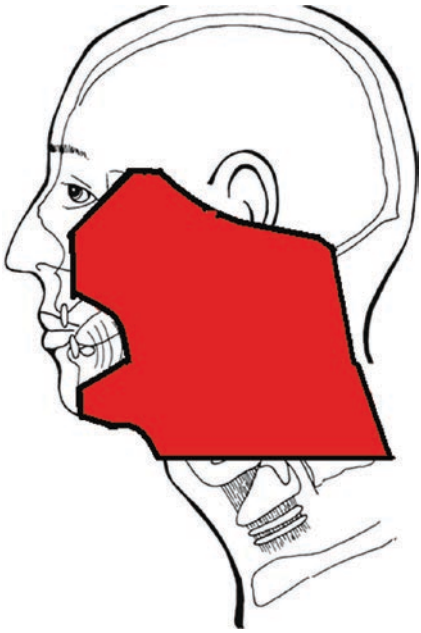


Fig. 5.13 Nasopharyngeal lateral RT field (from [17], p 460, Fig. 18c, reproduced with the permission from Springer Science and Business Media)

Supraclavicular Field (Fig. 5.14). Superior border; inferior border of lateral fields if collimator or couch angle is given to lateral fields. 0.3–0.5 cm gap if no angle is given. Inferior border: bottom of sternoclavicular joint; lateral border: includes two-thirds of the clavicula.

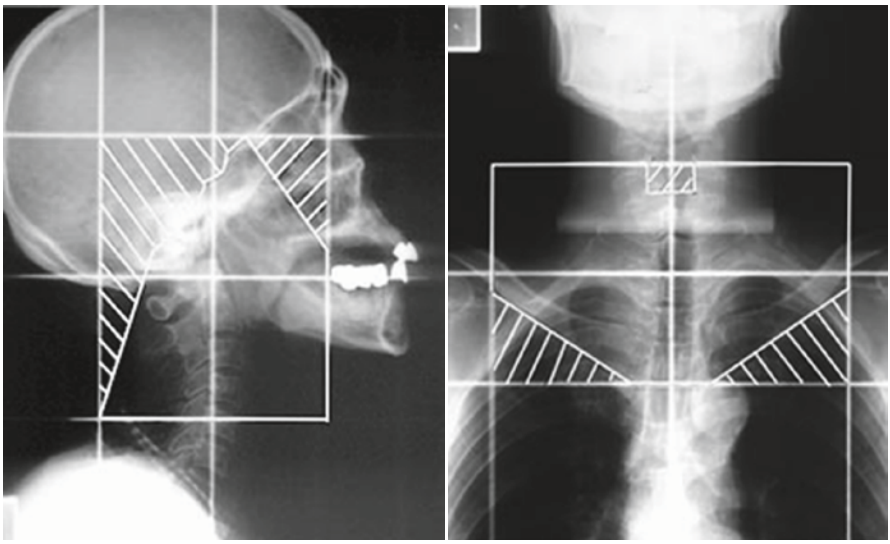


Fig. 5.14 Simulation films for lateral and anterior SCF fields for nasopharyngeal cancer

Conformal RT Fields (Fig. 5.15) [18]

GTV: gross disease.
CTV1: nasopharynx, sphenoid sinus, cavernous sinus, cranial base, anterior half of nasal cavity, posterior third of maxillary sinus, posterior of ethmoid sinus, pterygoid fossa, side and lateral pharyngeal walls at midtonsillar fossa level, and retropharyngeal lymph nodes.
CTV2: elective nodal regions (II, III, IV, V, and supraclavicular lymph nodes).

Radiotherapy Dose

- Parallel opposed fields 2 Gy/day 46 Gy, 6 MeV X-ray or Co-60, then give 50 Gy after sparing spinal cord. Posterior neck dose is completed to 50 Gy with suitable electron energy.
- After 50 Gy, remaining 20 Gy dose is given to (primary tumor + 2 cm) (total dose to primary is 70 Gy).
- Elective neck dose (N0 neck) is 50 Gy.
- Lymph node <3 cm: total lymph dose is 66 Gy.
- Lymph node >6 cm: total lymph dose is 70 Gy.
- Anterior field (supraclavicular field) dose is 50 Gy.

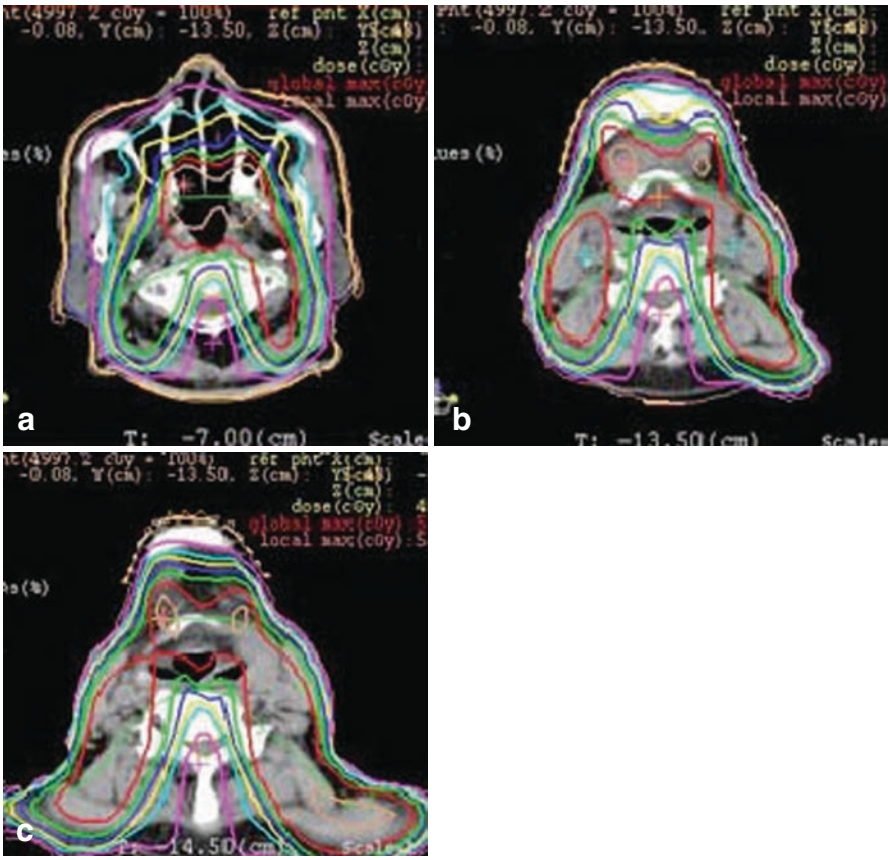


Fig. 5.15 Conformal radiotherapy fields for nasopharyngeal cancer

Table 5.3 TD5/5 doses to critical organs in head and neck radiotherapy

Organ	Single fraction	Conventional fractionation
Brain	15–25	60–70
Lens	2–10	6–12
Skin	15–20	50–60
Spinal cord	8–10	46–50
VCTS	10–20	50–60
Mucosa	5–20	65–77
Peripheral nerve	15–20	65–77

(*continued*)

Table 5.3 (continued)

Organ	Single fraction	Conventional fractionation
Muscle	>30	>70
Bone–cartilage	>30	>70
Thyroid	–	30–40
Optic pathways	8–10	55–60

VCTS vascular connective tissue system
Modified from [54]

Side Effects Related to Radiotherapy (Table 5.3)

Skin → early period: hyperemia, dry desquamation, wet desquamation, and ulceration; late period: telangiectasia, fibrosis, and tissue necrosis.

Hair → alopecia starts after seven days (temporary until 7 Gy, permanent >7 Gy).

Mucosa → erythema, edema, patchy mucositis, and confluent mucositis (mucositis starts after >3 Gy).

Esophagus → early period: retrosternal pain due to esophagitis (10–12 days). This heals in 1–2 weeks. Late effects: muscular and epithelial changes, fibrosis, ulceration, and swallowing difficulty.

Salivary gland → decrease in saliva starts in 24 h, and its viscosity decreases. pH becomes acidic, bicarbonate and IgA levels decrease. If irradiated volume of salivary gland is more than 50%, marked xerostomia is seen.

5.1.1.6 Selected Publications

Radiotherapy alone

RTOG, 1980 → complete response 96% for T1, 88% for T2, 81% for T3, 74% for T4. N (+) → 5-year survival 71–93%.

Marcial VA et al (1980) Split-course radiation therapy of carcinoma of the nasopharynx: results of a national collaborative clinical trial of the Radiation Therapy Oncology Group. Int J Radiat Oncol Biol Phys. 6(4):409–14

Yeh SA et al., 2005 → 849 cases. Five-year survival 59%, 5-year disease-free survival 52%.

Yeh SA et al (2005) Treatment outcomes and late complications of 849 patients with nasopharyngeal carcinoma treated with radiotherapy alone. Int J Radiat Oncol Biol Phys. 62(3):672–9

Altered fractionation

Wang et al., 1989 → nonrandomized. Accelerated hyperfractionation (twice daily). Five-year local control in T1–2 tumors: 89% in hyperfractionation arm, 55% in conventional arm. Five-year local control in T3–4 tumors: 77% in hyperfractionation arm, 45% in conventional arm.

Wang CC (1989) Accelerated hyperfractionation radiation therapy for carcinoma of the nasopharynx. Techniques and results. Cancer. 63(12):2461–7

Chemoradiotherapy

VUMCA I trial—International Nasopharynx Cancer Study Group 1996 → randomized. 339 cases. N2–3 and undifferentiated (WHO II–III) histology (70 Gy RT alone) vs. neoadjuvant three cycles CT + concurrent chemoradiotherapy (BEC in every 3 weeks). Two-year disease-free survival: 60% in chemoradiotherapy arm vs. 40% in RT alone arm. No difference in OS.

International Nasopharynx Cancer Study Group: Vumca I. Trial. Preliminary results of a randomized trial comparing neoadjuvant chemotherapy (cisplatin, epirubicin, bleomycin) plus radiotherapy vs. radiotherapy alone in stage IV (≥N2, M0) undifferentiated nasopharyngeal carcinoma: A positive effect on progression-free survival. Int J Radiat Oncol Biol Phys. 1996 Jun 1;35(3):463–9.

RTOG 88-17/Intergroup 0099 (Al Sarraf et al.) → The most important randomized trial showing the survival benefit of chemoradiotherapy. 147 cases. Median follow-up 2.7 years. Three-year progression-free survival: 69% (RT + cisplatin arm) vs. 24% (RT-alone arm). Three-year overall survival: 78% (chemoradiotherapy arm) vs. 47% (RT-alone arm).

Al-Sarraf M et al (1998) Chemoradiotherapy versus radiotherapy in patients with advanced nasopharyngeal cancer: phase III randomized Intergroup study 0099. J Clin Oncol. 16(4):1310–1317

Meta-analysis 2002 → six trials. 1,528 cases. Chemotherapy was used concurrently in only one trial (Al Sarraf et al.). Chemotherapy: 25–40% increase in disease- or progression-free survival and 20% increase in OS. Significant survival increase was only observed in concomitant chemoradiotherapy.

Huncharek M et al (2002) Combined Chemoradiation Versus Radiation Therapy Alone in Locally Advanced Nasopharyngeal Carcinoma: Results of a Meta-analysis of 1,528 Patients From Six Randomized Trials. Am J Clin Oncol. 25(3):219–223

IMRT

UCSF, 2002 → 67 patients with nasopharyngeal cancer. 65–70 Gy to GTV, 60 Gy to CTV, 50–60 Gy to negative neck RT. 1.8 Gy/fraction CTV and neck; 2.12–2.25 Gy/fraction GTV. CTV = nasopharynx, posterior one-third of nasal cavity and maxillary sinus, retropharyngeal lymph node, clivus, base of cranium, pterygoid fossa, parapharyngeal space, and inferior sphenoid sinus. Median follow-up: 31 months.

- One local recurrence at the primary site. One patient failed in the neck. Seventeen patients developed distant metastases; five of these patients have died.
- Four-year local progression-free, locoregional progression-free, and distant metastasis-free rates were 97, 98, and 66%, respectively. The 4-year estimate for overall survival was 88%.
- Excellent locoregional control for NPC was achieved with IMRT.

Lee N et al (2002) Intensity-modulated radiotherapy in the treatment of nasopharyngeal carcinoma: an update of the UCSF experience. Int J Radiat Oncol Biol Phys. 53(1):12–22

Hong Kong, 2007 → randomized. 60 cases of T1–2bN0 nasopharyngeal cancer. IMRT 66 Gy (CTV = GTV + 1 cm; PTV = CTV + 3 mm)/lower neck LN (+) 66 Gy, LN (−) 54–60 Gy/intracavitary brachytherapy boost vs. 66 Gy conventional RT + intracavitary brachytherapy boost. Serious xerostomia: IMRT 39% vs. 2D-RT 82%. No difference in the feeling of xerostomia.

Wu SX et al Outcome of Fractionated Stereotactic Radiotherapy for 90 Patients With Locally Persistent and Recurrent Nasopharyngeal Carcinoma. Int J Radiat Oncol Biol Phys 69(3): 761–769

Reirradiation

Guangzhou et al. 2007 → retrospective. 90 cases [persistent ($n=34$) or recurrent ($n=56$)] of stereotaxic RT. Three-year progression-free survival: 55%. Late complications: 19%; fatal hemorrhage: two cases. Stereotaxic RT is more efficient and safe than stereotaxic radiosurgery.

5.1.2 Oropharyngeal Cancer

The oropharynx starts from the soft palate and extends to the superior portion of the epiglottis (Fig. 5.16) [19].

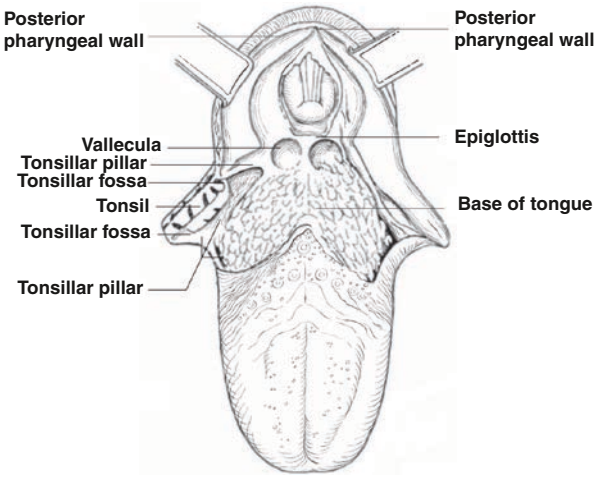


Fig. 5.16 Normal anatomical structures of the oropharynx (from [11], reproduced with the permission from the American Joint Committee on Cancer)

Normal anatomical structures of the oropharynx (Fig. 5.17) [19]:
Anterior: oral cavity
Anterior–superior: front side of soft palate
Mid-anterior: isthmus faucium and oral cavity
Lower-anterior: base of tongue and vallecula
Lateral: palatine tonsils
Posterior: posterior pharyngeal wall and prevertebral fascia of C2–3 vertebrae
Regions of the oropharynx in which malignancies may develop [19]:
Posterior one-third of tongue (base of tongue)
Lingual site of epiglottis, vallecula
Soft palate and uvula
Tonsils and tonsil plicae
Mucosa of posterior oropharyngeal wall

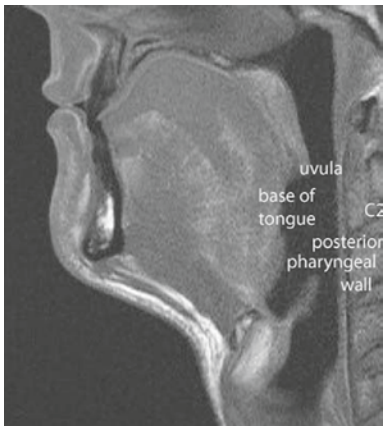


Fig. 5.17 Normal anatomical structures of the oropharynx

5.1.2.1 Pathology

Most oropharyngeal tumors are squamous cell cancers, although other types like lymphoma and minor salivary glands may also be observed.

Squamous cell cancer: 75%
Lymphoma: 15%
Lymphoepithelioma: 5%
Others: 5% (minor salivary gland cancer, sarcoma)

Squamous cell cancer is particularly seen in older men. However, the male/female ratio has decreased to 4:1. Smoking with the use of alcohol leads to a very high risk for oropharyngeal cancers [20].

5.1.2.2 General Presentation

The first symptom is usually unilateral, progressive otalgia, and dysphagia with throat discomfort. Most patients have a feeling of a mass in throat posteriorly. Lymph node metastasis at presentation is frequent. Thus, neck mass may be the first symptom at presentation. The risk of bilateral neck node metastases is very high, especially in base of tongue cancers. In more advanced cases, dysfunctions in swallowing and speaking abilities, oral fetor, bleeding, hemoptysis, fixed tongue, trismus, and weight loss may be seen. The tumor is usually ulcerated in a routine physical exam, and unilateral tonsil enlargement may be observed. Therefore, unilateral tonsil hypertrophy in older patients should be examined for possible malignancy.

Indirect laryngoscopy with a mirror should be performed to see the base of the tongue and vallecula. A tumor in this region may easily invade the surrounding soft tissues and present at more advanced stages. However, the actual size of the tumor is determined by bimanual palpation and advanced imaging modalities (MRI, CT). Mandibular invasion is

also detected via radiological techniques. The risk of distant metastasis is a bit higher than that for the oral cavity. Furthermore, the presence of a secondary malignancy or later development in the upper or lower airways is also higher. Thus, the patient should be evaluated and followed up for this possibility. The final and exact diagnosis is made via biopsy.

Etiology → cigarette smoking, alcohol, chronic irritation, and HPV 16 [21]

5.1.2.3 Staging

Primary Tumor (T) (Fig. 5.18) [14]

T1: Tumor 2 cm or smaller in greatest dimension
T2: Tumor larger than 2 cm but 4 cm or smaller in greatest dimension
T3: Tumor larger than 4 cm in greatest dimension or extension to lingual surface of epiglottis
T4a: Moderately advanced local disease: Tumor invades the larynx, deep/extrinsic muscle of tongue, medial pterygoid, hard palate, or mandible
T4b: Very advanced local disease: Tumor invades lateral pterygoid muscle, pterygoid plates, lateral nasopharynx, or skull base or encases carotid artery

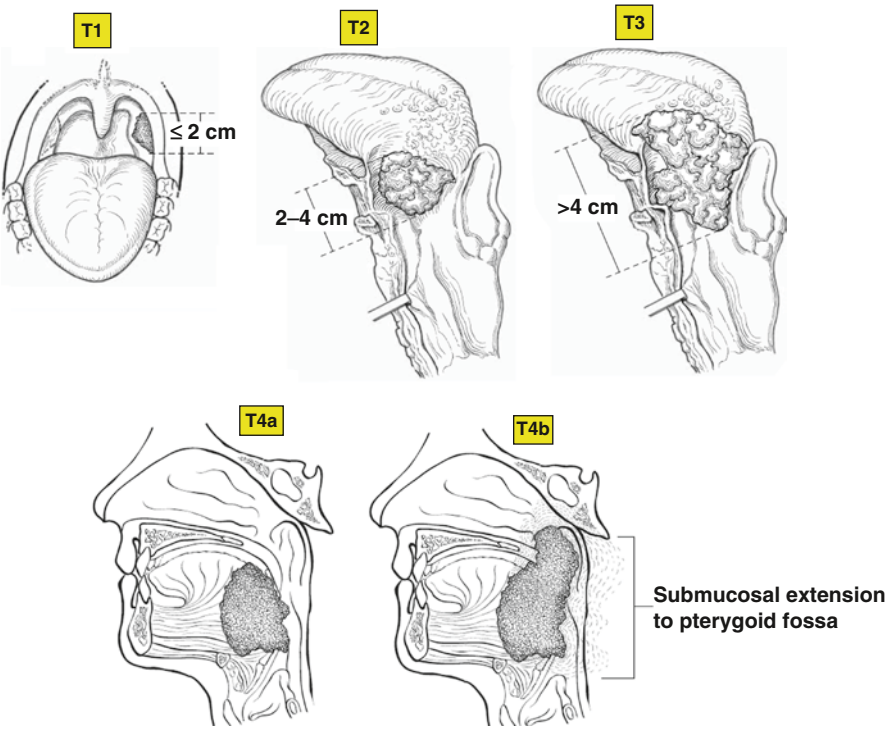


Fig. 5.18 T staging in oropharyngeal cancer (from [11], reproduced with the permission from the American Joint Committee on Cancer)

AJCC stage groups
Stage 0: TisN0M0
Stage I: T1N0M0
Stage II: T2N0M0
Stage III: T3N0M0, T1N1M0, T2N1M0, T3N1M0
Stage IVA: T4aN0M0, T4aN1M0, T1N2M0, T2N2M0, T3N2M0, T4aN2M0
Stage IVB: T4b, any N, M0; any T, N3M0
Stage IVC: any T, any N, M1

5.1.2.4 Treatment Algorithm

Treatment Algorithm for Oropharyngeal Cancer [16]

T1,2–N0,1 → three alternative approaches:
Definitive radiotherapy
In case of residual disease after RT → salvage surgery
Primary tumor excision + uni/bilateral neck dissection
One lymph node (+), poor prognostic factor (−) → RT
Poor prognostic factor (+):
One or two major risk factors or ≥2 minor risk factors (+) → chemoradiotherapy
Less than two minor risk factors (+) → RT
T1–2 N1 tumors → RT + CT
In case of residual disease after RT → salvage surgery
T3,4a– N0 → three alternative approaches
Concurrent chemoradiotherapy
In case of residual disease after RT → salvage surgery
Primary tumor excision + uni/bilateral neck dissection
WPoor prognostic factor (+)
One or two major risk factors or ≥2 minor risk factors (+) → chemoradiotherapy
Less than two minor risk factors (+) → RT
Induction chemotherapy followed by chemoradiotherapy
In case of residual disease after RT → salvage surgery
T3,4a– N or any T and N2,3 → three alternative approaches
Concurrent chemoradiotherapy
Complete response in primary after chemo-RT → neck dissection
Residual disease in primary after chemo-RT
Salvage surgery + neck dissection

(*continued*)

(continued)

Residual disease in neck after chemo-RT
N1 → surveillance
N2, N3 → surveillance or neck dissection
Induction chemotherapy followed by chemoradiotherapy
Complete response in primary after chemo-RT → neck dissection
Residual disease in primary after chemo-RT
Salvage surgery + neck dissection
Residual disease in neck after chemo-RT
N1→ surveillance
N2, N3 → surveillance or neck dissection
Primary tumor excision + uni/bilateral neck dissection
N1, N2a, N2b, N2c. N3 → RT and/or CT

Poor prognostic factors

- *Major risk factors* (postoperative chemo-RT indications):
  Surgical margin positivity and/or extracapsular nodal extension
- *Minor risk factors* (postoperative RT alone indications):
  pT3, pT4
  N2, N3
  IV and V lymphatic involvement
  Vascular embolism

5.1.2.5 Radiotherapy

Conventional Orthogonal Radiotherapy Fields (Fig. 5.19)

Two parallel–opposed lateral fields and supraclavicular anterior field
Borders of lateral fields (primary tumor + upper neck) (Fig. 5.20)
Superior: cranial base
Inferior: whole neck by pulling shoulders as far down as possible
Posterior: spinous processes of vertebrae
Anterior: 2–3 cm margin to tumor

- Anterior and superior borders should be modified by the clinician according to tumor localization (e.g., base of tongue, tonsil, vallecula) and tumor size.

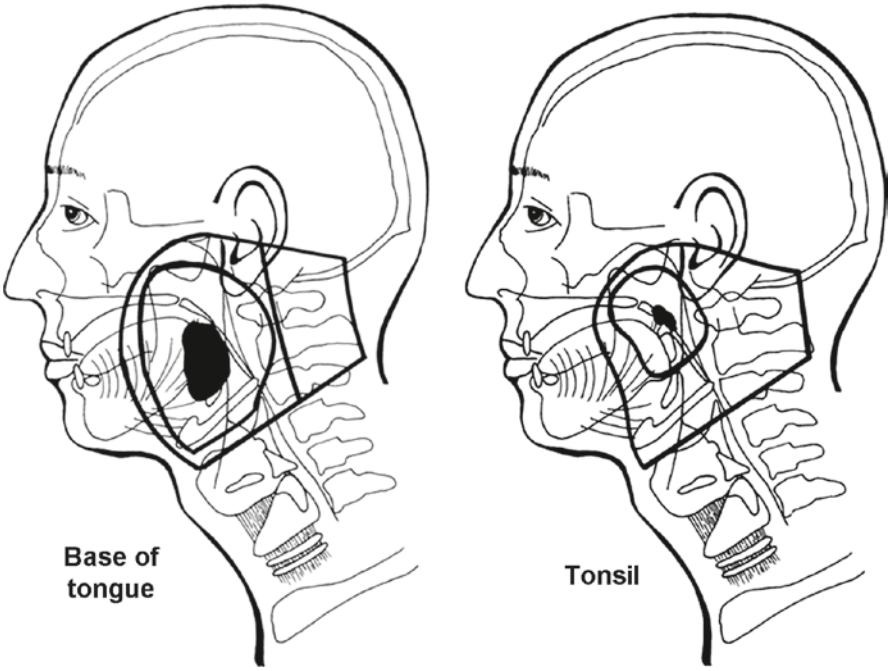


Fig. 5.19 Lateral RT fields for oropharyngeal cancer (from [17], p 459, 460, Figs. 18.6, 18.7, reproduced with the permission from Springer Science and Business Media)

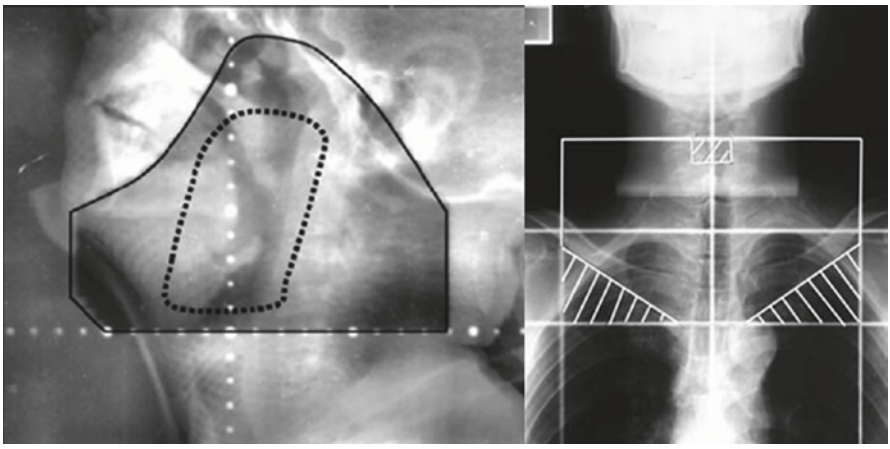


Fig. 5.20 Conventional RT films for oropharyngeal cancer

Dose

Parallel–opposed fields until 46 Gy in 2 Gy/day by 6 MeV X-rays or Co-60. Then 4 Gy with spinal cord sparing. Four grays to protected posterior neck using adequate electron energies.

- After 50 Gy (primary tumor + 2 cm), 66–72 Gy.
- If N (−), elective neck dose is 50 Gy.
- Lymph node <3 cm, 60 Gy.
- Lymph node >6 cm, 66–72 Gy.

5.1.2.6 Selected Publications

See also Sect. 5.8

Base of tongue

MDACC, 2004 → retrospective. 299 cases. T1–T2 oropharyngeal tumor, stage III–IV. RT alone. Median follow-up: 82 months. Five-year local relapse 15%, OS 64%. Locoregional control 95% for T1, 79% for T2.

Garden AS et al (2004) Is concurrent chemoradiation the treatment of choice for all patients with Stage III or IV head and neck carcinoma? Cancer. 100(6):1171–1178

Interstitial brachytherapy

Mass General Hospital, 2005 → 40 cases. Primary or recurrent base of tongue. 54% T3/T4 tumor. Median implant dose 17.4 and 61 Gy external RT (equivalent total dose 80 Gy). Five-year OS: 62%. Local control: 78%. Ten-year local control: 70%. Organ preservation rate: 78%. Grade III osteoradionecrosis in two patients (2%).

Foote RL et al (1990) Is interstitial implantation essential for successful radiotherapeutic treatment of base of tongue carcinoma? Int J Radiat Oncol Biol Phys. 18(6): 1293–8

Neck control

MSKCC, 1997 → 68 base of tongue tumors. 54 Gy external RT + 20–30 Gy interstitial implant. 50 Gy neck RT (clinically (+) lymph nodes 60 Gy). Neck dissection if palpable lymph node after RT. Five-year neck control 95%, 10-year neck control 86%. Grade III fibrosis (−).

Lee HJ et al (1997) Long-term regional control after radiation therapy and neck dissection for base of tongue carcinoma. Int J Radiat Oncol Biol Phys. 38(5):995–1000

Tonsil

University of Florida, 2000 → retrospective. 400 cases. T1–T4, N0–N3, tonsil cancer. RT alone. Minimum 2 years of follow-up. Five-year local control: 83% in T1, 81% in T2, 74% in T3, 60% in T4. Local relapse in 83 cases; 36 had salvage surgery and 17 were salvaged (nearly 50%). Grade III–IV toxicity (−). Local control was similar to surgery, and had lower rate of fatal complications than surgery.

Mendenhall WM eta al (2000) Radiation Therapy for Squamous Cell Carcinoma of the Tonsillar Region: A Preferred Alternative to Surgery? J Clin Oncol. (11):2219–25

Ipsilateral RT

Princess Margaret, 2001 → retrospective. 228 cases. Ipsilateral RT only. T1–2 N0 tumors. Recurrence in contralateral neck was 3.5%. Conclusion: ipsilateral neck RT is feasible in selected cases with unilateral tonsil cancer.

Int J Radiat Oncol Biol Phys 2001; 51(2):332–343

Hyperfractionation

EORTC 22791 → 356 cases. T2–3, N0–1 oropharyngeal cancers except base of tongue. Tumor size <3 cm. 70 Gy/7–8 weeks vs. 80.5 Gy hyperfractionated 7 weeks (1.15 Gy BID). Increase in local control of T3 tumors receiving hyperfractionated schedule. No increase in local control of T2 tumors. There was a trend for increased OS.

Horiot HJ et al (1992) Hyperfractionation versus conventional fractionation in oropharyngeal carcinoma: final analysis of a randomized trial of the EORTC cooperative group of radiotherapy. Radiother Oncol. 25(4):231–241

IMRT

Washington University, 2004 → 74 oropharyngeal cancer patients treated with IMRT. 31 patients received definitive IMRT; 17 also received platinum-based chemotherapy. 43 patients received combined surgery and postoperative IMRT. Median follow-up for all patients was 33 months.

- Ten locoregional failures were observed. Six patients died of the disease and three died of concurrent disease. Distant metastasis developed in six patients.
- Four-year estimate of overall survival was 87%, and the 4-year estimate of disease-free survival was 81% (66% in the definitive vs. 92% in the postoperative RT group).
- Four-year estimate of locoregional control was 87% (78% in the definitive vs. 95% in the postoperative RT group); the 4-year estimate of distant metastasis-free survival was 90% (84% in the definitive vs. 94% in the postoperative group).
- Multivariate analysis showed that GTV and nGTV were independent risk factors determining locoregional control and disease-free survival for definitive oropharyngeal IMRT patients.
- IMRT was found to be an effective treatment modality for locally advanced oropharyngeal carcinoma.

Chao KS, Ozyigit G, Blanco AI et al (2004) Intensity-modulated radiation therapy for oropharyngeal carcinoma: impact of tumor volume. Int J Radiat Oncol Biol Phys 59(1):43–50

5.1.3 Hypopharyngeal Cancer

The hypopharynx is located between the epiglottis and the bottom of the cricoid cartilage (cricopharyngeal sphincter) (Fig. 5.21) [10].

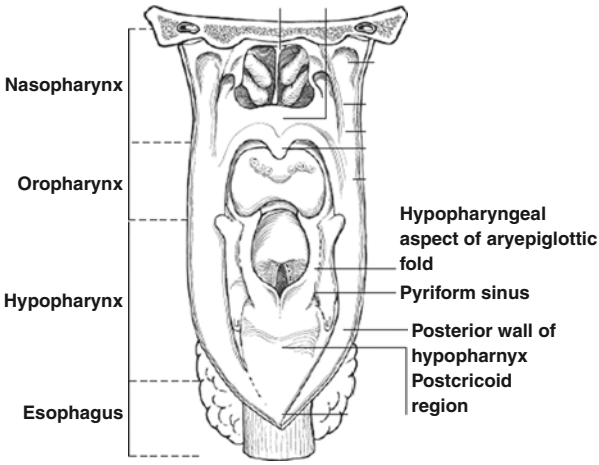


Fig. 5.21 Hypopharynx, oropharynx and nasopharynx (from [11], reproduced with the permission from American Joint Committee on Cancer)

Normal Anatomical Structures of the Hypopharynx (Fig. 5.22) [10]

Anterior–superior: laryngeal entrance (aditus ad laryngeum), aryepiglottic folds, and arytenoids
Anterior–inferior: postcricoid region
Posterior: prevertebral fascia of C3–6 vertebrae
Lateral: pyriform sinuses (food is transferred into the esophagus from these sinuses)
Inferior: cervical esophagus

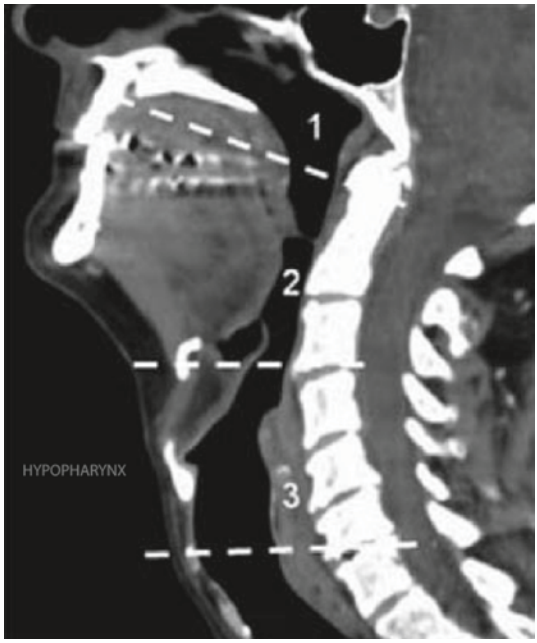


Fig. 5.22 Hypopharyngeal anatomy

5.1.3.1 Pathology

Almost all hypopharyngeal malignancies are squamous cell cancers, and the most frequent is the poorly differentiated type.

The frequencies of all hypopharyngeal cancers according to subsite:
Pyriform sinuses: 60%
Postcricoid region: 30%
Posterior wall: 10%

5.1.3.2 General Presentation

Primary hypopharyngeal cancer, particularly pyriform sinus cancer, frequently metastasizes to neck lymph nodes. Postcricoid region tumors frequently bilaterally invade neck nodes as well as mediastinal and paratracheal lymphatics.

The major clinical findings in hypopharyngeal neoplasms are otalgia, palpable neck nodes, dysphagia, dysphonia, and weight loss.

Actual dysphagia is a late finding where the tumor has become very advanced until it obstructs the upper airway and digestive passages. The first signs are usually odynophagia (pain and discomfort during swallowing) and an irritating feeling during the movement of nutrition from the pharyngoesophagus. Dysphagia is usually severe at presentation and almost always associated with weight loss. Reflective pain (otalgia) in the ear is common. Dysphonia is due to either the direct invasion of the larynx or vocal cord paralysis as a result of recurrent laryngeal nerve involvement, and dyspnea may also be seen. Fetor oris (foul smelling breath) and hemoptysis may also be observed. Aspiration of nutrition (particularly liquids) and related aspiration pneumonia may be seen, resulting from an obstruction at the level of the hypopharynx.

Unfortunately, most cases are at an advanced stage at presentation. The risk of distant metastasis is approximately 10%, and the most frequent sites are lung, bone and liver, respectively.

- Posterior pharyngeal wall tumors usually drain into level II, III and IV neck nodes [9].
- Surgical findings also show that they frequently drain into the retropharyngeal lymph nodes (Rouviere's lymph nodes).

5.1.3.3 Staging

Primary tumor (T) (Fig. 5.23) [14].

T1: Tumor limited to one subsite* of the hypopharynx and 2 cm or less in greatest dimension

T2: Tumor invades more than one subsite* of the hypopharynx or an adjacent site, or measures more than 2 cm but 4 cm or less in greatest diameter without fixation of hemilarynx

T3: Tumor measures more than 4 cm in greatest dimension or with fixation of hemilarynx or extension to esophagus

T4a: Moderately advanced local disease: Tumor invades thyroid/cricoid cartilage, hyoid bone, thyroid gland, or central compartment soft tissue, which includes prelaryngeal strap muscles and subcutaneous fat

T4b: Very advanced local disease: Tumor invades prevertebral fascia, encases carotid artery, or involves mediastinal structures

**Subsites of the hypopharynx are as follows*:

Pharyngoesophageal junction (i.e., the postcricoid area), extending from the level of the arytenoid cartilages and connecting folds to the inferior border of the cricoid cartilage.

Pyriform sinus, extending from the pharyngoepiglottic fold to the upper end of the esophagus, bounded laterally by the thyroid cartilage and medially by the surface of the aryepiglottic fold and the arytenoid and cricoid cartilages.

Posterior pharyngeal wall, extending from the level of the floor of the vallecula to the level of the cricoarytenoid joints.

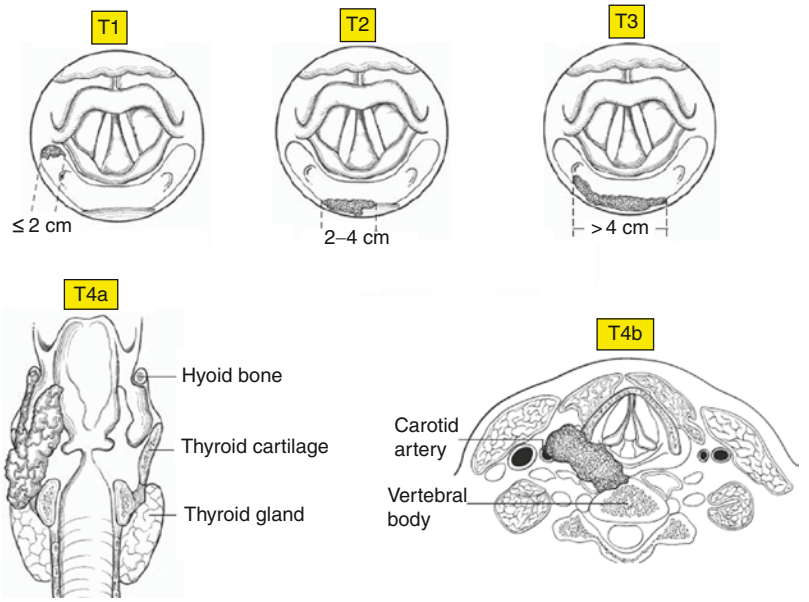


Fig. 5.23 T staging in hypopharyngeal cancer (from [11], reproduced with the permission from the American Joint Committee on Cancer)

5.1.3.4 Treatment Algorithm

Treatment Algorithm for Hypopharyngeal Cancer [16]

T1 N0–1; T2N0 → total laryngectomy is not always required.
Definitive radiotherapy
Residual disease after RT → salvage surgery ± neck dissection
Residual disease in neck after RT → surveillance
Surgery (partial laryngectomy + ipsilateral/bilateral neck dissection)
Poor prognostic factor after surgery (+)
One or two major risk factor(s) or ≥2 minor risk factors (+) → chemoradiotherapy
Less than two minor risk factors (+) → RT
T1N2, T2–3 any N → total laryngectomy may be required.
Induction chemotherapy *(two cycles of neoadjuvant chemotherapy)*
Complete response in primary → definitive RT
Residual disease in primary after RT → neck dissection
Neck node residual after RT
N1 → surveillance
N2, N3 → surveillance or neck dissection
Partial response in primary after induction (endoscopy (+))
One more cycle of chemotherapy is added
Complete response in primary after treatment → definitive RT
Residual disease in primary after RT → neck dissection
Neck node residual after RT
N1 → surveillance
N2, N3 → surveillance or neck dissection
Partial response in primary after treatment → salvage surgery
Poor prognostic factor after surgery (−) → RT
Poor prognostic factor after surgery (+)
One or two major risk factor(s) or ≥2 minor risk factors (+) → chemoradiotherapy
Less than two minor risk factors (+) → RT
No response in primary after induction → surgery
Poor prognostic factor after surgery (−) → RT
Poor prognostic factor after surgery (+)
One or two major risk factors or ≥2 minor risk factors (+) → chemoradiotherapy
Less than two minor risk factors (+) → RT
Laryngopharyngectomy uni/bilateral neck dissection
Poor prognostic factor after surgery (−) → RT
Poor prognostic factor after surgery (+)
One or two major risk factor(s) or ≥2 minor risk factors (+) → chemoradiotherapy
Less than two minor risk factors (+) → RT
Concurrent chemoradiotherapy
Residual disease in primary after treatment

(*continued*)

(continued)

Salvage surgery + neck dissection
Residual disease in neck after treatment
N1 → surveillance
N2, N3 → surveillance or neck dissection
T4a, any N →
Surgery + bilateral neck dissection
After surgery → RT and/or chemotherapy
Concurrent chemoradiotherapy
Residual disease in primary after treatment
Salvage surgery + neck dissection
Residual disease in neck after treatment
N1 → surveillance
N2, N3 → surveillance or neck dissection

Poor prognostic factors

- *Major risk factors:*
  Positive surgical margin and/or extracapsular nodal involvement
- *Minor risk factors:*
  pT3, pT4
  N2, N3
  Level IV and V lymph node involvement
  Vascular embolism

5.1.3.5 Radiotherapy

Conventional Orthogonal RT Fields

Two parallel–opposed lateral fields and supraclavicular anterior field (Fig. 5.24)
Borders of lateral fields (primary tumor + upper neck)

Superior: mastoids and cranial base, including retropharyngeal lymph nodes
Inferior: whole neck, by pulling shoulders down as much as possible (at least 1 cm below tumor)
Posterior: spinous processes of vertebrae
Anterior: 2–3 cm anterior to tumor (Ia and Ib lymphatics are left outside if not involved)

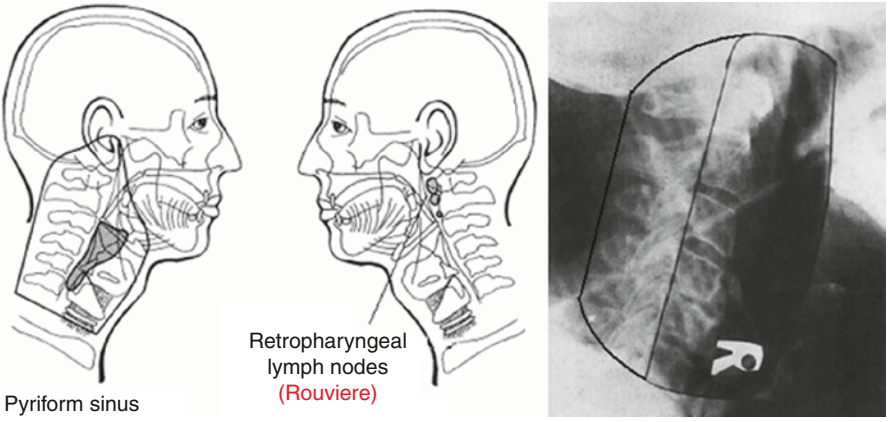


Fig. 5.24 Conventional RT fields for hypopharyngeal cancer (from [17], pp 457–458, Figs. 18.3, 18.4, reproduced with the permission from Springer Science and Business Media)

Conformal RT Fields (Fig. 5.25) [18]

CTV1: GTV + 1–2 cm and involved lymph nodes
CTV2: elective nodal regions (determined individually by clinician)

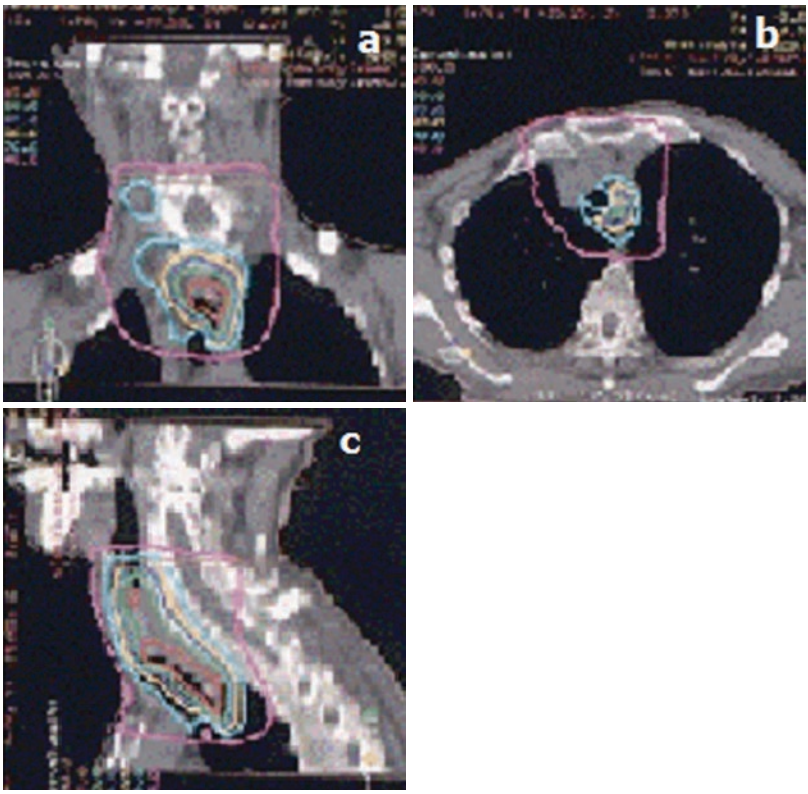


Fig. 5.25 Conformal RT fields

Radiation Dose

- Parallel opposed fields until 46 Gy in 2 Gy/day by 6 MeV X-rays or Co-60. Then 4 Gy with spinal cord sparing. Four grays to protected posterior neck using adequate electron energies.
- After 50 Gy, (primary tumor + 2 cm) 66–72 Gy.
- If N (−), elective neck dose is 50 Gy.
- Lymph node <3 cm, 60 Gy.
- Lymph node >6 cm, 66–72 Gy.
- Anterior supraclavicular field: 46 Gy if not involved.
- Postoperative (adjuvant) total dose 60 Gy (if surgical margin (+), 66 Gy.

5.1.3.6 Selected Publications

See Sect. 5.8

5.2 Laryngeal Cancer

The larynx is located between the tip of the thyroid (bottom of the C3 vertebral corpus) and the bottom of the cricoid cartilages (C6 vertebra) [22].

The larynx is divided into three compartments (Fig. 5.26) [22]:

Supraglottic region. Section above the vocal cords. This region includes epiglottis, aryepiglottic plica, arythenoids, ventricular bands (false vocal cords), and laryngeal ventricles.

Glottic region. Region of the vocal cords. It includes the vocal cords, rima glottidis, anterior, and posterior commissure. The vocal cords consist of the vocal ligaments, vocalis muscle, and mucosal layers. The vocal cords are 1.7 cm long in females and 2–2.4 cm long in males.

Subglottic region. This is the region inferior to the vocal cords until the first tracheal ring.

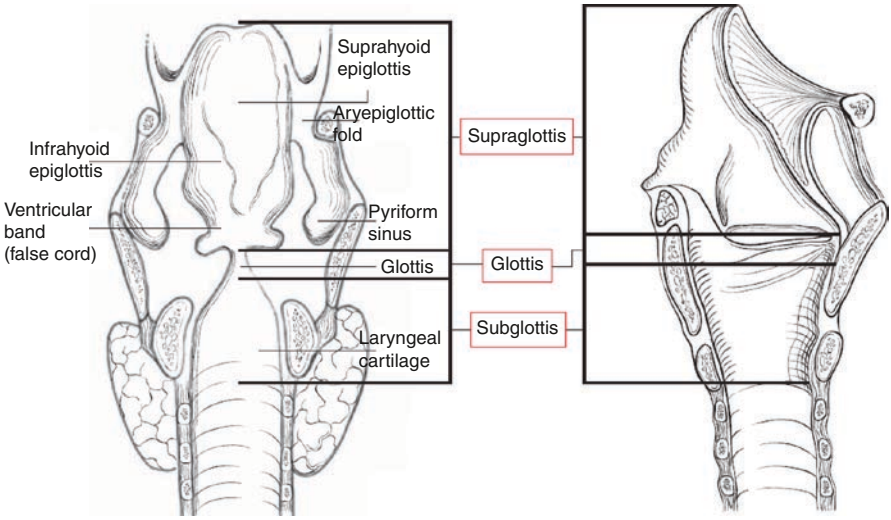


Fig. 5.26 Anatomy of the larynx (from [11], reproduced with the permission from the American Joint Committee on Cancer)

5.2.1 Pathology

Most (95–96%) malignant tumors of the larynx are squamous cell cancers of epithelial origin. Other malignancies, such as verrucous, basocellular and fusiform cell carcinomas, adenocarcinoma, adenoid cystic carcinoma, and mesenchymal malignancies such as sarcomas, are very rare [23].

The incidence of synchronous carcinoma in a patient with laryngeal cancer is approximately 1%. The probability of a metachronous primary tumor is 5–10% [24].

- Laryngeal cancer is the most frequent tumor seen together with another type of malignancy.

5.2.2 General Presentation

Hoarseness. This is the most common sign, particularly glottic lesions. Laryngeal cancer should be ruled out if the hoarseness lasts for more than 2 weeks with a detailed ENT exam.

Dysphagia (difficulty swallowing). This is more common in supraglottic cancers.

Dyspnea and stridor. This symptom is seen when the tumor mass in the larynx obstructs the airway. Supraglottic tumors must be larger than glottic and subglottic tumors to narrow the airways.

Otalgia (ear pain). This is a referred pain that is particularly seen in supraglottic cancers via Arnold's nerve, a branch of the vagus nerve.

Cough. This is observed in cases with involvement of the superior laryngeal nerve (sensory nerve of the larynx), causing swallowing dysfunctions and sensory disorders. Hemoptysis associated with cough may be observed in ulcerated tumors.

Neck mass. Swelling or skin invasion seen in the laryngeal region or the bottom of the hyoid is a sign of advanced disease, since it shows that the tumor has invaded the thyroid cartilage and thyrohyoid membranous barrier. A mass combined with the larynx at the front of the neck may be palpated. Sometimes lymph node metastasis (delphian node) in the front of the larynx at the level of the cricothyroid or thyrohyoid membranes may be observed as an anterior mass. Neck masses palpated at lateral sites are a sign of neck metastases.

5.2.3 Staging

Supraglottis (Fig. 5.27) [14]

T1: Tumor limited to one subsite* of supraglottis with normal vocal cord mobility
T2: Tumor invades mucosa of more than one adjacent subsite* of supraglottis or glottis or region outside the supraglottis (e.g., mucosa of base of tongue, vallecula, or medial wall of pyriform sinus) without fixation of the larynx
T3: Tumor limited to larynx with vocal cord fixation and/or invades any of the following: postcricoid area, pre-epiglottic tissues, paraglottic space, and/or minor thyroid cartilage erosion (e.g., inner cortex)
T4a: Moderately advanced local disease: Tumor invades through the thyroid cartilage, and/or invades tissues beyond the larynx (e.g., trachea, soft tissues of the neck including deep extrinsic muscle of the tongue, strap muscles, thyroid, or esophagus)

T4b: Very advanced local disease: Tumor invades prevertebral space, encases carotid artery, or invades mediastinal structures
Subsites include the following: Ventricular bands (false cords), Arytenoids, Suprahyoid epiglottis, Infrahyoid epiglottis, Aryepiglottic folds (laryngeal aspect)

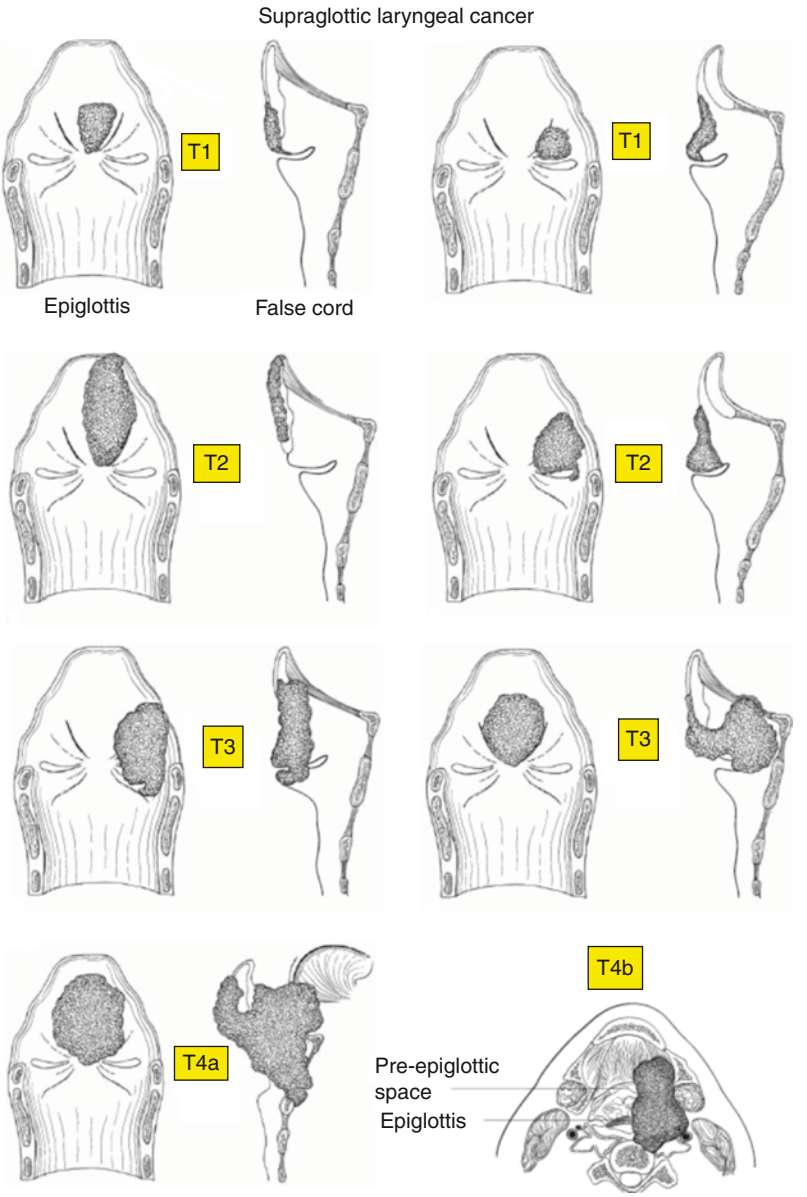


Fig. 5.27 T staging for supraglottic laryngeal cancer (from [11], reproduced with the permission from the American Joint Committee on Cancer)

Glottis (Fig. 5.28) [14]

T1: Tumor limited to the vocal cord(s), which may involve anterior or posterior commissure, with normal mobility
T1a: Tumor limited to one vocal cord
T1b: Tumor involves both vocal cords
T2: Tumor extends to supraglottis and/or subglottis and/or with impaired vocal cord mobility
T3: Tumor limited to the larynx with vocal cord fixation and/or invades paraglottic space, and/or minor thyroid cartilage erosion (e.g., inner cortex)
T4a: Moderately Advanced Disease: (Midline nodes are considered ipsilateral nodes) Tumor invades through the thyroid cartilage and/or invades tissues beyond the larynx (e.g., trachea, soft tissues of neck, including deep extrinsic muscle of the tongue, strap muscles, thyroid, or esophagus)
T4b: Very Advanced Local Disease: Tumor invades prevertebral space, encases carotid artery, or invades mediastinal structures

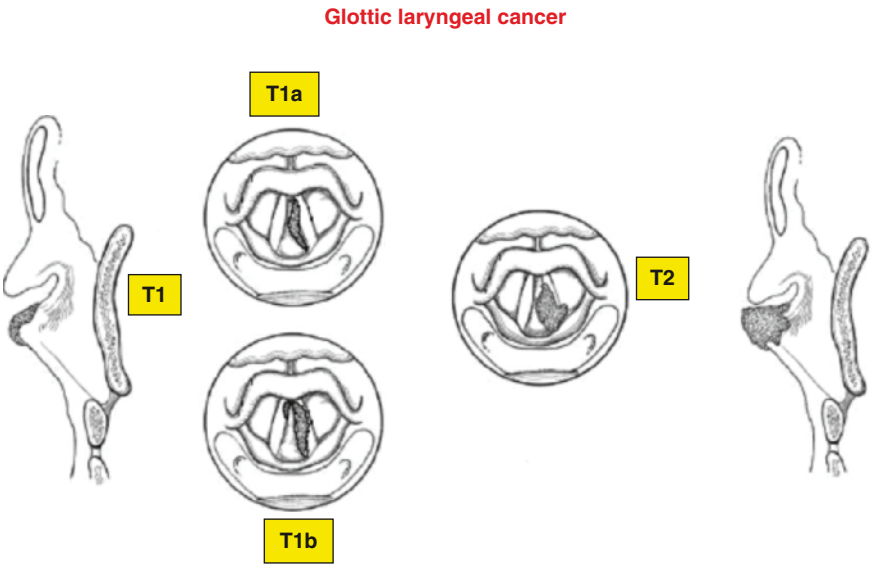


Fig. 5.28 T staging for glottic laryngeal cancer (from [11], reproduced with the permission from the American Joint Committee on Cancer)

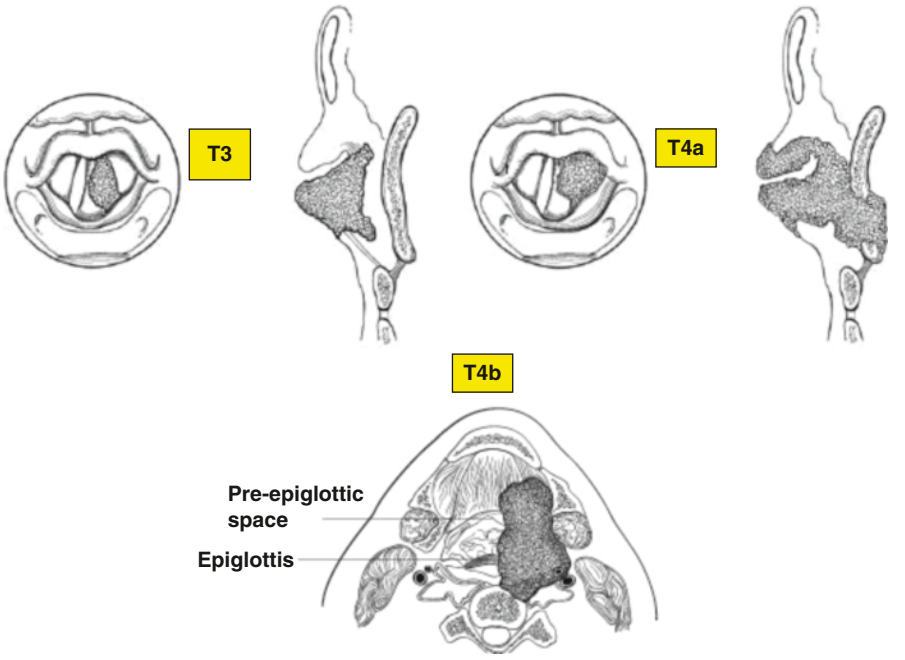


Fig. 5.28 (continued)

Subglottis (Fig. 5.29) [14]

T1: Tumor limited to the subglottis
T2: Tumor extends to vocal cord(s) with normal or impaired mobility
T3: Tumor limited to larynx with vocal cord fixation
T4a: Moderately Advanced Local Disease: Tumor invades cricoid or thyroid cartilage and/or invades tissues beyond the larynx (e.g., trachea, soft tissues of neck, including deep extrinsic muscles of the tongue, strap muscles, thyroid, or esophagus)
T4b: Very Advanced Local Disease: Tumor invades prevertebral space, encases carotid artery, or invades mediastinal structures

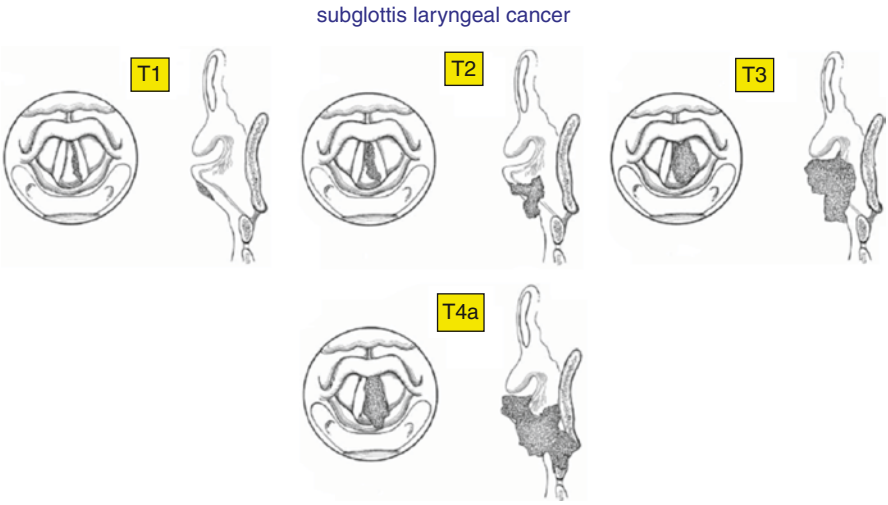


Fig. 5.29 T staging for subglottic laryngeal cancer (from [11], reproduced with the permission from the American Joint Committee on Cancer)

Supraglottic larnyngeal cancer generally metastasizes to level II, III and IV cervical lymph nodes [25]

Clinical lymph node positivity: 55%

Bilaterality: 16%

The true vocal cords have no lymphatics, so lymphatic involvement is observed in the presence of supraglottic or subglottic tumor extension.

Lymph node involvement in glottic cancers:

- T1: <2%
- T2: 5%
- T3: 15–20%
- T4: 20–40%

5.2.4 Treatment Algorithm

Treatment Algorithm for Laryngeal Cancer [26]

Tis
Endoscopic excision (stripping, laser) or definitive RT
T1–2, N0
Glottic definitive RT, or
Surgery (cordectomy, partial laryngectomy ± selective neck dissection)

T1–2, N0 supraglottic
Definitive RT, or
Surgery (partial laryngectomy ± selective neck dissection)
Resectable T1–2, N (+); T3N0; T3N (+)
Concurrent chemoradiotherapy
Complete response in primary → surveillance
Residual in primary (+) → salvage surgery + neck dissection
Or surgery
N0–1 → laryngectomy + bilateral/ipsilateral neck dissection
N2–3 → laryngectomy + extended neck dissection
Resectable T4N0/(+)
Surgery

N0–1 → total laryngectomy + bilateral/ipsilateral neck dissection
N2–3 → total laryngectomy + extended neck dissection

Unresectable T4–N0/(+)
Concurrent chemoradiotherapy or definitive RT

Postoperative chemoradiotherapy indications
Surgical margin (+)
Extranodal capsular extension
Postoperative RT or chemoradiotherapy indications
Surgical margin (−)
Perineural invasion (+)
Lymphovascular space involvement (+)
Multiple lymph node involvement (+)
Less than or equal to 1 cm subglottic extension
T3–4 tumor
Cartilage invasion (+)

5.2.5 Radiotherapy

T1–2 Glottic Laryngeal Cancer (Fig. 5.30)

Superior: top of thyroid cartilage
Inferior: bottom of cricoid cartilage
Anterior: 0.5–1 cm fall-off to skin
Posterior: in front of vertebral bodies
C3 vertebra level → hyoid bone
C4 vertebra level → top of thyroid cartilage
C6 vertebra level → cricoid cartilage

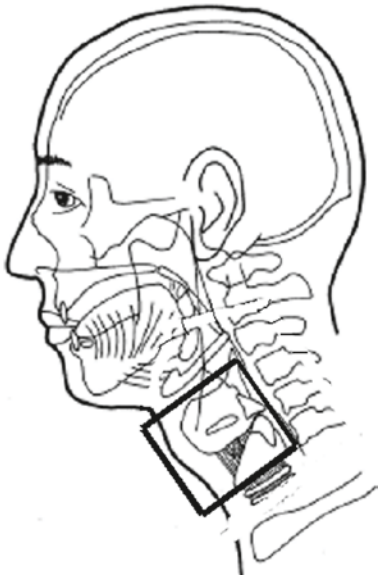


Fig. 5.30 Conventional RT fields for T1–2 glottic laryngeal cancers (from [17], p 455, Figs. 18.2, 18.4, reproduced with the permission from Springer Science and Business Media)

T3–4 Glottic and Supraglottic Laryngeal Cancer (Fig. 5.31)

Superior: superior to mandibular angle
Inferior: bottom of cricoid cartilage

- Subglottic extension (+), shoulders should be pulled down as much as possible.
- If patient is operated, 1.5 cm superior to stoma (stoma is treated in supraclavicular field).

  Anterior: 0.5–1 cm skin fall-off to neck and one-third of mandible
  Posterior: usually spinous processes

- Lymph node (+); lymph node should be included.

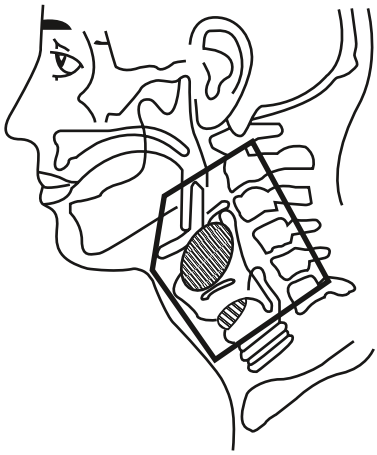


Fig. 5.31 Conventional RT fields for T3–4 glottic–supraglottic laryngeal cancer (from [17], p 455, Figs. 18.2, 18.4, reproduced with the permission from Springer Science and Business Media)

Subglottic Laryngeal Cancer
Superior: level II (upper jugular) lymph nodes are included.

Inferior: 2 cm below primary tumor
Anterior and posterior: same as supraglottic field

- Lower neck lymphatics and upper mediastinal lymph nodes are treated in anterior supraclavicular field.

5.2.6 Selected Publications

See also Sect. 5.8

Supraglottic laryngeal cancer
Italy, 1997 → retrospective. 166 supraglottic patients. Larynx-preserving surgery vs. definitive RT.

- DFS: 88% in surgery vs. 76% in RT.
- Local control: 92% in RT.
- Larynx preservation: 95% in surgery vs. 72% in RT.

Spriano G et al (1997) Conservative management of T1–T2N0 supraglottic cancer: a retrospective study. Am J Otolaryngol 18(5):299–305

Rotterdam, 1990 → 203 supraglottic cancer 193 cases with RT. Reevaluation after 40 Gy: 60–70 Gy boost or surgery (33 patients).

- RFS in T2: 53%, T4: 39%.

Hoekstra CJ et al (1990) Squamous cell carcinoma of the supraglottic larynx without clinically detectable lymph node metastases: problem of local relapse and influence of overall treatment time. Int J Radiat Oncol Biol Phys 18(1):13–21

MDACC, 1989 → 41 supraglottic cancer cases. 1.2 Gy/fractions two times a day; 72–79 Gy (76.8 median) definitive RT.

- Local control: 87% in hyperfractionated arm vs. 76% in conventional arm.

Wendt CD, Peters LJ, Ang KK, Morrison WH, Maor MH, Goepfert H, Oswald MJ (1989) Hyperfractionated radiotherapy in the treatment of squamous cell carcinomas of the supraglottic larynx. Int J Radiat Oncol Biol Phys 17(5):1057–1062

Glottic laryngeal cancer
RTOG 95-12/EORTC 22992 → randomized. 250 cases of T2a–bN0 glottic cancer. Randomization: standard fractionation (SFX) 70 Gy (2 Gy/fractions) vs. hyperfractionation (HFX) 79.2 Gy (1.2 Gy BID).

- Five-year local control: 79% in HFX vs. 70% in SFX (no significance).
- Five-year DFS: 51% in HFX vs. 37% in SFX (no significance).
- Five-year OS: 73 vs. 62% (no significance).

Trotti A (2006) A randomized trial of hyperfractionation vs. standard fractionation in T2 squamous cell carcinoma of the vocal cord. IJRBOP 66(3 Suppl 1):S15

Italy, 2005 → retrospective. 831 T1 cases.

- Five-year OS 77%, local control 84%, organ preservation 95%.
- Ten-year OS 57%, local control 83%, organ preservation 93%.
- Twenty-year secondary malignancy 23%.
- Field size 39–49 cm^2: >65 Gy may be used.

Cellai E (2005) Radical radiotherapy for early glottic cancer: results in a series of 1087 patients from two Italian radiation oncology centers. I. The case of T1N0 disease. Int J Radiat Oncol Biol Phys 63(5):1378–1386

New Zealand, 2006 → retrospective. 145 T1–T2 cases. Median follow-up: 4.9 years.

- 6 MV standard fractionation (SFX) 60–66 Gy, 30–33 fractions (2 Gy/fractions), >6–6.5 weeks vs. accelerated hyperfractionation (AHFX) 52.5–55 Gy, 20 fractions (2.75 Gy/fractions), >4 weeks.
- T1N0: locoregional control, 95% in AHFX vs. 75% in SFX ($p < 0.05$).
- T2N0: locoregional control, 81% in AHFX vs. 80% in SFX ($p > 0.05$).
- AHFX can be used in T1 glottic tumors.

Short S (2006) T1/T2 glottic carcinoma: a comparison of two fractionation schedules. Australas Radiol 50(2):152–157

Subglottic laryngeal cancer

Ocshner clinic, 2006 → retrospective. 15 cases, >25 years. RT alone.

- Three-year OS: 25%.
- Recommendations: stage I–II → RT (including lower neck and upper mediastinal lymphatics); stage III–IV → surgery + RT.

Garas J (2006) Squamous cell carcinoma of the subglottis. Am J Otolaryngol 27(1):1–4

Toronto, 2002 → retrospective, 43 cases. Definitive RT + salvage surgery.

- Local control: 56% (82% salvage surgery).
- Five-year OS: 50%.

Paisley S (2002) Results of radiotherapy for primary subglottic squamous cell carcinoma. Int J Radiat Oncol Biol Phys 52(5):1245–1250

5.3 Oral Cavity Cancers

The oral cavity is located between the vermillion line (the mucosa–skin boundary of the upper and lower lips) anteriorly and the isthmus faucium posteriorly. It is an anatomical space that is bounded by the floor of the mouth inferiorly, the hard palate superiorly, and the buccal mucosa laterally. Although the oral cavity is a space, it is not a homogeneous region, and it includes various subsites [27].

Normal Anatomical Structures of the Oral Cavity (Fig. 5.32) [27]

Upper and lower lips
Buccal mucosa
Gingiva and teeth (arches of the upper and lower teeth)
Hard palate
Part of the soft palate
Anterior two-thirds of tongue
Floor of mouth
Retromolar trigone

The oral cavity is divided into two parts via the arches of the upper and lower teeth when the mouth is closed [27]:

- Anterior part: vestibulum oris (entrance to the oral cavity)
- Posterior part: cavum oris proprium (true oral cavity)

Retromolar trigone. This is located between the ramus of the mandible and the last molar tooth, connecting these two spaces when the mouth is closed. This region is important due to the fact that patients with maxillofacial trauma or maxillary fixation may feed via the retromolar trigone [27].

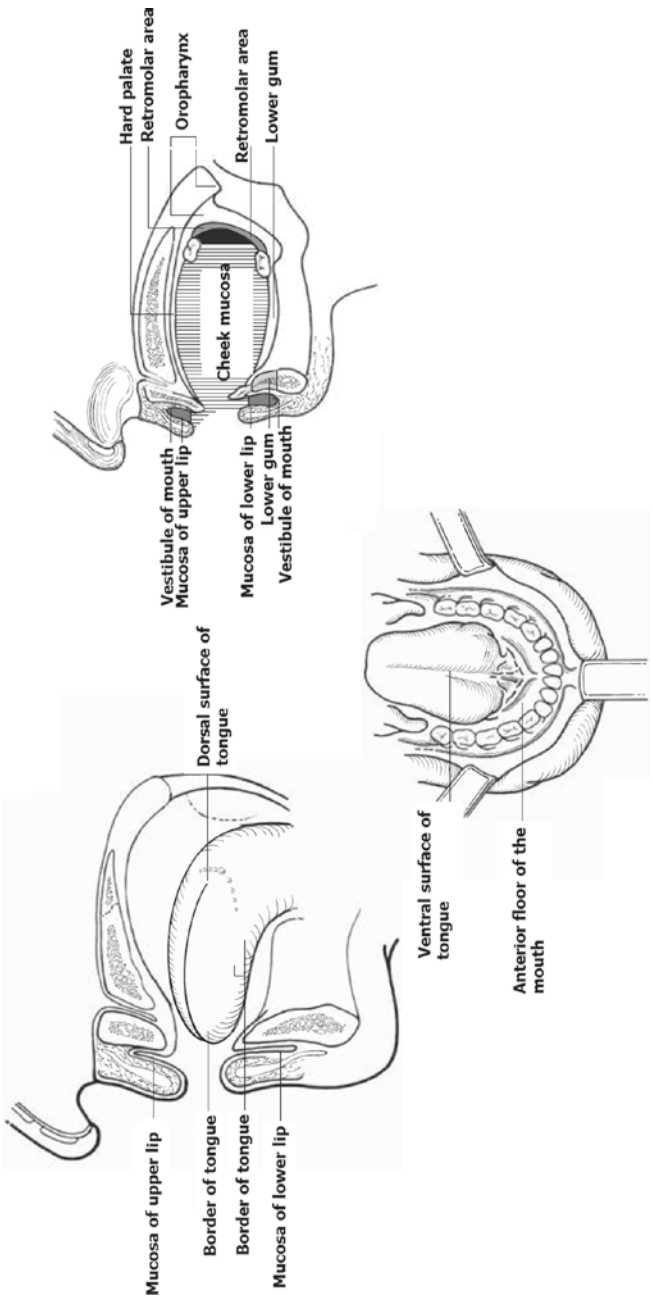


Fig. 5.32 Normal anatomical structures of the oral cavity (from [11], reproduced with the permission from the American Joint Committee on Cancer)

Oral cavity cancers are the second most common head–neck cancers after laryngeal cancers.

5.3.1 Pathology

Premalignant lesions of the oral cavity: some epithelial lesions have the potential for malign transformation (Fig. 5.33) [28]. These are as follows [28]:

- *Leukoplakia*. This is the most common premalignant lesion in the head–neck region. The white macules may have several histological features, from simple hyperkeratosis, dysplasia and carcinoma in situ to invasive carcinoma. They are most commonly observed in the oral cavity and laryngeal mucosa. The risk of malignant transformation in these lesions is higher in smokers and in women.
- *Erythroplakia*. This is less common than leukoplakia. The oral cavity is the most frequent localization. The risk of malignant transformation is much higher, and biopsy is essential for histological evaluation.
- *Lichen planus*. Erosive lichen planus in the oral cavity may transform into malignancy. These are benign lesions and are frequently localized in the buccal mucosa and tongue symmetrically. The erosive type is seen in the floor of the mouth. Biopsy is essential to determine lichen type and for differential diagnosis from leukoplakia.
- In addition, pemphigus, papilloma, chronic fungal infections, and Plummer–Vinson syndrome are also followed for possible malignant transformations.

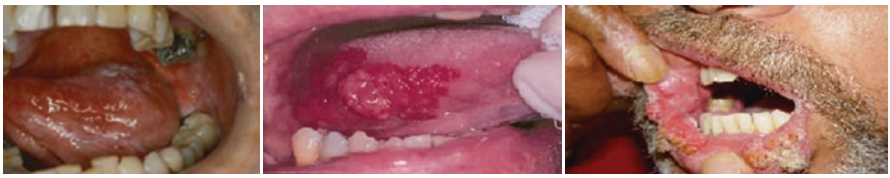


Fig. 5.33 Leukoplakia, erythroplakia, and lichen planus (from *left* to *right*)

Most oral cavity malignancies are squamous cell cancers (epidermoid cancers) [29].
Other malignant tumors of the oral cavity:
Epithelial origin: basal cell carcinoma, malignant melanoma
Glandular origin: adenocarcinoma, adenoid cystic carcinoma
Lymphoid origin: lymphoma
Soft tissue origin: sarcoma

5.3.2 General Presentation

The most prominent symptoms are a scar that does not heal and swelling or masses. The swelling or mass may be located in the primary region as well as the neck, since they have the potential to metastasize to cervical lymph nodes. In addition, pain (e.g., during chewing, swallowing, throat pain, ear pain), bleeding, speaking disorders, swallowing dysfunctions and dyspnea may also be seen.

5.3.3 Staging

Primary tumor (T) (Fig. 5.34) [14]

T1: Tumor no larger than 2 cm in greatest dimension
T2: Tumor larger than 2 cm but no larger than 4 cm in greatest dimension
T3: Tumor larger than 4 cm in greatest dimension
T4: Moderately Advanced Local Disease: (lip) Tumor invades through cortical bone, inferior alveolar nerve, floor of mouth, or skin of face, i.e., chin or nose
- T4a: Moderately Advanced Local Disease: (oral cavity) Tumor invades adjacent structures (e.g., through cortical bone (mandible or maxilla), into deep [extrinsic] muscle of tongue [genioglossus, hyoglossus, palatoglossus, and styloglossus], maxillary sinus, and skin of face)
- T4b: Very Advanced Local Disease: Tumor invades masticator space, pterygoid plates, or skull base and/or encases internal carotid artery (superficial erosion alone of bone/tooth socket by gingival primary is not sufficient to classify a tumor as T4).

N staging is similar to those of other head–neck cancers, except nasopharynx cancer.

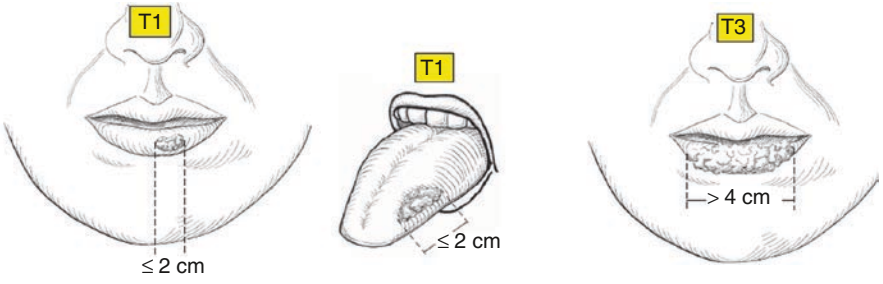


Fig. 5.34 T staging for oral cavity cancer (from [11], reproduced with the permission from the American Joint Committee on Cancer)

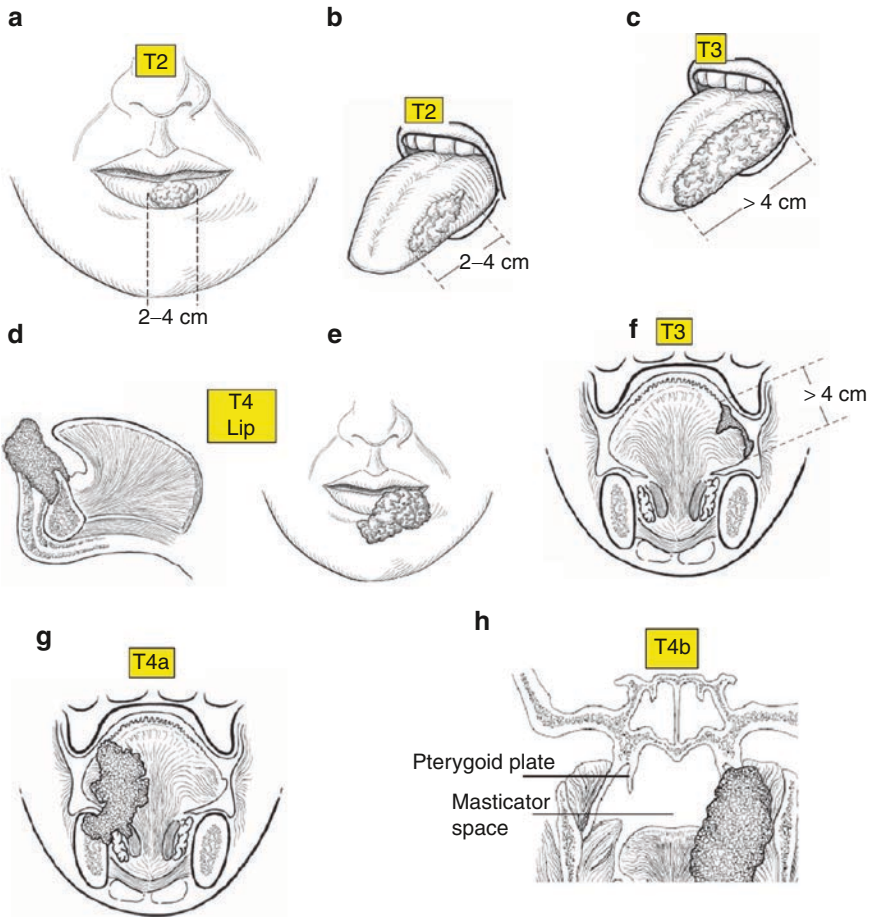


Fig. 5.34 (continued)

Approximately 50% of all oral cavity malignancies are located in the lower lip or tongue, 10% in the buccal mucosa, and 10% in the mandible (teeth arches) or maxilla (hard palate) [31].

Five-year survival is nearly 90% in lip cancers smaller than 2 cm in size, but decreases to 40% in advanced cases [31].

Five-year survival is nearly 90% in stage I tongue cancers, but decreases to 10% in stage IV cases [32].

Oral cavity cancer frequently involves the submandibular (level Ib), upper jugular (level II) and mid-jugular lymph nodes (level III) [30].

When clinical N (−) tongue cancers are examined histopathologically after neck dissection, pathological lymph node positivity is nearly 33% [30].

5.3.4 Treatment Algorithm

Stage I–II [16]
Definitive RT (66–72 Gy), or
Alternative → Surgery ± postoperative RT
Stage III–IV [16]
Concurrent chemoradiotherapy, or
Alternative → Surgery + postoperative chemoradiotherapy

Postoperative chemoradiotherapy indications (major risk factors):

- Extracapsular nodal involvement
- Surgical margin (+)

Postoperative radiotherapy indications (minor risk factors):

- Multiple lymph node (+)
- Perineural invasion
- Lymphovascular space invasion

5.3.5 Radiotherapy

Conventional RT Fields (Fig. 5.35).
Superior: 2 cm above primary tumor.
Inferior: below hyoid bone.

- Lymph node (+): level III is included
- Anterior: 2 cm in front of primary tumor (usually in front of mandible).
- Posterior: Back of vertebral corpuses.
- Lymph node (+): back of vertebral spinous processes.
- Two lateral parallel–opposed fields are used.
- Lymph node (+): neck and supraclavicular field is also treated.

(Two lateral and one anterior field.)

Interstitial brachytherapy can be used alone or in combination with external RT in the management of floor of mouth, tongue, lip and buccal mucosa cancers.

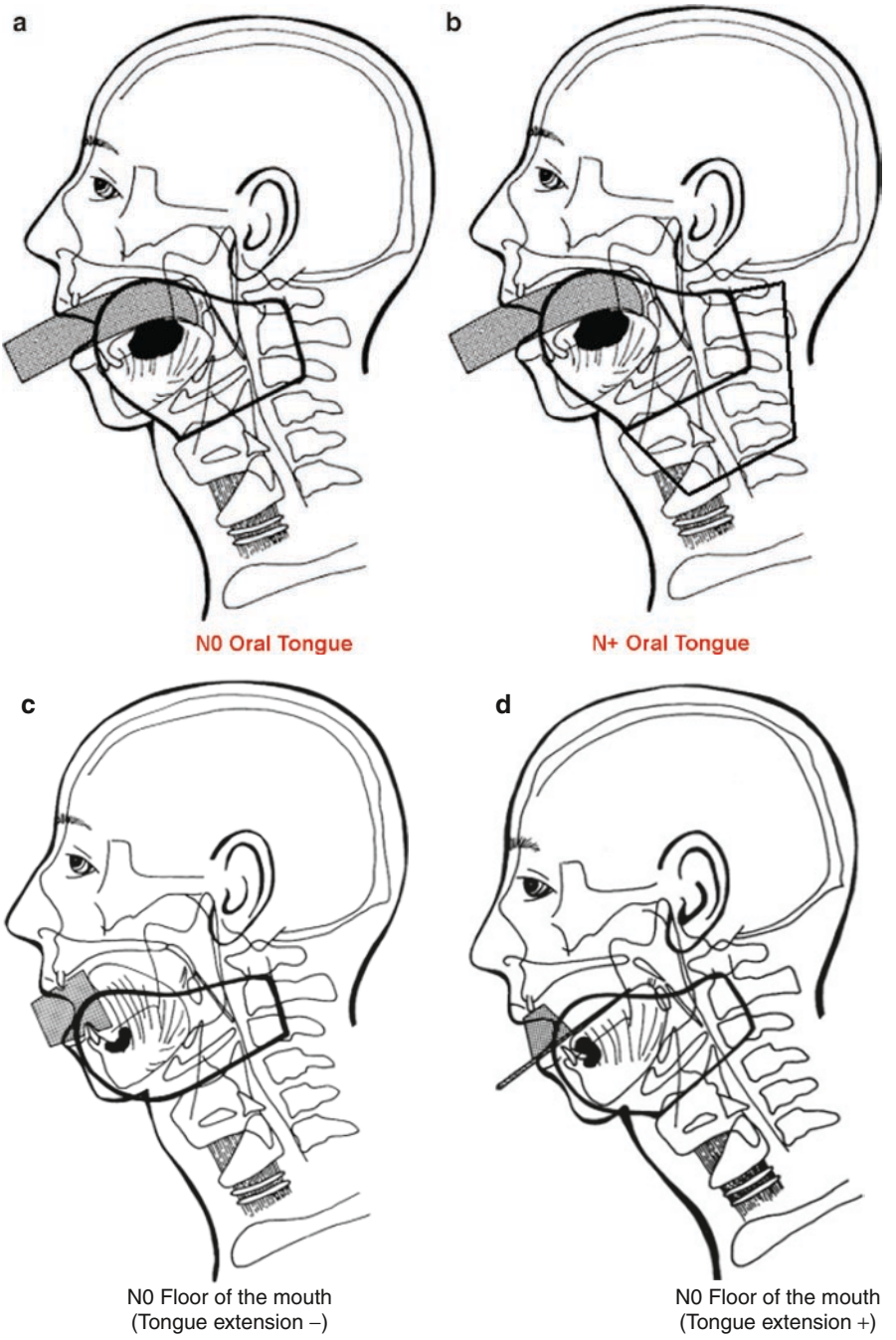
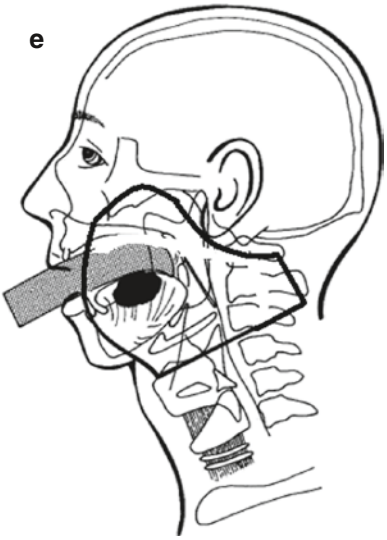
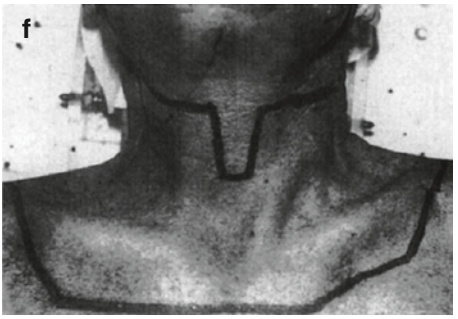


Fig. 5.35 Conventional RT fields for oral cavity cancers (from [17], p 459, 467, Figs. 18.11, 18.12, 18.16a, reproduced with the permission from Springer Science and Business Media)



T4N0
Retromolar Trigone
(Postoperative)



Supraclavicular field

Fig. 5.35 (continued)

Reasons for tongue depressor or cork use:

- To spare upper teeth, upper gingiva and soft palate and to stabilize the tongue in floor of mouth, lower lip, retromolar trigone and tongue tumors
- Tongue stabilization in other oral cavity tumors

Conformal RT Fields [33]:
CTV1: GTV + 1 cm
CTV2: level Ib, II, III lymphatics
PTV: CTV + 0.5–1 cm

5.3.6 Selected Publications

See also Sect. 5.8

Tongue

MDACC, 1990 → retrospective. 103 patients with T1–2 N0 tongue SCC (18 T1, 85 T2). RT: interstitial brachytherapy (BRT) + hypofractionated RT (16–37 Gy, 2.4–4.0 Gy/fractions or 40–50 Gy), interstitial BRT alone (38–55 or 40–50 Gy), normofractionated RT (45–82 Gy).

- RT alone: local recurrence in 5/8 patients.
- BRT alone: local recurrence in 6/18.
- BRT dose >40 Gy: two-year local control 92%.
- BRT dose <40 Gy: two-year local control 65%.
- Neck recurrence in patients with no neck RT: 44%.

Wendt CD et al (1990) Primary radiotherapy in the treatment of stage I and II oral tongue cancers: importance of the proportion of therapy delivered with interstitial therapy. Int J Radiat Oncol Biol Phys 18(6):1287–1292

Buccal mucosa

Indian Randomized Trial, 1996 → randomized. Stage III–IV buccal mucosa SCC. Surgery vs. surgery + postoperative RT.

- Disease-free survival: 38% in surgery-alone arm vs. 68% in combined arm.

Mishra RC et al (1996) Post-operative radiotherapy in carcinoma of buccal mucosa, a prospective randomized trial. Eur J Surg Oncol 22(5):502–504

Floor of mouth

Institute Gustave-Roussy, 2002 → retrospective. 160 cases: T1N1 49%, T2N1 51%; interstitial BRT in all cases.

- Two-year survival: 89%; 5-year survival: 75%.
- Serious necrosis <10%.
- Bone necrosis 18%.

Marsiglia H et al (2002) Brachytherapy for T1–T2 floor-of-the-mouth cancers: the Gustave-Roussy Institute experience. Int J Radiat Oncol Biol Phys 52(5):1257–1263

Retromolar trigone

Gainesville, 2005 → retrospective. 99 patients: RT alone in 35, surgery + RT in 64.

- Five-year locoregional control for stage I–III: 51% in RT alone vs. 87% in surgery + RT.
- Five-year locoregional control for stage IV: 42% in RT alone vs. 62% in surgery + RT.
- Multivariate analysis: RT + surgery was better than RT alone.

Mendenhall WM et al (2005) Retromolar trigone squamous cell carcinoma treated with radiotherapy alone or combined with surgery. Cancer 103(11):2320–2325

5.4 Sinonasal Cancers

Sinonasal cancers include malignancies of the nasal cavity and paranasal sinuses (maxillary sinus, frontal sinus, ethmoid sinuses, and sphenoid sinus) (Fig. 5.36).

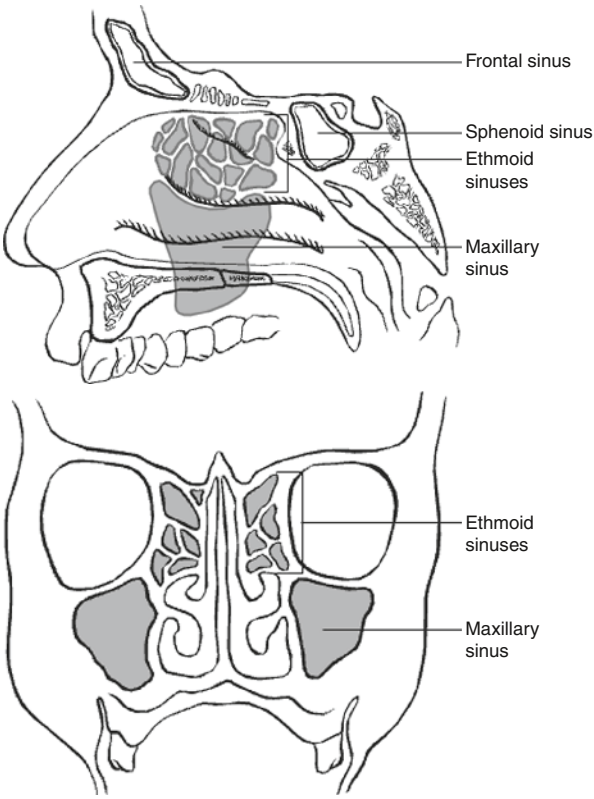


Fig. 5.36 Nasal cavity and paranasal sinuses (anterior view)

Paranasal Sinuses (Fig. 5.36) [34]

Frontal sinus. This is not present at birth. Pneumatization becomes prominent at 12 years, and reaches adult size in 20 years (28 mm in height, 24 mm in width and 20 mm in depth).

Maxillary sinus. This is filled with fluid at birth. The base of the sinus reaches to the level of the base of the nose at 8 years and reaches adult size in adolescence (33 mm in height, 25 mm in width, and 34 mm in depth).

Ethmoid sinus. This reaches adult size in 8–12 years. It consists of 3–15 cells. The region that it makes with sphenoid sinus is important due to their neighboring structures.

Sphenoid sinus. This starts growing at the age of 3 years and reaches adult size at adolescence (20 mm in height, 23 mm in depth, and 17 mm in width). The optic nerve, internal carotid artery, and maxillary sinus occur from superior to inferior in the lateral wall of the sphenoid sinus. The superior wall of the sphenoid sinus is separated from the dura by a bone 1 mm thick.

Nasal cavity
Inferior–posterior: soft palate
Inferior–anterior: maxillary bone (os palatinum)
Superior–anterior: nasal bones (os nasale), superior lateral cartilage
Superior–posterior: lamina cribrosa (cribriform plate)
Superior–lateral: lamina papyracea, which separates bone from orbita

5.4.1 Pathology

Sinonasal cancers are rare tumors that constitute 3% of all head–neck cancers and 1% of all cancers.

Nasal Cavity Cancers

- Squamous cell cancers: 50%
- Esthesioneuroblastoma (olfactory neuroblastoma): 13%
- Malignant melanoma: 10%
- Nasal vestibule cancers, squamous cell cancer: 80%

5.4.2 General Presentation

The benign and malignant pathologies of the sinonasal region have similar clinical signs and symptoms at presentation. Therefore, malignant diseases are usually advanced at diagnosis.

Symptoms in Maxillary Sinus Cancers

- Nasal symptoms (50%): nasal obstruction, rhinorrhea, epistaxis, and nasal mass
- Oral symptoms (25–35%): sensitivity in upper teeth, pain, trismus, ulceration, fullness in hard palate, and alveolar site
- Ocular symptoms (25%): propulsion of orbita upwards, unilateral increase in tears, diplopia, swelling in eye lids, and exophthalmos
- Facial symptoms: infraorbital nerve hypoesthesia, swelling in cheek, pain and asymmetry in face
- Otological symptoms: serous otitis media and hearing loss due to nasopharyngeal extension

The classical triad of sinonasal cancer is seen in advanced stages:

1. Facial asymmetry
2. Palpable or visible mass in oral cavity
3. Mass in nasal cavity observed during anterior rhinoscopy

- All three findings are seen in 40–60% of patients at diagnosis; at least one of them is observed in 90% of cases.

Ohngren's line. This is used in anatomical definitions of paranasal tumors. It is a virtual line passing from the medial chantus of the eye to the angle of the mandible, and it divides the maxillary antrum into anterointerior and posterosuperior parts. A tumor in front of this line is more benign, while one behind it is more malignant in character.

- Tumors that pass the base of the maxillary sinus and reach the oral cavity are an exception.

5.4.3 Staging

Nasal Cavity and Ethmoid Sinus [14]

Primary tumor (T)
TX: Primary tumor cannot be assessed
T0: No evidence of primary tumor
Tis: Carcinoma *in situ*
T1: Tumor restricted to any one subsite, with or without bony invasion
T2: Tumor invading two subsites in a single region or extending to involve an adjacent region within the nasoethmoidal complex, with or without bony invasion
T3: Tumor extends to invade the medial wall or floor of the orbit, maxillary sinus, palate, or cribriform plate
T4a: Moderately Advanced Local Disease: Tumor invades any of the following: anterior orbital contents, skin of nose or cheek, minimal extension to anterior cranial fossa, pterygoid plates, sphenoid or frontal sinuses
T4b: Very Advanced Local Disease: Tumor invades any of the following: orbital apex, dura, brain, middle cranial fossa, cranial nerves other than (V_2), nasopharynx, or clivus

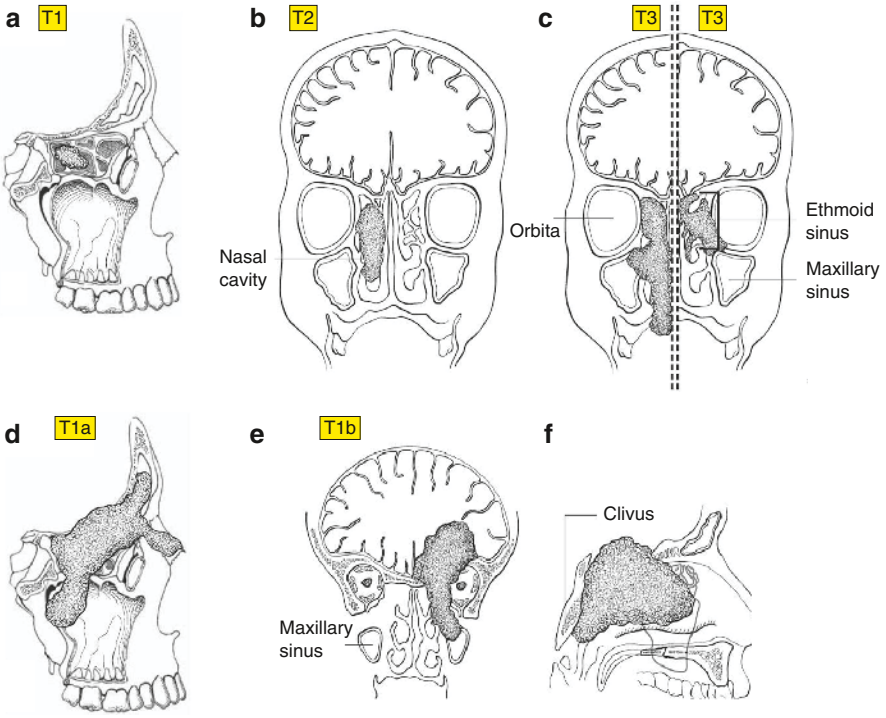


Fig. 5.37 T staging in nasal cavity and ethmoid sinus cancers (from [11], reproduced with the permission from the American Joint Committee on Cancer)

Maxillary Sinus (Fig. 5.38) [14]

Primary tumor (T)
TX: Primary tumor cannot be assessed
T0: No evidence of primary tumor
Tis: Carcinoma *in situ*
T1: Tumor limited to maxillary sinus mucosa with no erosion or destruction of bone
T2: Tumor causing bone erosion or destruction including extension into the hard palate and/or the middle of the nasal meatus, except extension to the posterior wall of maxillary sinus and pterygoid plates
T3: Tumor invades any of the following: bone of the posterior wall of maxillary sinus, subcutaneous tissues, floor or medial wall of orbit, pterygoid fossa, ethmoid sinuses
T4a: Moderately Advanced Local Disease: Tumor invades anterior orbital contents, skin of cheek, pterygoid plates, infratemporal fossa, cribriform plate, sphenoid or frontal sinuses
T4b: Very Advanced Local Disease: Tumor invades any of the following: orbital apex, dura, brain, middle cranial fossa, cranial nerves other than maxillary division of trigeminal nerve (V_2), nasopharynx, or clivus

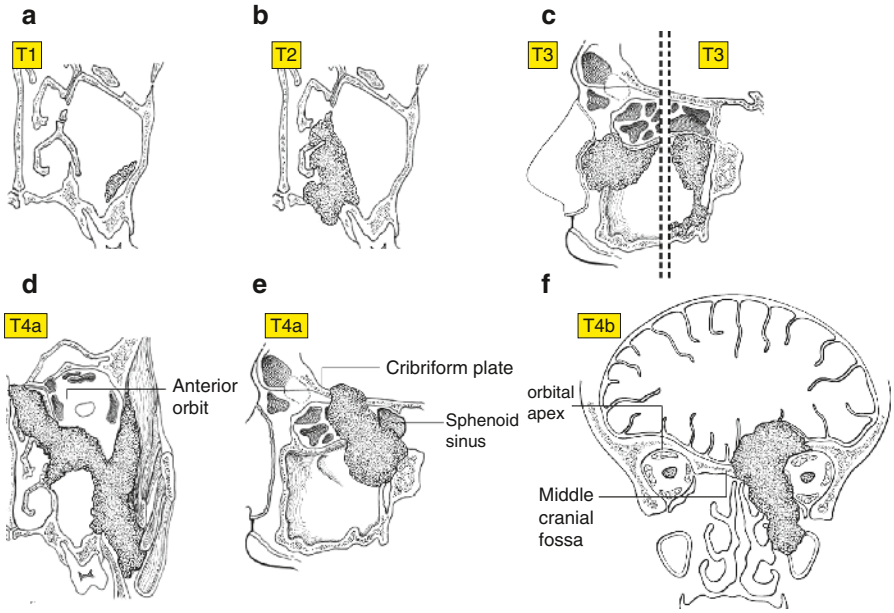


Fig. 5.38 T staging for maxillary sinus cancers (from [11], reproduced with the permission from the American Joint Committee on Cancer)

AJCC Stage Groupings

Stage I:	T1N0M0
Stage II:	T2N0M0
Stage III:	T3N0M0, T1N1M0, T2N1M0, T3N1M0
Stage IVA:	T4aN0M0, T4aN1M0, T1N2M0, T2N2M0, T3N2M0, T4aN2M0
Stage IVB:	T4b, any N, M0; any T, N3, M0
Stage IVC:	Any T, any N, M1

N staging is the same as for other head and neck cancers, except nasopharyngeal cancers.

Wang staging for the nasal vestibule:
T1: tumor is limited to skin
T2: tumor invades subcutaneous tissue and cartilage
T3: tumor invades bone

Sinonasal cancers rarely metastasize to neck lymphatics [36].

- 10% at presentation
- Elective neck RT is not routinely recommended
- Clinical, radiological or pathological lymph node (+): neck RT is given
- Elective neck RT is recommended for posterior pharyngeal wall extension (due to rich lymphatic supply to this region)

Sinonasal cancers primarily drain into the retropharyngeal (Rouviere's), submandibular (Ib), jugulodigastric (II), and periparotid lymph nodes [36].

Nasal vestibule tumors primarily drain into the submental/submandibular (Ia/Ib), facial and preauricular lymph nodes.

Esthesioneuroblastoma [35]

- This is a neurogenic tumor that originates from the olfactory epithelium. This epithelium is limited to the upper conchae, the nasal septum and the cribriform area in humans.
- It can be seen at any age, but two-thirds of patients are between 10 and 34 years of age.
- Symptoms are nonspecific, like other intranasal tumors (epistaxis, anosmia, and nasal obstruction). Therefore, most patients are at advanced stages at presentation.
- It usually appears as a reddish mass.
- Although it grows slowly, local invasion is possible, and it has a metastasis potential of nearly 20%. The most frequently involved sites are lung and cervical lymph nodes.

Salivary Gland Tumors of the Sinonasal Region

- These constitute 6–17% of all sinonasal cancers
- In order of frequency: adenoid cystic carcinoma; adenocarcinoma; malignant pleomorphic adenoma; mucoepidermoid carcinoma; undifferentiated carcinoma
- All are generally very aggressive

Adenoid cystic carcinoma [37]

These are also known as cylindromas due to their histological appearance.

- They have a tendency for early perineural invasion.
- Perineural invasion is generally along the maxillary and mandibular branches of the trigeminal nerve.
- Regional lymph node involvement is very rare, but the risk of distant metastasis (mostly to lung) is high.

5.4.4 Treatment Algorithm

Nasal Cavity and the Ethmoid Sinus [38]

T1–2 N0
Resection → close surgical margin/(+) or perineural invasion → postoperative RT
Alternative → definitive RT
T3–4 N0 resectable
Resection + postoperative RT
T3–4 N0 unresectable, inoperable
Definitive RT or chemoradiotherapy
N (+)
Resection + postoperative RT/chemoradiotherapy
Alternative → definitive chemoradiotherapy
Maxillary sinus[38]
T1–2 N0
Resection → close surgical margin/(+) or perineural invasion, adenoid cystic histology → re-resection (if possible) → postoperative RT
T3–4 N0 resectable
Resection + postoperative RT/chemoradiotherapy
T3–4 N0 unresectable, inoperable
Definitive RT or chemoradiotherapy
N (+)
(Resection + neck dissection) + postoperative RT/chemoradiotherapy
Alternative → definitive chemoradiotherapy

5.4.5 Radiotherapy

Generally one anterior field and one ipsilateral wedge field (5° towards the back to spare the contralateral eye) are used. The weight of the anterior field is greater.

Sinonasal Cancer (Fig. 5.39)

Inferior: lip corner
Posterior: includes retropharyngeal lymph nodes
Superior: 1 cm above ethmoid sinus

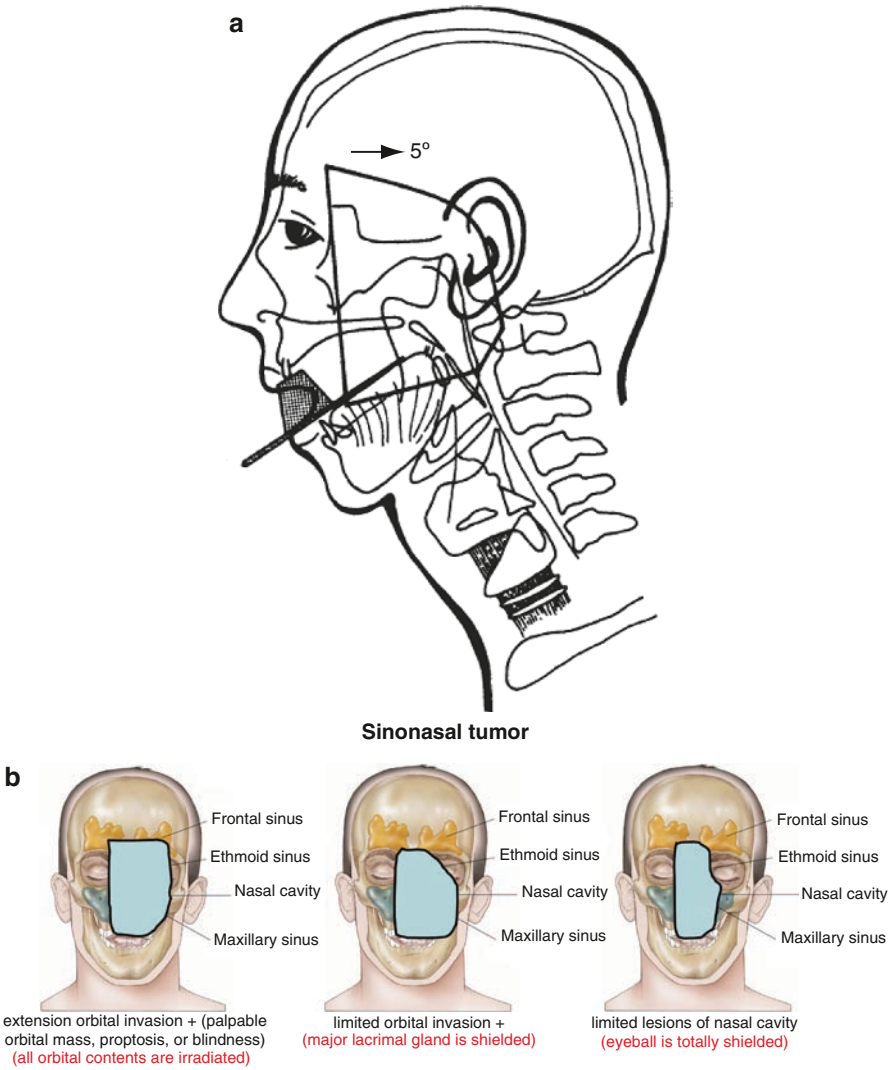


Fig. 5.39 Conventional RT fields for sinonasal cancer (from [17], p 471, 472, Figs. 18.23d, 18.24, reproduced with the permission from Springer Science and Business Media)

Anterior: lateral orbital chantus
RT fields for nasal vestibule are shown in Fig. 5.40.

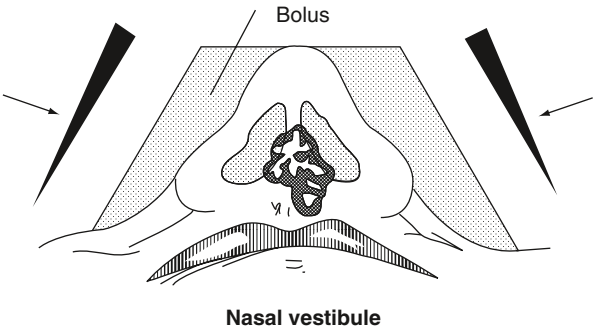


Fig. 5.40 Conventional RT fields for nasal vestibule cancer

- Simulation is done in the supine position with a thermoplastic mask.
- Eyes should be open and look to the front at right angles to the plane of the ground.
- A tongue depressor may be used to spare the tongue.
- If the patient is operated, spaces should be filled with tissue-equivalent material (e.g., bolus).
- 3D-CRT is recommended if available.

Dose:

- Fraction dose: 1.8–2 Gy
- Total dose in definitive RT/chemoradiotherapy: 66–70 Gy
- Total dose in postoperative RT: 60 Gy (66 Gy in positive surgical margin)

Energy:

- Four to six megavolt X-rays
- Co-60 is not recommended due to its large penumbra

Conformal RT Volumes [39] (Fig. 5.41):
CTV1 = GTV + 0.5/2 cm

- Upper neck lymphatics are treated if involved.

PTV1 = CTV1 + 0.5 cm

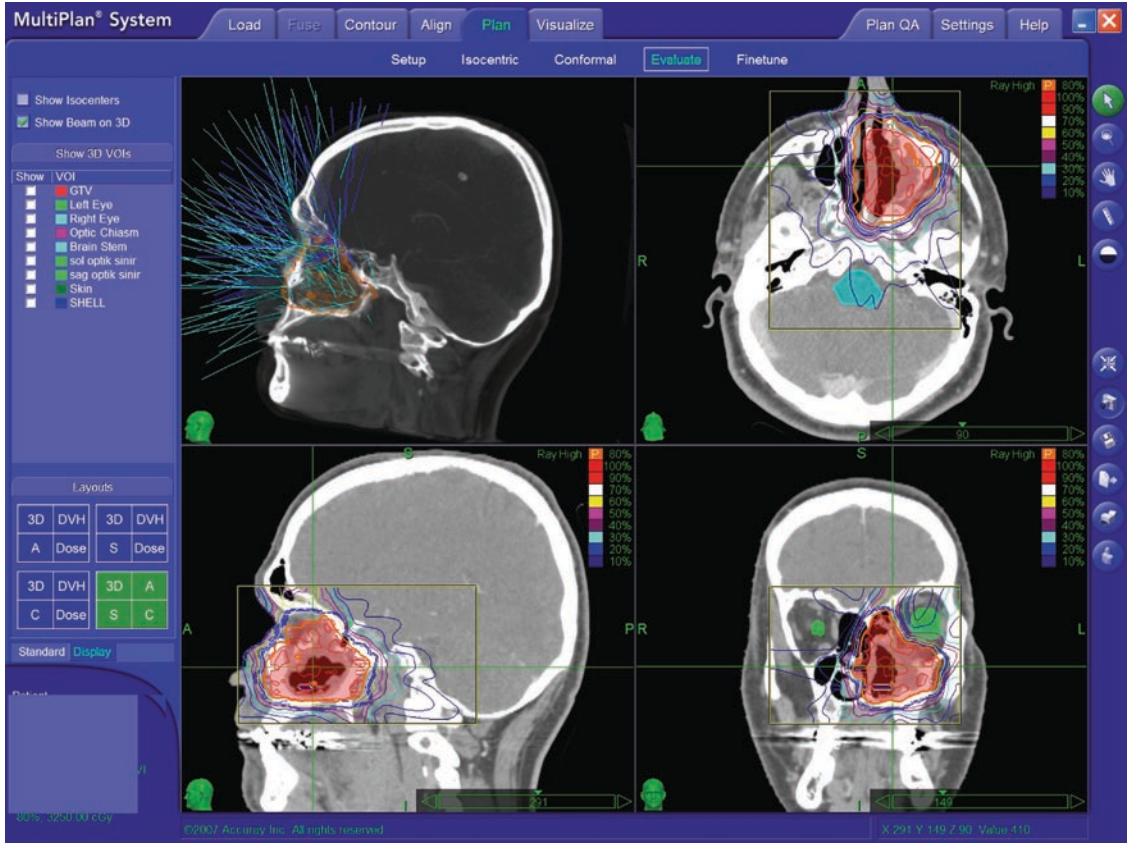


Fig. 5.41 Robotic radiosurgery planning in a patient with paranasal carcinoma (reproduced courtesy of Hacettepe University)

5.4.6 Selected Publications

Nasal vestibule

Netherland, 2004 → retrospective. 56 T1–2 (Wang classification) cases. External RT + endocavitary brachytherapy boost.

- Two-year local control: 56%.
- 12% nodal metastasis.

Langendijk JA et al (2004) Radiotherapy of squamous cell carcinoma of the nasal vestibule. Int J Radiat Oncol Biol Phys 59(5):1319–1325

Gainesville, 1999 → retrospective. 56 cases of RT alone, 4 cases of surgery + postoperative RT.

- Five-year local control: 94% (T4 → 71%).
- Five-year disease-specific survival: 94% (T4 → 86%).

Mendenhall WM et al (1999) Squamous cell carcinoma of the nasal vestibule. Head Neck 21(5):385–393

Nasal cavity

SEER analysis, 2002 → 981 cases. 97% nonmetastatic, 50% SCC, 13% esthesioneuroblastoma, 50% received RT.

- Five-year survival (OS): 57%

Bhattacharyya N (2002) Cancer of the nasal cavity: survival and factors influencing prognosis. Arch Otolaryngol Head Neck Surg 128(9):1079–1083

MD Anderson, 1992 → 45 nasal cavity cases. 18 RT alone, 27 surgery + RT.

- Five-year overall survival: 75%; 5-year progression-free survival: 60%.
- Four blindness (+) (two due to exenteration, two due to RT).

Ang KK (1992) Carcinomas of the nasal cavity. Radiother Oncol 24(3):163–168

Sinonasal cancer, adjuvant RT

UCSF, 2007 → retrospective. 36 cases. 32 gross total resections. 13 ethmoid, 10 maxillary, 7 nasal cavity, and 6 other. Median follow-up: 51 months. Treated with IMRT.

- IMRT dose: 70 Gy to GTV, 60 Gy to CTV.
- Five-year local control: 58%; DFS: 55%; OS: 45%.
- Toxicity is minimal (no visual loss, one dry eye, one cataract, and one lacrimal stenosis.
- Conclusion: IMRT has no effect on survival, but decreases the risk of toxicity.

Daly ME (2007) Intensity-modulated radiation therapy for malignancies of the nasal cavity and paranasal sinuses. Int J Radiat Oncol Biol Phys 67(1):151–157

Maxillary sinus

MDACC 1991 → 73 cases treated with surgery + RT. 50–60 Gy, two or three wedge fields.

- Five-year local control: 78%.
- Five-year relapse-free survival: 51%.
- After elective nodal RT: 38% nodal recurrence in squamous cell cancers and undifferentiated cancers; 5% in adenoid cystic cancers.

Jiang GL et al (1991) Maxillary sinus carcinomas: natural history and results of postoperative radiotherapy. Radiother Oncol 21(3):193–200

Washington University, 2004 → 106 patients with paranasal sinus carcinoma. Most of the tumors originated in the maxillary (76%) or ethmoid (18%) sinus. Most tumors were locally advanced at presentation. All patients underwent radiotherapy (RT), combined with surgery in 65%; 2% received chemotherapy. Median follow-up: 5 years.

- Five-year local tumor control, locoregional tumor control, disease-free survival (DFS), and overall survival rates were 58, 39, 33, and 27%, respectively.
- Significant improvement in DFS with the addition of surgical resection to RT (35 vs. 29%, $p = 0.05$).
- Nodal status at presentation emerged as a statistically significant predictor for locoregional tumor control and DFS in multivariate analysis. Distant metastases occurred in 29% of the patients.
- DFS improved slightly with combined modality treatment. The overall survival rates remained suboptimal, suggesting a need for more accurate determination of tumor extent, as well as more effective locoregional and systemic therapies.

Blanco AI, Chao KS, Ozyigit G et al (2004) Carcinoma of paranasal sinuses: long-term outcomes with radiotherapy. Int J Radiat Oncol Biol Phys 59(1):51–58

Maxillary sinus, elective nodal RT

Stanford, 2000 → 97 patients (61 surgery + RT, 36 RT alone).

- Five-year survival: 34%, 10-year survival: 31%.
- Most nodal recurrences were level I–II.
- After elective nodal RT: 5-year actuarial nodal relapse risk: 0%
- After no elective nodal RT, 5-year nodal relapse risk: 20%.
- Five-year distant metastasis risk: 29% in patients with no neck relapse.
- Five-year distant metastasis risk: 81% in patients with neck relapse

Le QT (2000) Lymph node metastasis in maxillary sinus carcinoma. Int J Radiat Oncol Biol Phys 46(3):541–549

Sinonasal cancer, photon/proton RT
MGH Photon/Proton Regimen, 2006 → 36 advanced-stage sinonasal cancer cases.

- Median GTV dose: 69.6 Gy CGE (cobalt gray equivalent dose), with accelerated hyperfractionation and concomitant boost with proton
- Acceptable ophthalmological complications
- No local control data

Weber DC (2006) Visual outcome of accelerated fractionated radiation for advanced sinonasal malignancies employing photons/protons. Radiother Oncol 81(3):243–249

5.5 Major Salivary Gland Tumors

The salivary glands consist of major glands such as the parotid, submandibular and sublingual glands as well as 6,000–10,000 minor salivary glands within the mucosal surface of the upper gastrointestinal tract (Fig. 5.42).

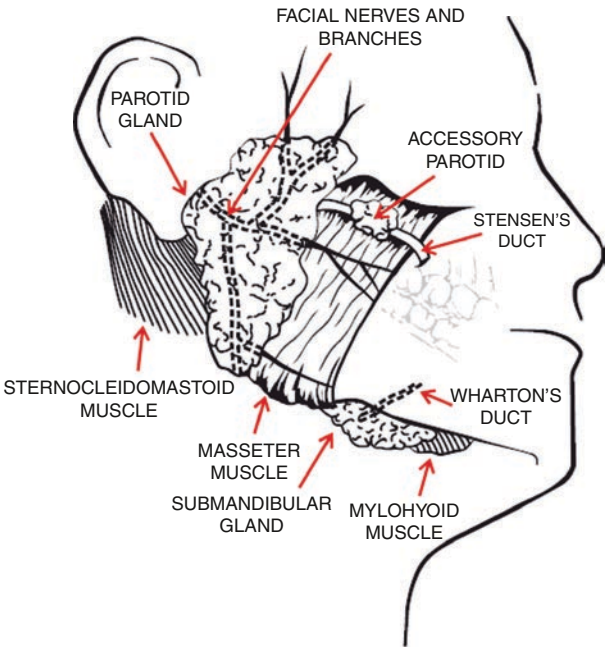


Fig. 5.42 Major salivary glands

Parotid gland [40]. This is an encapsulated gland just beneath the skin that is surrounded by tight connective tissue. It is the largest salivary gland located in the retromandibular–preauricular region. The surrounding connective tissue at the bottom of the gland is less dense, and there is an aperture here from which infections or tumor may extend into the pterygopalatine fossa or the paraphrayngeal space.

- The canal of the parotid (Stenon's duct) is approximately 6 cm in length; it exits from the anterior side of the gland and crosses the masseter muscle, before entering the oral cavity by passing between the buccinator muscle and the buccal mucosa.
- The facial nerve leaves the temporal bone by exiting the stylomastoid foramen and entering the parotid parenchyma after a distance of 0.5–1.5 cm.

Submandibular salivary gland [41]. This is bounded anteriorly by the anterior belly of the digastrics, posteriorly by the stylomandibular ligament, and superiorly by the mandible. The majority of the gland is inferior to the mylohyoid muscle and is covered by the cervical fascia.

- The canal of the gland (Wharton's duct) is approximately 5 cm in length. It extends anteriorly from beneath the floor of the mouth mucosa, and ends in the ostium at the sublingual caruncle.

Sublingual salivary gland [41]. This is the smallest of the major salivary glands. It is located in the floor of the mouth mucosa. Its posterior is in contact with the anterior part of the submandibular gland.

- It has multiple canals (Bartholin's canals) that exit through multiple ostia located in the sublingual plicae of the mouth floor.
- *Minor salivary glands*. These are located in the pharynx, oral cavity, nasal cavity, sinuses, larynx, and tracheal mucosa.

5.5.1 Pathology

Salivary gland tumors are found in the [42]:

- Parotid glands: 80%
- Submandibular glands: 10–15%
- Sublingual and minor glands: 5–10%

Parotid tumors are benign in nearly 80% of cases.

This ratio is 50% for the submandibular glands; malign tumors are more common in the sublingual and minor salivary glands.

Ninety-five percent of salivary gland tumors are seen in adults.

The most common benign salivary gland tumor is the pleomorphic adenoma (benign mixed tumor), followed by Warthin's tumor (papillary cystadenoma lymphomatosum).

Malignant tumors are varied, and those most commonly seen are the mucoepidermoid carcinoma, malignant mixed tumor, adenoid cystic carcinoma, acinic cell carcinoma, and polymorphic low-grade adenocarcinoma.

Pleomorphic adenoma (benign mixed tumor). Almost all are observed in the parotid gland, while a small proportion may be in the submandibular gland.

- Almost all are ipsilateral, and they are more frequent in females.
- The first sign is usually the presence of a slowly growing, painless retromandibular mass for years.
- Facial functions are normal, even in large benign tumors.
- Facial pain and paresis is a sign of malignancy.
- A painless, hard nodular mass is palpated.
- Pleomorphic adenoma has a pseudocapsule, so there is almost certainly residual tumor after simple excision, resulting in frequent relapses.
- They have a 5–10% risk of malignant transformation.

Warthin's tumor (cystadenolymphoma). Almost all of these are observed in older men, and bilaterally in 10–15%.

- This is only seen in parotids.
- An ovoid, mobile, fluctuating, elastic and painless mass is usually located in the parotid tail.
- The tumor includes lymphoid tissue, so enlargement with associated pain may be seen with upper airway infections.

Mucoepidermiod carcinoma. More than 90% of these cases are found in parotids, followed by the hard palate and minor salivary glands.

- This is the salivary gland tumor most frequently seen in children.
- Well-differentiated lesions behave like benign tumors; undifferentiated types have a tendency for local invasion and distant metastasis, like high-grade malignancies.
- Well-differentiated low-grade tumors grow slowly, while poorly differentiated high-grade tumors grow rapidly and result in pain, facial paralysis, lymph node involvement, and distant metastasis.
- Five-year survival is 90% in well-differentiated and very low in poorly differentiated tumors.

Acinic cell tumor. This originates from the parotids in particular.

- It presents as a very slowly growing mass.
- It metastasizes in nearly 10% of cases, and is mostly bilateral.
- Risk of recurrence is low.
- Prognosis is better than for carcinomas, although it is malignant.

Adenoid cystic carcinoma. This is the most common malignant tumor of salivary glands other than the parotids.

- It has a tendency to localize in the submandibular, sublingual and minor salivary glands, but seldom in the parotids.
- The facial nerve is almost always involved in such tumors originating from the parotids
- Nerve invasion is possibly due to the extension of the tumor into perineural lymphatics, which is a characteristic of adenoid cystic cancer.
- Local lymph node metastasis is rare, while lung metastasis is frequent.
- Recurrences may be seen even 10 years after therapy; 5-year OS is 60%.

5.5.2 General Presentation

Salivary gland tumors generally start with a progressively growing painless mass. Benign salivary gland tumors usually present as a slowly growing mass with no discomfort.

Parotid neoplasm usually presents as a mass in the tail, whereas submandibular gland tumors present as a swelling of the entire gland and those of minor salivary glands as a painless mass under healthy mucosa.

Signs of malignant tumor: rapidly growing mass, pain, associated nerve paralysis (facial nerve, tongue nerve), fixation to skin or deep tissues (fixed mass), ipsilateral lymphadenopathy.

Most malignant salivary gland tumors are seen in patients 50–60 years old, 2% in children <10 years old, and 16% in patients <30 years old.

5.5.3 Staging

Primary Tumor (T) (Fig. 5.43) [14]

T1: Tumor 2 cm or less in greatest dimension without extraparenchymal extension*
T2: Tumor more than 2 cm but 4 cm or less in greatest dimension without extraparenchymal extension*
T3: Tumor more than 4 cm and/or tumor having extraparenchymal extension*
T4a: Moderately Advanced Local Disease: Tumor invades skin, mandible, ear canal, and/or facial nerve
T4b: Very Advanced Disease: Tumor invades skull base and/or pterygoid plates and/or encases carotid artery
*Extraparenchymal extension is clinical or macroscopic evidence of invasion of soft tissues. Microscopic evidence alone does not constitute extraparenchymal extension for classification purposes.

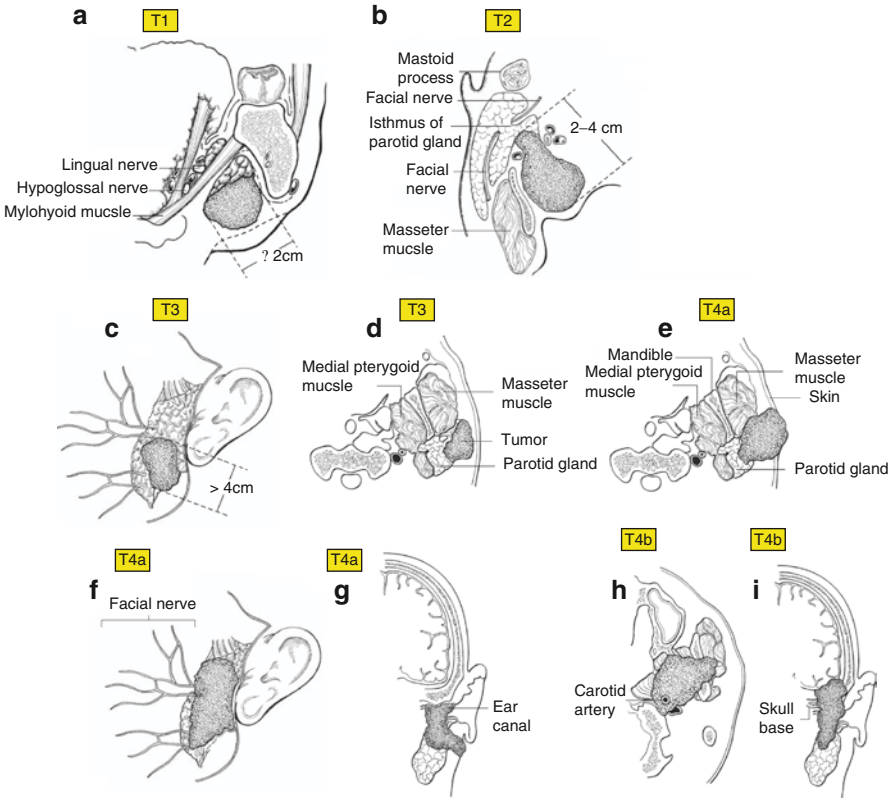


Fig. 5.43 T staging for major salivary glands (from [11], reproduced with the permission from the American Joint Committee on Cancer)

- *Parotid lymphatics*: periparotid, intraparotid lymph nodes, levels I, II, III.
- *Submandibular gland lymphatics*: levels I, II, III.

5.5.4 Treatment Algorithm

Treatment Algorithm for Salivary Gland Cancer [43]

Stage I–II surgery ± RT
Stage III–IV surgery + RT

5.5.5 Radiotherapy

RT indications in malignant salivary gland tumors

- Surgical margin (+) or close
- Stage III–IV
- Lymph node (+)
- High-grade tumor
- Recurrence
- Deep lobe involvement in parotids
- Inoperable or unresectable tumor

RT indications in benign salivary gland tumors

- Inoperable or unresectable tumor
- Facial nerve involvement
- Recurrent tumor
- Subtotal excision

Single field technique with photon–electron combination (Fig. 5.44)

This is a technique used to deliver a homogeneous dose distribution sparing the contralateral parotid gland.

Superior: above zygomatic bone, including parotid and scar

Inferior: above thyroid cartilage

Anterior: anterior edge of masseter muscle

Posterior: posterior to mastoid

Lymph node (+) or neck irradiation is required: posterior to spinous processes

Anterior–posterior oblique double wedge technique (Fig. 5.45)

This technique allows dose homogeneity and the contralateral parotid gland sparing. However, this technique may cause set-up errors.

Submandibular gland RT field. Single field is enough. Possible regions that should be included in RT portal: submandibular angle, neighboring oral cavity, pterygomaxillary fossa, cranial base, ipsilateral neck.

- *Superior border*: hard palate; *inferior border*: hyoid bone; *anterior border*: anterior to mentum; *posterior border*: posterior to mandibular angle.
- Four to six megavolt X-rays, Co-60 or 6–18 MeV electrons are used.

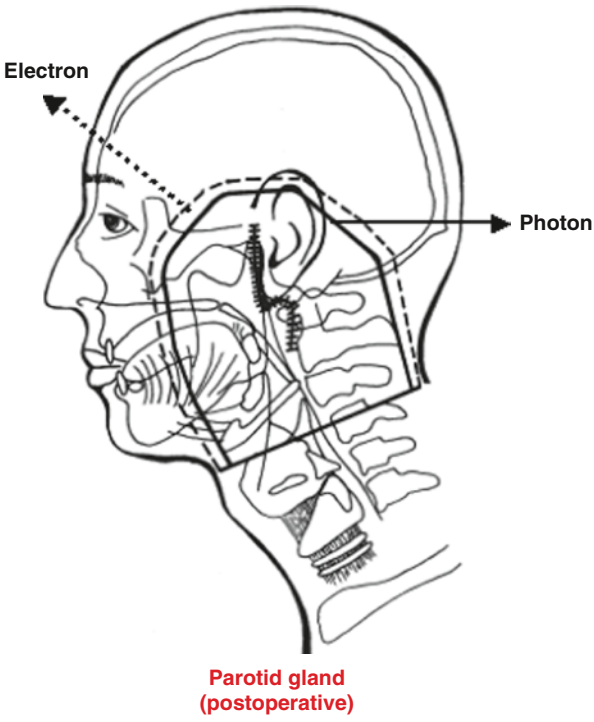


Fig. 5.44 Photon–electron combination for parotid gland cancers (from [17], p 471, 474 Fig. 18.27, reproduced with the permission from Springer Science and Business Media)

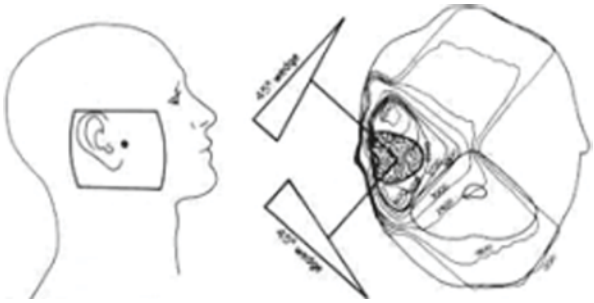


Fig. 5.45 Double wedge technique for parotid gland cancer

- Contralateral elective neck RT is not required in cases of ipsilateral lymph node positivity.
- Elective neck RT may be skipped in low-grade tumors; parotid RT alone is adequate.
- Parotid RT with elective neck RT is required in cases of positive neck nodes, high-grade tumors and recurrent tumors.

Dose

- Tumor bed: 60 Gy, 2 Gy/day or 63 Gy 1.8 Gy/day
- Neck dissection (+): 60 Gy to neck
- Neck dissection (−): 50 Gy to neck (neck is clinically and radiologically (−))

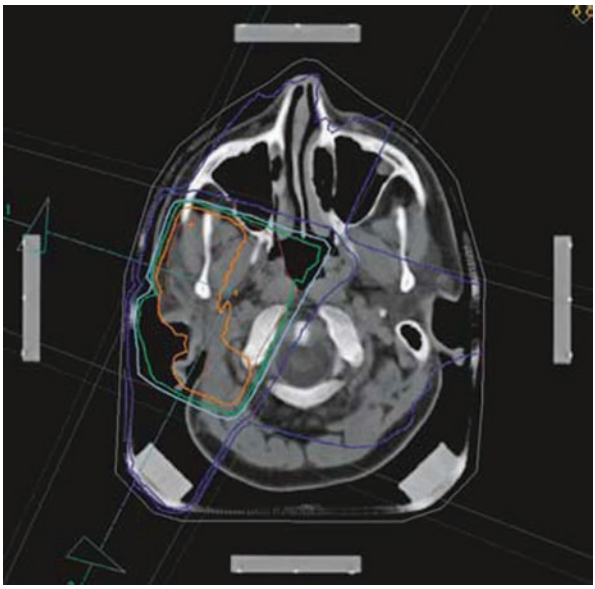


Fig. 5.46 Conformal RT fields for parotid gland cancer

Conformal RT Volumes (Fig. 5.46) [39]

CTV: tumor or tumor bed
+ Levels I, II, III, peri- and intraparotid lymphatics for parotid
+ Retropharyngeal LN for deep lobe tumors
+ Levels I, II, III for submandibular/sublingual glands
PTV: CTV + 0.5–1 cm

5.5.6 Selected Publications

Adjuvant radiotherapy

Netherland Head–Neck Oncology Cooperative Group (NHNOCG), 2005 → 498 cases. All with surgery and 78% postoperative RT. Median RT dose: 62 Gy.

- Adjuvant RT significantly increased local control in T3–T4 tumors, close surgical margins, incomplete resections, bone invasions and perineural infiltrations.
- Surgery-only group: T1–2 tumors and surgical margin (−); five-year local control 95%, 10-year local control 90%.

Terhaard CHJ et al (2005) The role of radiotherapy in the treatment of malignant salivary gland tumors. Int J Radiat Oncol Biol Phys 61(1):103–111

Definitive radiotherapy

- *UCSF, 2006* → 45 malignant salivary gland tumors treated with RT alone. Median 66 Gy.
- Five-year local control: 70%; 10-year local control: 57%.
- Local recurrences are frequent in T3–4 tumors and for RT doses <66 Gy.

Chen AM et al (2006) Long-term outcome of patients treated by radiation therapy alone for salivary gland carcinomas. Int J Radiat Oncol Biol Phys 66(4):1044–1050

Elective nodal RT

- *UCSF; 2007* → 251 N0 malignant salivary gland tumors. Adenocystic 33%, mucoepidermoid 24%, adenocarcinoma 23%. Gross total resection R0 44%, R1 56%. No neck dissection. All with adjuvant RT. Median primary RT dose 63 Gy. Elective neck RT: ipsilateral 69%, bilateral 31%.
- Nodal relapse: T1 7%, T2 5%, T3 12%, T4 16%.
- Elective nodal RT: 10-year nodal relapse risk decreased from 26% to 0% (decrease in risk: squamous 67%, undifferentiated 50%, adenocarcinoma 34%).
- Whether or not elective nodal RT was given, no nodal relapse was observed in adenocystic (0/84) and acinic cell (0/21) tumors.
- Conclusion: elective nodal RT is required for high-grade tumors, but not for adenoid cystic and acinic cell tumors.

Chen AM (2007) Patterns of nodal relapse after surgery and postoperative radiation therapy for carcinomas of the major and minor salivary glands: what is the role of elective neck irradiation? Int J Radiat Oncol Biol Phys 67(4):988–994

Neutron RT

RTOG-MRC Neutron Trial, 1993 → randomized. 32 inoperable or recurrent major/minor salivary gland tumors, Neutrons (17–22 nGy) vs. photons/electrons (55 Gy/4 weeks or 70 Gy/7 weeks).

- Ten-year locoregional control: 56% in neutron vs. 17% photon/electron arm ($p = 0.009$).
- Median survival: 3 years in neutron vs. 1.2 years in photon/electron arm.
- No difference in OS (25–15%).

Laramore G et al (1993) Neutron versus photon irradiation for unresectable salivary gland tumors: final report of an RTOG-MRC randomized clinical trial. Int J Radiat Oncol Biol Phys 27(2):235–240

Adenoid cystic carcinoma

MSKCC, 2007 → 59 adenoid cystic carcinomas (oral cavity 28%, paranasal sinus 22%, parotid 14%, submandibular gland 14%). T1–4 tumors. Treated with surgery + RT. Included cranial base in 90% of cases. Median follow-up: 5.9 years.

- Five-year local control: 91%; OS: 87%.
- Ten-year local control: 81%; OS: 65%.
- Poor prognostic factors: T4 tumor, gross and/or clinical nerve involvement, LN (+).
- Adjuvant RT after surgery had excellent local control rates.

Gomez DR (2008) Outcomes and prognostic variables in adenoid cystic carcinoma of the head and neck: a recent experience. Int J Radiat Oncol Biol Phys 70(5):1365–1372

Minor salivary glands

Netherland Cancer Institute, 2000 → retrospective. 55 minor salivary gland tumors. Median follow-up: 11 years.

- Five-year disease-specific survival: 76%; 10-year: 74%.
- Prognostic factors: age, stage, lymph node status, vascular invasion, nasopharynx/paranasal sinus localization.

Vander Poorten VL (2000) Stage as major long term outcome predictor in minor salivary gland carcinoma. Cancer 89(6):1195–1204

5.6 Thyroid Cancer

The thyroid gland originates from the pharyngeal pouches of the base of the tongue in the middle of the neck and move inferiorly within the thyroglossal canal (Fig. 5.47). It consists of two lobes connected to each other by an isthmus. The upper pole of the thyroid gland extends into the space formed by the sternothyroid muscle, inferior constrictor muscle and posterior thyroid lamina. The lower pole extends to the level of the fifth or sixth tracheal rings. The lobes of the thyroid are close to the carotid sheath posterolaterally, the prevertebral muscles and sympathetic ganglion posteriorly, and the trachea and cricoid. The thyroid glands move together with the larynx and trachea during the process of swallowing.

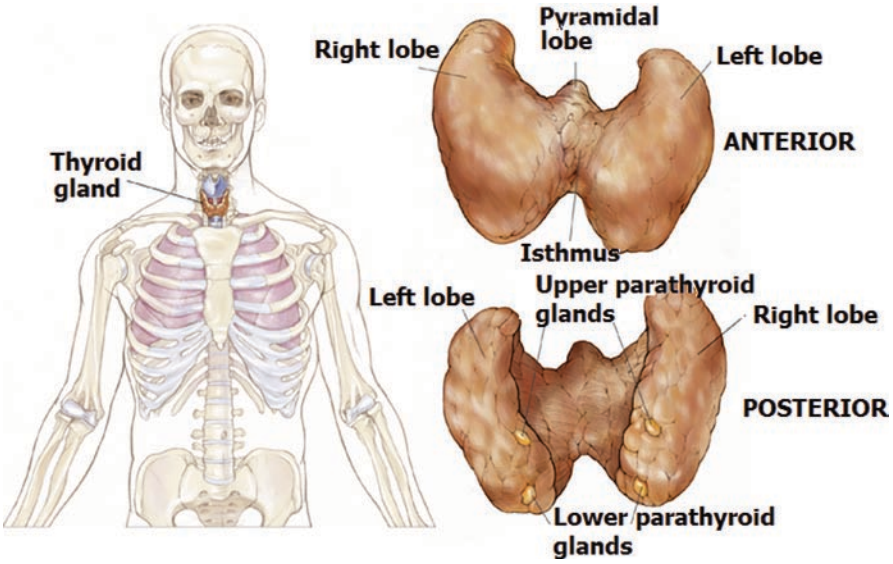


Fig. 5.47 Thyroid gland

Thyroid cancer is the most frequently seen endocrine tumor, but it constitutes only a very small proportion of other thyroid gland disorders. Thyroid cancers represent 1% of all new cancer cases each year. This cancer leads to 0.5% of all cancer-related mortalities [44].

Solitary thyroid nodules have a malignancy incidence of 10–30%. Therefore, all thyroid nodules should be carefully examined for malignancy risk [45].

Epidemiological studies have not demonstrated any prominent relation between thyroid cancer and iodine deficiency in the diet. A relationship between the presence of a benign goiter and well-differentiated thyroid cancer has not been demonstrated beyond doubt. Follicular carcinoma is frequently observed in geographical regions where goiter is endemic [44].

The risk of a palpable thyroid anomaly is high in patients receiving low-dose radiotherapy to the head–neck and upper mediastinal regions: 25% of patients receiving 0.02 Gy of external radiotherapy develop a goiter; 25% of these, or 7% of all cases receiving thyroid irradiation, develop thyroid cancer (most often papillary adenocarcinoma) [44].

- The latent period for the development of thyroid anomalies is 10–20 years [46].

Only a small percentage of all papillary and follicular thyroid cancers have a genetic basis. Gardner syndrome and Cowden's disease (familial goiter and skin hamartoma) have a well-established relationship to differentiated thyroid carcinomas.

Thyroid lymphomas, particularly the B cell type, are commonly seen in autoimmune thyroiditis.

5.6.1 Pathology

Thyroid cancers are evaluated in several groups: differentiated and undifferentiated carcinomas of the follicular epithelium, and medullary carcinoma of parafollicular cells [47].

Differentiated Thyroid Cancers

1. Papillary cancer
2. Follicular cancer
3. Intermediate-type cancer

Undifferentiated thyroid cancers (anaplastic carcinomas)

1. Small cell type
2. Giant cell type
3. Osteoclastic giant cell type

Medullary thyroid cancer
Other thyroid cancers (lymphoma, sarcoma, and metastatic tumors)

Papillary thyroid cancer [48]

- This is the most common thyroid cancer. Ninety percent of radiation-related cancers are papillary thyroid cancers. They grow slowly, and are three times more common in females.
- They are characterized by papillary extension of the thyroidal epithelium and connective tissue. The tumor tissue contains concentric calcium deposits called psammoma bodies.
- In 80% of cases they are multicentric within the gland.

Follicular thyroid cancer [49]

- These comprise one-quarter of all malign thyroid cancers. They are commonly seen in older females.
- They are less multicentric than papillary thyroid cancers.

- They have a 15% risk of lymph node metastasis, but more commonly show early hematogenous metastases to bone, lung and liver.
- They have a good prognosis, but also a tendency for frequent recurrence.

Hurthle cell thyroid cancer (oncocytic carcinoma) [50]

- Three percent of all thyroid malignancies are of this type.
- They take up less radioactive iodine (RAI) than follicular cancers, and bilateralism and lymph node involvement are 25% higher than those of follicular cancer.
- They have a poorer prognosis than follicular cancer.

Medullary carcinoma [51]

- Five to ten percent of all thyroid malignancies are medullary carcinomas.
- They originate from parafollicular cells (C cells). Amyloid in stroma is diagnostic.
- They are more commonly seen in females and in older patients.
- The tumor may become 10 cm in size macroscopically.
- Ninety percent of them are sporadic, while the remaining may be termed familial and are a component of multiple endocrine neoplasia type 2.
- Sporadic cases have a solitary nodule, while familial cases have bilateral multicentric tumors.
- Prognosis is somewhere between those for differentiated and anaplastic thyroid cancers.
- They do not usually respond to RAI treatment and external radiotherapy.

Undifferentiated thyroid cancer (anaplastic carcinoma) [52]

- These comprise 10% of all thyroid malignancies.
- They are usually observed in females and in patients over 50 years of age.
- The tumor has no capsule, and extensively invades surrounding tissues. There are three subhistological types: small cell, giant cell and osteoclastic giant cell.
- The disease progresses rapidly and metastasizes to the lungs. Masses can be identified using ultrasonography, but no iodine uptake is observed in scintigraphy. Diagnosis is performed with fine needle aspiration.
- Thyroidectomy is impossible in most cases. Tracheostomia may be required to open the airway due to its rapid course.
- Survival is very short (between 3 weeks and 6 months).

5.6.2 General Presentation

- Benign thyroid nodule incidence is high in females aged between 20–40 years, and these cases have a cancer risk of approximately 5–10%.
- Males show a higher incidence of cancer below 20 years and over 40 years of age, so age and gender are important risk factors.

- Swallowing difficulty, stridor, and hoarseness may be signs of malignancy, as well as a large goiter and retrosternal thyroid enlargement.
- Hoarseness is almost always a sign of malignancy, but is rarely seen in large benign thyroid adenomas.
- The characteristic sign of cancer is a firm and fixed mass larger than 2 cm in size.
- Thyroid mass along with substantial lymphadenopathy may also be a sign of malignancy.

5.6.3 Staging

Primary tumor (T) (Fig. 5.48) [14]
All categories may be subdivided into (a) solitary tumor or (b) multifocal tumor (the largest determines the classification).

T0: No evidence of primary tumor
T1: Tumor 2 cm or less in greatest dimension, limited to the thyroid
T1a: Tumor ≤ 1 cm
T1b: Tumor 1–2 cm
T2: Tumor larger than 2 cm but 4 cm or smaller in greatest dimension, limited to the thyroid
T3: Tumor larger than 4 cm in greatest dimension limited to the thyroid or any tumor with minimal extrathyroid extension (e.g., extension to sternothyroid muscle or perithyroid soft tissues)
T4a: Moderately Advanced Disease: Tumor of any size extending beyond the thyroid capsule to invade subcutaneous soft tissues, larynx, trachea, esophagus, or recurrent laryngeal nerve
T4b: Very Advanced Disease: Tumor invades prevertebral fascia or encases carotid artery or mediastinal vessels
All anaplastic carcinomas are considered T4 tumors.
T4a: Intrathyroidal anaplastic carcinoma
T4b: Extrathyroidal anaplastic carcinoma

Regional lymph nodes (N) (Fig. 5.49)
Regional lymph nodes are the central compartment, lateral cervical, and upper mediastinal lymph nodes.

N0: No regional lymph node metastasis
N1: Regional lymph node metastasis
N1a: Metastasis to level VI (pretracheal, paratracheal, and prelaryngeal/Delphian lymph nodes)
N1b: Metastasis to unilateral, bilateral, or contralateral cervical (Levels I, II, III, IV or V) or retropharyngeal or superior mediastinal lymph nodes (Level VII)

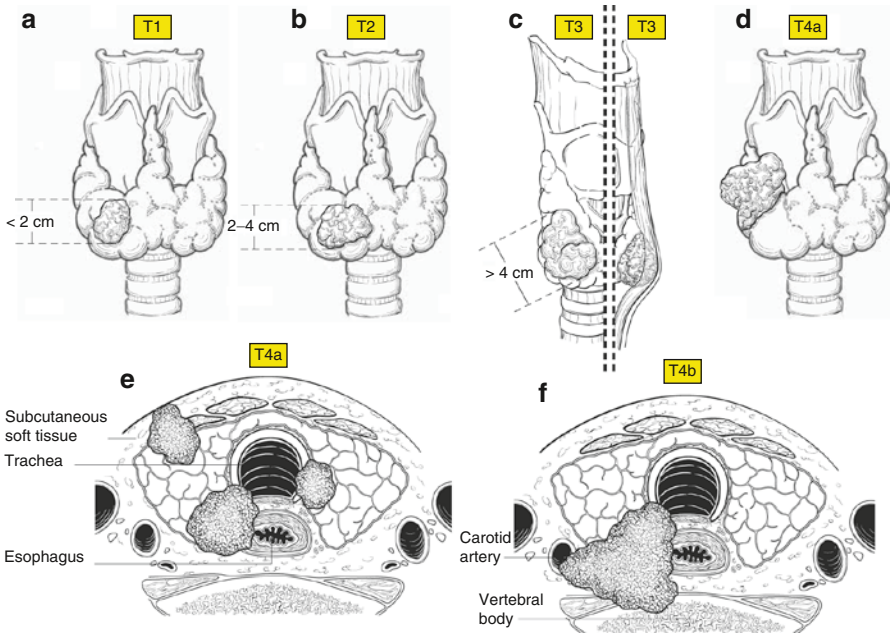


Fig. 5.48 T staging for thyroid cancer (from [11], reproduced with the permission from the American Joint Committee on Cancer)

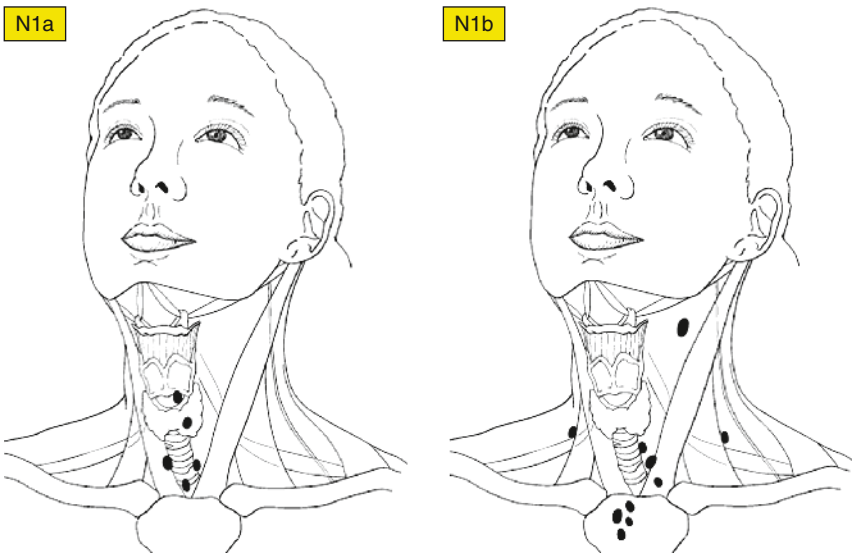


Fig. 5.49 N staging for thyroid cancer (from [11], reproduced with the permission from the American Joint Committee on Cancer)

Distant metastases (M)

MX: Distant metastasis cannot be assessed
M0: No distant metastasis
M1: Distant metastasis

AJCC Stage Groupings

Papillary or follicular thyroid cancer
Younger than 45 years
Stage I: any T, any N, M0
Stage II: any T, any N, M1
Age 45 years and older
Stage I: T1N0M0
Stage II: T2N0M0
Stage III: T3N0M0, T1N1aM0, T2N1aM0, T3N1aM0,
Stage IVA: T4aN0M0, T4aN1aM0, T1N1bM0, T2N1bM0, T3N1bM0, T4aN1bM0
Stage IVB: T4b, any N, M0
Stage IVC: any T, any N, M1
Medullary thyroid cancer
Stage I: T1N0M0
Stage II: T2N0M0
Stage III: T3N0M0, T1N1aM0, T2N1aM0, T3N1aM0
Stage IVA: T4aN0M0, T4aN1aM0, T1N1bM0, T2N1bM0, T3N1bM0, T4aN1bM0
Stage IVB: T4b, any N, M0
Stage IVC: any T, any N, M1
Anaplastic thyroid cancer
All anaplastic carcinomas are considered stage IV.

5.6.4 Treatment Algorithm

Papillary/Follicular/Hurthle Cell Thyroid Cancers [16]

Low-risk disease

- Well differentiated
- Age 15–45 years
- RT history (−)
- Lymph node (−)
- Metastasis (−)
- Extrathyroidal extension (−)

- Tumor <4 cm
- Favorable histology FH (−)

Treatment: total thyroidectomy

RAI indications after surgery

- Thyroglobulin >1 ng/mL
- RAI thyroid scintigraphy (+)

High-risk disease

- Age <15 or >45 years
- RT history (+)
- Lymph node (+)
- Metastasis (+)
- Extrathyroidal extension (+)
- Extracapsular extension (+)
- Tumor >4 cm
- FH (+)

Treatment: total thyroidectomy + neck dissection ± external RT (LN (+))

RAI indications after surgery

- Thyroglobulin >1 ng/mL
- RAI thyroid scintigraphy (+)

Local/regional recurrence

Lymph node relapse

Neck dissection + RAI

Small lymph node in upper mediastinum (+) → RAI

Large (bulky) lymph node in upper mediastinum (+) → upper mediastinal LN dissection + RAI

No response/unresectable/RAI uptake (−): external RT

Metastatic disease

RAI/RT/chemotherapy (doxorubicin)

Medullary cancer[16]

Locoregional disease

- Total thyroidectomy + neck dissection (ipsilateral levels II, III, IV, V, VI)
- Contralateral LN dissection if contralateral LN (+)

RT indications after surgery

- Gross/microscopic residue
- Wide regional LN (+)
- T4a tumor
- Unresectable tumor

No role of RAI and chemotherapy

Metastatic disease

Palliative chemotherapy (doxorubicin/cisplatin)

Hormone therapy (octreotide)

And/or RT

Anaplastic carcinoma [16]
Only chance of cure is surgical resection.
If unresectable, tracheostomy should be opened.
RT for local control and palliation.
Concurrent chemoradiotherapy may be tried.
No role of RAI.

5.6.5 Radiotherapy

External radiotherapy is used for definitive, palliative or adjuvant purposes either alone or in combination with radioactive I-131. Indications for external radiotherapy in the management of thyroid cancers may be summarized as follows:

- Primary treatment for unresectable or RAI (−) tumors
- Large tumors that cannot be brought under control with RAI (e.g., mediastinal involvement)
- Residual tumors in trachea, esophagus or neck after surgery and RAI
- Tumors compressing vital organs
- Superior vena cava syndrome
- Recurrence (RAI uptake is not important)
- Metastasis or relapse after maximal RAI

RT in Differentiated Thyroid Cancers

T4b (extrathyroidal) lesions, after surgery + RAI: 50 Gy external RT.

- Gross residual: 60 Gy
- Locoregional relapse: RT
- Recommended in the case of recurrence after neck dissection + RAI
- Bilateral neck + upper mediastinal lymph nodes: 50 + 10–16 Gy boost

Borders of RT fields in thyroid cancers (Fig. 5.50)
Superior border: 1–1.5 cm above angle of the mandible.
Inferior border: includes upper mediatinal lymph nodes.
Lateral borders: two-thirds of the clavicle.

In cases of mediastinal extension, the field is enlarged to include upper mediastinal lymphatics down to the carina. Anterior–posterior fields are recommended.

Boost: single electron field/two lateral fields with photons/two oblique fields with photons.

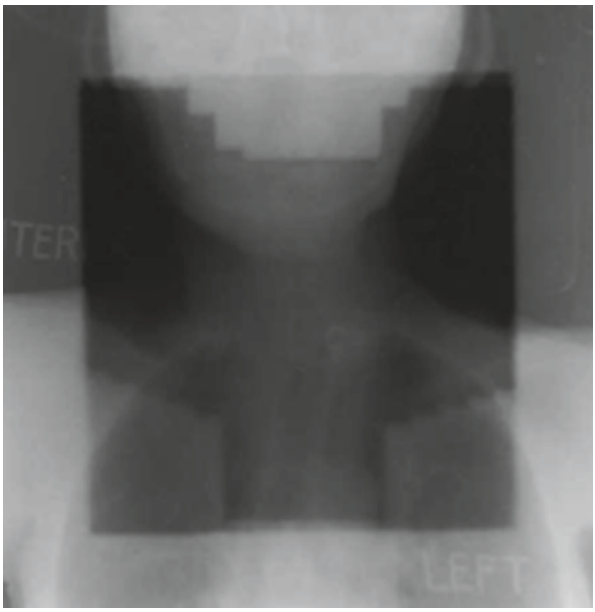


Fig. 5.50 RT portals for thyroid cancer

RT in medullary thyroid cancer
Include thyroid bed + neck + upper mediastinum.

- 40 Gy to lymph nodes and 10 Gy boost to tumor bed.

RT in anaplastic (undifferentiated) thyroid cancer

- Concurrent chemoradiotherapy may be used.
- Hyperfractionated RT (HF-RT) (60 Gy/40 fractions 1.5 Gy/2 fractions/day) may be gven.
- HF-RT: acute effects are relatively common.

The patient is simulated and treated in the supine position with the head at hyperextension. Co-60, 4–6 MV X-rays and 9–15 MeV electrons may be used.

Conformal RT Volumes [53]

CTV: tumor/tumor bed, neck lymphatics (II, III, IV, V, VI and SCF) ± upper mediastinum
PTV: CTV + 0.5/1 cm

5.6.6 Selected Publications

IMRT

MSKCC, 2005 → 20 nonanaplastic thyroid cancer cases treated with IMRT. Microscopic disease: 54 Gy; high-risk regions: 59.4–63 Gy; surgery (+) regions: 63–66 Gy; gross disease: 63–70 Gy. Nodal RT: between level II and aortic arch. High-risk region: tumor bed and level VI.

- Local relapse in two cases and mortality in six cases.
- Two-year local control: 85%.
- Two-year OS: 60%.
- Conclusion: IMRT is an effective modality in selected thyroid cancers.

Rosenbluth BD et al (2005) Intensity-modulated radiation therapy for the treatment of nonanaplastic thyroid cancer. Int J Radiat Oncol Biol Phys 63(5):1419–1426

Medullary thyroid cancer

Toronto University, 1996 → 73 cases. Median 40 Gy postoperative RT in 40 of them.

- Prognostic factors for cause-specific survival: extraglandular extension and postoperative gross residual disease.
- RT was beneficial in cases with microscopic residue (+), extraglandular extension, LN (+).
- Conclusion: postoperative RT was recommended for the high-risk group.

Brierley J, Tsang R, Simpson WJ, Gospodarowicz M, Sutcliffe S, Panzarella T (1996) Medullary thyroid cancer: analyses of survival and prognostic factors and the role of radiation therapy in local control. Thyroid 6(4):305–310

Hurthle cell thyroid cancer

Mayo Clinic, 2003 → retrospective. 18 patients. Five cases with adjuvant RT, seven unresectable cases with salvage RT, six metastatic cases with palliative RT.

- Five-year OS: 66.7%.
- Five-year disease specific survival: 71.8%.
- Conclusion: Hurthle cell thyroid cancer seems to be radiosensitive, so RT may be beneficial in the prevention of relapses at advanced stages as well as in palliation.

Foote RL et al (2003) Is there a role for radiation therapy in the management of Hurthle cell carcinoma? Int J Radiat Oncol Biol Phys 56(4):1067–1072

Anaplastic thyroid cancer (altered fractionated RT)

Princess Margaret Hospital, 2006 → 47 cases between 1983 and 2004. 23 cases with radical RT (14 cases with once daily and 9 cases with twice daily; 1.5 Gy/45–66 Gy). 24 cases with palliative RT (<40 Gy).

- Six-month local control in palliative arm: 64%.
- Six-month local control in radical RT arm: 94%.
- Median OS was 3.3 months longer in the hyperfractionation arm than the conventional arm (13.6 months vs. 10.3 months).

Wang Y et al (2006) Clinical outcome of anaplastic thyroid carcinoma treated with radiotherapy of once- and twice-daily fractionation regimens. Cancer 107(8):1786–1092

5.7 Radiotherapy in Unknown Primary Head–Neck Cancers

When a head-neck cancer has been determined histologically based on nodal excision, but the primary site cannot be established, it is known as an unknown primary head-neck cancer.

- These constitute 3–5% of all head–neck cancers.
- Biopsy from high-risk regions should be done by panendoscopy following physical exam and radiological tests; diagnostic tonsillectomy may also be performed.

Curative therapy: ipsilateral neck dissection and adjuvant radiotherapy including all cervical neck nodes.

Ninety-five percent of cervical lymph node metastases originate from head and neck cancers.

Radiotherapy indications for unknown primary metastatic cervical lymph nodes:

- Number of involved lymph nodes >1
- Extracapsular extension (+)

Borders of lateral fields (Fig. 5.51)
Superior: includes nasopharynx and cranial base.
Posterior: C2 vertebral spinous process.
Anterior: two-thirds of tongue, half of mandible.
Inferior: thyroid notch.
Borders of anterior SCF field
Superior: thyroid notch.
Inferior: bottom of sternoclavicular joint.
Lateral: two-thirds of clavicle.

Dose: 50 Gy to whole neck; 60–66 Gy to involved nodes.

5.8 Selected Publications for Head and Neck Cancers

Risk groups

Review, 2007 → definition of subgroups of head and neck squamous cell cancers with different risks of treatment failure according to AJCC classification: low risk: T1–2N0; intermediate risk: T3N0, T1–3N1; high-risk: T4aN0–1, T1–4N2; very high risk: T4b any N, any T N3; and poor prognosis: M1.

Corvo R (2007) Evidence-based radiation oncology in head and neck squamous cell carcinoma. Radiother Oncol 85:156–170

Fractionation trials

RTOG 90-03, 2000 → randomization: (1) standard fractionation at 2 Gy/fraction/day, 5 days/week, to 70 Gy/35 fractions/7 weeks; (2) hyperfractionation at 1.2 Gy/fraction, twice daily, 5 days/week to 81.6 Gy/68 fractions/7 weeks; (3) accelerated fractionation with split at 1.6 Gy/fraction, twice daily, 5 days/week, to 67.2 Gy/42 fractions/6 weeks, including a 2-week rest after 38.4 Gy; or (4) accelerated fractionation with concomitant boost at 1.8 Gy/fraction/day, 5 days/week and 1.5 Gy/fraction/day to a boost field as a second daily treatment for the last 12 treatment days to 72 Gy/42 fractions/6 weeks.

- Hyperfractionation and accelerated fractionation with concomitant boost are more efficacious than standard fractionation for locally advanced head and neck cancer. Acute but not late effects are also increased.

Fu KK et al (2000) A Radiation Therapy Oncology Group (RTOG) phase III randomized study to compare hyperfractionation and two variants of accelerated fractionation to standard fractionation radiotherapy for head and neck squamous cell carcinomas: first report of RTOG 9003. Int J Radiat Oncol Biol Phys 48:7–16

CHART, 1997 → CHART: 54 Gy given in 36 fractions over 12 days, vs. conventional therapy: 66 Gy given in 33 fractions over 6.5 weeks.

- Similar local tumor control was achieved with CHART, supporting the importance of repopulation as a cause of radiation failure.

Dische S et al (1997) A randomized multicentre trial of CHART versus conventional radiotherapy in head and neck cancer. Radiother Oncol 44:123–136

GORTEC, 2006 → randomized: conventional RT (70 Gy in 7 weeks to the primary tumor and 35 fractions of 2 Gy over 49 days) vs. very accelerated RT (62 to 64 Gy in 31–32 fractions of 2 Gy over 22–23 days; 2 Gy/fraction bid).

- The very accelerated RT regimen was feasible and provided a major benefit in locoregional control, but had a modest effect on survival.

Bourhis J et al (2006) Phase III randomized trial of very accelerated radiation therapy compared with conventional radiation therapy in squamous cell head and neck cancer: a GORTEC trial. J Clin Oncol 24:2873–2878

MARCH, 2006 → meta-analysis. 15 trials with 6,515 patients were included. The median follow-up was 6 years.

- Altered fractionated radiotherapy improves survival in patients with head and neck squamous cell carcinoma. Comparison of the different types of altered radiotherapy suggests that hyperfractionation has the greatest benefit.

Bourhis J (2006) Hyperfractionated or accelerated radiotherapy in head and neck cancer: a meta-analysis. Lancet 368:843–854

German Meta-analysis, 2006 → 32 trials with a total of 10,225 patients were included in the meta-analysis.

- RT combined with simultaneous 5-FU, cisplatin, carboplatin, and mitomycin C as a single drug or combinations of 5-FU with one of the other drugs result in a large survival advantage irrespective of the radiation schedule employed. If radiation therapy is used as a single modality, hyperfractionation leads to a significant improvement in overall survival. Accelerated radiation therapy alone, especially when given as split course radiation schedule or extremely accelerated treatments with decreased total dose increases overall survival.

Budach W (2006) A meta-analysis of hyperfractionated and accelerated radiotherapy and combined chemotherapy and radiotherapy regimens in unresected locally advanced squamous cell carcinoma of the head and neck. BMC Cancer 6:28

Chemoradiotherapy trials

Adelstein, 2003 → concurrent high-dose, single-agent cisplatin with conventional fractionated radiation significantly improved survival, but this schedule increased toxicity.

Adelstein DJ (2003) An intergroup phase III comparison of standard radiation therapy and two schedules of concurrent chemoradiotherapy in patients with unresectable squamous cell head and neck cancer. J Clin Oncol 21:92–98

Calais, 1999 → Concomitant chemotherapy as an adjunct to radiotherapy in the management of carcinoma of the oropharynx significantly improved overall survival.

Calais G (1999) Randomized trial of radiation therapy versus concomitant chemotherapy and radiation therapy for advanced stage oropharynx carcinoma. J Natl Cancer Inst 91:2081–2086

Pignon Meta-analysis, 2000 → 63 trials (10,741 patients) of locoregional treatment with or without chemotherapy yielded a pooled hazard ratio for death of 0.90 ($p < 0.0001$), corresponding to an absolute survival benefit of 4% at 2 and 5 years in favor of chemotherapy. There was no significant benefit associated with adjuvant or neoadjuvant chemotherapy.

Pignon JP (2000) Chemotherapy added to locoregional treatment for head and neck squamous cell carcinoma: three meta-analyses of updated individual data. Lancet 355 949–955

RTOG 95-01, 2004 → concurrent postoperative chemotherapy and RT significantly improved locoregional control and disease-free survival in high-risk patients with resected head and neck cancer. The combined treatment was associated with a substantial increase in adverse effects.

Cooper JS (2004) Postoperative concurrent radiotherapy and chemotherapy for high risk squamous cell carcinoma of the head and neck. N Engl J Med 350:1937–1944

EORTC, 2004 → postoperative concurrent cisplatin with RT is more efficient than RT alone in patients with locally advanced head and neck cancer, and did not cause an excessive number of late complications.

Bernier J (2004) Postoperative irradiation with or without concomitant chemotherapy for locally advanced head and neck cancer. N Engl J Med 350:1945–1952

IMRT

Washington University, 2003 → 126 patients (52 treated with definitive IMRT and 74 treated with postoperative IMRT). Median follow-up was 26 months.

- Seventeen locoregional failures (persistent or recurrent disease) were found. Of these 17 failures, nine (53%) were inside CTV1. One failure (6%) was marginal to CTV1 but inside CTV2. One failure (6%) occurred outside CTV1 but inside CTV2. Another failure was marginal to CTV2. Of the 17 failures, five (28%) were found outside of the IMRT field and in the lower neck.
- The 2-year locoregional control rate was 85%, and the ultimate locoregional control rate after surgical salvage was 89%.

Chao KS et al (2003) Patterns of failure in patients receiving definitive and postoperative IMRT for head-and-neck cancer. Int J Radiat Oncol Biol Phy 55(2):312–321

UCSF, 2003 → 150 patients treated with IMRT for head-and-neck cancer.

- For the primary definitive cases with a median follow-up of 25 months, four patients failed in the GTV. The 2- and 3-year local freedom from progression (LFFP) rates were 97% and 95%.
- With a median follow-up of 17 months, seven patients failed in the postoperative setting. The 2-year LFFP rate was 83%.
- There were few recurrences with excellent LFFP rates and no marginal failures.

Lee N et al (2003) Intensity-modulated radiation therapy for head-and-neck cancer: the UCSF experience focusing on target volume delineation. Int J Radiat Oncol Biol Phys 57:49–60

University of Iowa, 2005 → 151 patients with head-and-neck carcinomas were treated with IMRT for curative intent.

- Two-year overall survival, local progression-free survival, locoregional progression-free survival, and distant disease-free survival rates were 85, 94, 92, and 87%, respectively
- Patients with oropharyngeal cancer did significantly better than patients with oral cavity and laryngeal cancer, with a 2-year localregional control rate of 98% compared with 78% for oral cavity cancer and 85% for laryngeal cancer ($p = 0.005$).

Yao M et al (2005) Intensity-modulated radiation treatment for head-and-neck squamous cell carcinoma—the University of Iowa experience. Int J Radiat Oncol Biol Phys 63(2):410–421

UCSF, 2008 → 71 oropharyngeal cancers. Median follow-up of 33 months.

- Three-year local, regional, and locoregional progression-free estimates were 94, 94, and 90%, respectively.
- The 3-year overall survival estimate was 83%.
- Excellent local and regional control was achieved with IMRT and concurrent chemotherapy without prior surgical resection in the treatment of stage III and IV oropharyngeal carcinoma.

Huang K (2008) Intensity-modulated chemoradiation for treatment of stage III and IV oropharyngeal carcinoma: the University of California–San Francisco experience. Cancer 113(3):497–507

MSKCC, 2006 → 50 oropharyngeal cancers.

- Two-year local progression-free, regional progression-free, distant metastasis-free, and overall survival rates were 98, 88, 84, and 98%, respectively.
- IMRT achieved encouraging local control rates in patients with oropharyngeal carcinoma. Treatment toxicity was acceptable, even in the setting of concurrent chemotherapy.

de Arruda FF et al (2006) Intensity-modulated radiation therapy for the treatment of oropharyngeal carcinoma: the Memorial Sloan–Kettering Cancer Center experience. Int J Radiat Oncol Biol Phys 64(2):363–373

Targeted therapy trials

Cetuximab, 2006 → randomized. 424 patients with stage III–IV head and neck cancers. Randomized to RT (70 Gy at 2 Gy/fractions qd, 72–76.8 Gy at 1.2 Gy b.i.d. or 72 Gy in 42 fractions concomitant boost 1.8+1.5 Gy)±cetuximab (400 mg/m^2 loading dose IV 1 week before RT, followed by weekly infusions of 250 mg/m^2 during RT). Median follow-up: 4.5 years.

- Three-year LRCs: 47 vs. 34%; cetuximab gave a 32% reduction in LR progression
- Three-year PFSs: 42 vs. 31%; DM risks were similar.
- Three-year OSs: 55 vs. 45%; cetuximab gave a 26% reduction in the risk of death.
- Improved survival and locoregional control were obtained with cetuximab (caution: control arm was RT alone not chemo-RT).

Bonner JA et al (2006) Radiotherapy plus cetuximab for squamous-cell carcinoma of the head and neck. N Engl J Med 354: 567–578

5.9 Pearl Boxes

Regional Lymph Nodes (N) (Fig. 5.51)

N0: no regional lymph node metastasis
N1: metastasis in a single ipsilateral lymph node 3 cm or smaller in greatest dimension

N2: metastasis in a single ipsilateral lymph node larger than 3 cm but 6 cm or smaller in greatest dimension; or in multiple ipsilateral lymph nodes 6 cm or smaller in greatest dimension; or in bilateral or contralateral lymph nodes 6 cm or smaller in greatest dimension

N2a: metastasis in a single ipsilateral lymph node larger than 3 cm but 6 cm or smaller in greatest dimension

N2b: metastasis in multiple ipsilateral lymph nodes 6 cm or smaller in greatest dimension

N2c: metastasis in bilateral or contralateral lymph nodes 6 cm or smaller in greatest dimension

N3: metastasis in a lymph node larger than 6 cm in greatest dimension

Note. In a clinical evaluation, the actual size of the nodal mass should be measured, and allowance should be made for intervening soft tissues. Most masses larger than 3 cm in diameter are not single nodes but confluent nodes or tumors in soft tissues of the neck. There are three stages of clinically positive nodes: N1, N2, and N3. The use of subgroups a, b, and c is not required but is recommended. Midline nodes are considered homolateral nodes.

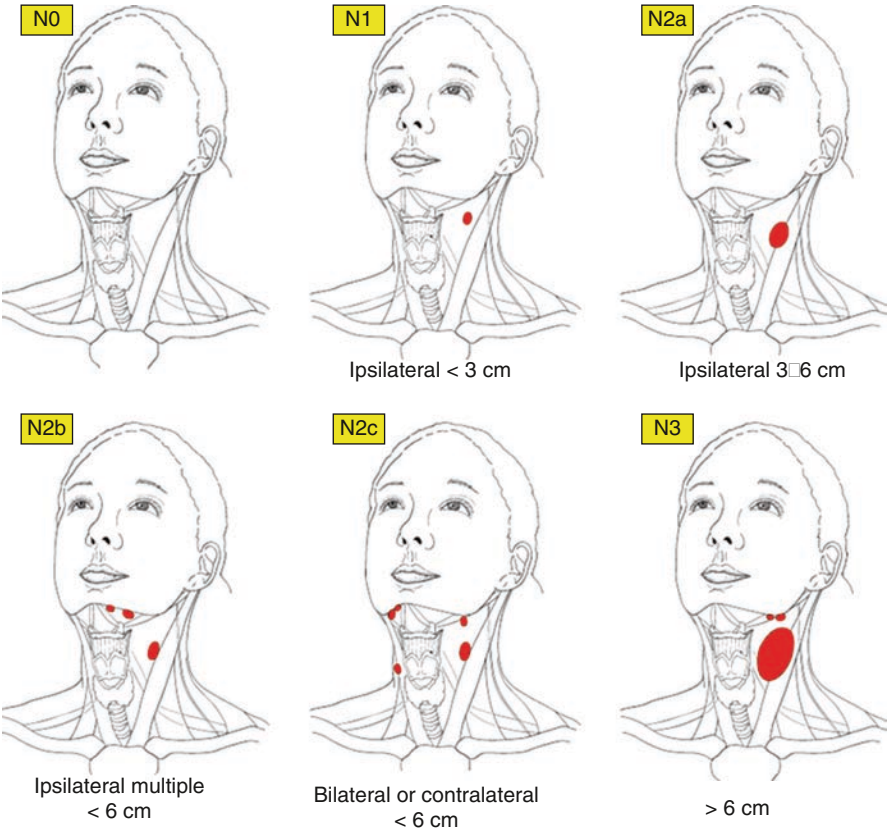


Fig. 5.51 N staging for head and neck cancers, excluding nasopharyngeal and thyroid cancers (from [11], reproduced with the permission from the American Joint Committee on Cancer)

Recurrence Factors in Head–Neck Cancers After Surgery

Close or positive surgical margin
Perineural invasion
Neural invasion
Involvement of two or more lymph nodes
Lymph node >3 cm
Extracapsular nodal extension
6 weeks after completion of surgery

Head–Neck Cancers Not Requiring Elective Neck RT (Table 5.4)

- T1–2 glottic laryngeal cancers
- Oral cavity cancers (T1 hard palate, gingiva, superficial oral tongue, buccal mucosa, T1–2 lip)
- Maxillary sinus cancers other than those with squamous cell histology
- Early-stage T1–2 nasal cavity cancers
- Low-grade adenoid cystic tumors
- N0 or N1 neck with no extracapsular nodal extension after neck dissection

Chinese Staging System for Nasopharyngeal Cancer (1998)

T1: tumor limited to nasopharynx
T2: tumor extends to nasal cavity, oropharynx, soft palate, anterior cervical vertebral soft tissue, proximal parapharyngeal region
T3: tumor invades distal parapharyngeal space, one cranial nerve, cranial base, pterygopalatine region, and fossa
T4: involvement of multiple cranial nerves, paranasal sinus, cavernous sinus, orbita, infratemporal fossa, C1–2 vertebrae
N1: presence in upper cervical lymph node of size <4 cm
N2: presence in lower cervical lymph node, or in a lymph node 4–7 cm in size
N3: presence in supraclavicular lymph node, or a lymph node >7 cm in size, or a fixed lymph node, or in a lymph node with skin infiltration
Stage I: T1N0M0
Stage II: T2 or N1
Stage III: T3 or N2
Stage IVA: T4 or N3
Stage IVB: M1

Table 5.4 RTOG/EORTC guidelines for the delineation of elective nodal CTV

Level	Superior	Caudal	Anterior	Posterior	Lateral	Medial
Ia	Geniohyoid muscle plane tangent to basilar edge of mandible	Plane tangent to body of hyoid bone	Symphysis menti, platysma muscle	Body of hyoid bone	Medial edge of anterior belly of digastric muscle	–
Ib	Mylohyoid muscle cranial edge of submandibular gland	Plane through central part of hyoid bone	Symphysis menti, platysma muscle	Posterior edge of submandibular gland	Basilar edge/ innerside of mandible, platysma muscle skin	Lateral edge of anterior belly of digastric muscle
IIa	Caudal edge of lateral process of C1	Caudal edge of the body of hyoid bone	Posterior edge of submandibular gland; anterior edge of internal carotid artery; posterior edge of posterior belly of digastric muscle	Posterior border of internal jugular vein	Medial edge of sternocleidomastoid	Medial edge of internal carotid artery, paraspinal (levator scapulae) muscle
IIb	Caudal edge of lateral process of C1	Caudal edge of the body of hyoid bone	Posterior border of internal jugular vein	Posterior border of the sternocleidomastoid muscle	Medial edge of sternocleidomastoid	Medial edge of internal carotid artery, paraspinal (levator scapulae) muscle
III	Caudal edge of the body of hyoid bone	Caudal edge of cricoid cartilage	Posterolateral edge of the sternohyoid muscle anterior edge of sternocleidomastoid muscle	Posterior edge of the sternocleidomastoid muscle	Medial edge of sternocleidomastoid	Internal edge of carotid artery, paraspinal (scalenus) muscle
IV	Caudal edge of cricoid cartilage	2 cm cranial to sternoclavicular joint	Anteromedial edge of sternocleidomastoid muscle	Posterior edge of the sternocleidomastoid muscle	Medial edge of sternocleidomastoid	Medial edge of internal carotid artery, paraspinal (scalenus) muscle

(*continued*)

Table 5.4 (continued)

Level	Superior	Caudal	Anterior	Posterior	Lateral	Medial
V	Cranial edge of body of hyoid bone	CT slice encompassing the transverse cervical vessels	Posterior edge of the sternocleidomastoid muscle	Anterior border of the trapezius muscle	Platysma muscle skin	Paraspinal (levator scapulae, splenius capitis) muscle
VI	Caudal edge of body of thyroid cartilage	Sternal manubrium	Skin, platysma muscle	Separation between trachea and esophagus	Medial edges of thyroid gland, skin and anterior–medial edge of sternocleidomastoid muscle	–
Retropharyngeal	Base of skull	Cranial edge of the body of hyoid bone	Fascia under the pharyngeal mucosa	Prevertebral muscle (longus colli, longus capitis)	Medial edge of the internal carotid artery	Midline

M muscle
Adapted from [55]

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Lung Cancer

6

Murat Beyzadeoglu, Gokhan Ozyigit, and Cuneyt Ebruli

Lung cancer is the malignant transformation of lung tissue. The term "lung cancer" is applied to tumors that develop from tracheal parenchyma, bronchi, bronchioles or lung parenchyma. Lung cancer is responsible for 12.4% of all new cancer cases and 17.6% of all deaths from cancer. Approximately one million people die of lung cancer each year. It is the most frequent cancer in males, and its incidence is rapidly increasing in females.

The trachea starts just after the larynx, and is 12 cm in length. It extends from the level of the C6 vertebra to the T4 vertebra, where it divides into two main bronchi (carina level). Its posterior wall is flat and has a membranous structure. Its other walls consist of serial half-ring-shaped cartilages with muscular and membranous structure. Tracheal mucosa is lined with ciliary epithelial cells to clear away small foreign bodies that come in with the air.

The right and left bronchi have similar structures to the trachea, but their cartilages are more irregular. The right main bronchus is shorter, thicker and more vertical, while the left main bronchus is thinner, longer and more horizontal. The bronchi divide into thin bronchioles.

There are two lungs in the thorax cavity, the right and left lungs (Fig. 6.1). The right lung has three and the left lung has two lobes. Each lung has a half conical base at the diaphragm. They have outer and inner faces, one base and one apex. Structures entering and exiting the lungs pass from the middle part of the inner face (hilar region), which includes the main arteries, veins, lymphatics, and the nerves of the lungs.

The bronchioles end with small saccules known as alveoli, which are filled with air. Small capillaries are spread across the walls of these saccules.

The pleura is a serous membrane that covers the outer part of the lung together with the upper part of the diaphragm. There is a region called the pleural space between the inner and outer sheets that is filled with fluid. This helps the lungs to inflate and deflate during respiration.

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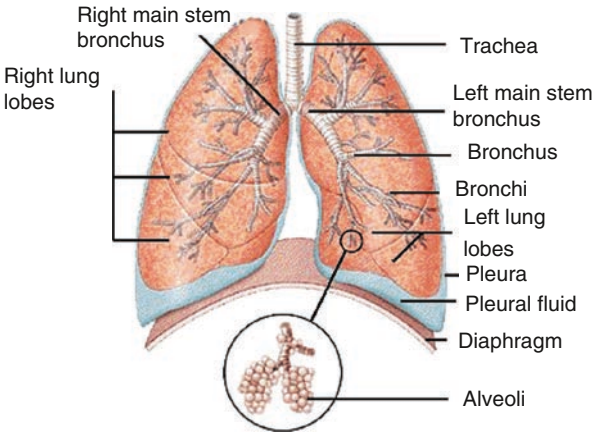

Fig. 6.1 Anatomy of the lung

Lung cancer is essentially divided into two broad categories: small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC).

6.1 Non-Small Cell Lung Cancer (NSCLC)

These constitute 75–80% of all lung cancers.

6.1.1 Pathology

The Three Major Subtypes of NSCLC [1]

- Adenocarcinoma
- Squamous cancer
- Large cell cancer

Adenocarcinoma [1]

- Forty percent of all lung cancers in the USA are adenocarcinomas.
- This is the most frequent lung cancer in females, and its incidence is increasing.
- Generally starts from the peripheral parts of the lung.
- May involve other parts of the body.
- Has subtypes, such as bronchoalveolar adenocancer.

Squamous cancer [1]

- Also known as epidermoid cancer.
- Constitutes 30–35% of all lung cancers in the USA.
- Commonly seen in males and older people.
- Generally starts at main bronchi.
- Has a tendency to grow relatively slowly.
- Has no tendency for early metastasis.
- Highly correlated with cigarette smoking.

Large cell carcinoma [1]

- Constitutes 5–15% of all lung cancers in the USA.
- Generally starts in the small bronchioles.
- May appear in any part of the lungs.
- Is generally large in size at diagnosis.
- Has a tendency to metastasize to the mediastinum and the brain.

6.1.2 General Presentation

Most patients have nonspecific symptoms or present no signs until the disease has progressed significantly. Subsequently, only a small portion of lung cancers are detected early, when curative treatment has the greatest chance of success.

Symptoms and Signs

- Cough
- Dyspnea
- Fatigue
- Chest, shoulder, arm or back pain
- Recurrent pneumonia or bronchitis
- Hemoptysis
- Anorexia and weight loss
- General pain
- Hoarseness
- Wheezing
- Swelling in face or neck

Sometimes the symptoms of lung cancer may not be related to the lungs or respiration. Since lung cancer is usually diagnosed at an advanced stage, the primary cancer may have spread to other parts of the body. Therefore, symptoms like headache, bone fractures, thrombosis and fatigue, related to the affected organs, may be seen.

Paraneoplastic syndromes [2–7]

- Gynecomastia (generally in large cell carcinoma).
- Hypercalcemia (generally in epidermoid cancer).
- Hypertrophic pulmonary osteoarthropathy (generally in the adenocarcinomatous type).
  Inappropriate ADH secretion is most frequently observed in SCLC.
- *Pancoast syndrome.* This is observed in superior sulcus tumors. It is characterized by lower brachial plexopathy, Horner syndrome, and pain in shoulder and ulnar site of arm.
- *Horner syndrome.* This characterized by enophthalmos, ptosis, miosis, ipsilateral sweating loss, and hoarseness due to laryngeal nerve invasion.

6.1.3 Staging

AJCC Staging [8]

T1: A tumor that is 3 cm or smaller in greatest dimension, is surrounded by lung or visceral pleura, and is without bronchoscopic evidence of invasion more proximal than the lobar bronchus (i.e., not in the main bronchus) (Fig. 6.2)
T1a: Tumor ≤ 2 cm
T1b: Tumor >2 cm but smaller or equal to 3 cm

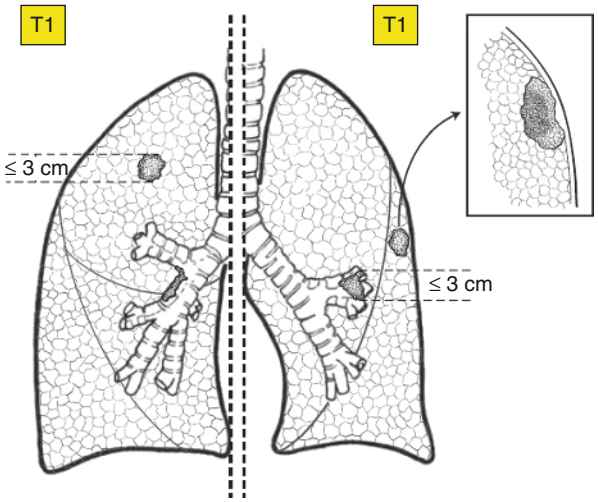

Fig. 6.2 T1 stage lung cancer (from [17], p 170, Fig. 19.3, reproduced with the permission from the American Joint Committee on Cancer)

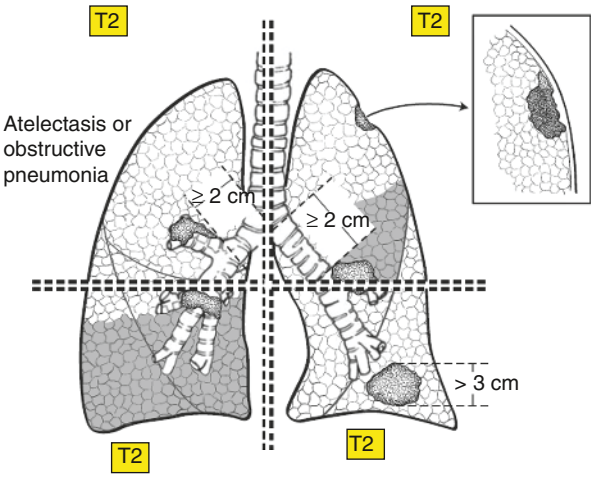

Fig. 6.3 T2 stage lung cancer (from [17], p.170, Fig. 19.4, reproduced with the permission from the American Joint Committee on Cancer)

T2: A tumor with any of the following features of size or extent (Fig. 6.3):
Larger than 3 cm in greatest dimension
Involves the main bronchus and is 2 cm or larger distal to the carina
Invades the visceral pleura
Associated with atelectasis or obstructive pneumonitis that extends to the hilar region but does not involve the entire lung
T2a: Tumor > 3–5 cm
T2b: Tumor > 5–7 cm

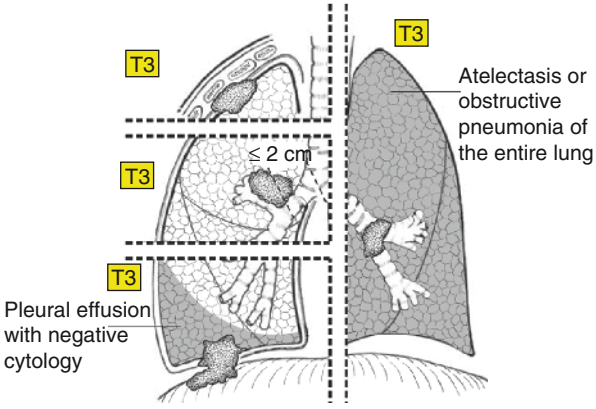

Fig. 6.4 T3 stage lung cancer (from [17], p.170, Fig. 19.5, reproduced with the permission from the American Joint Committee on Cancer)

T3: A tumor more than 7 cm or one that directly invades any of the following (Fig. 6.4): Chest wall (including superior sulcus tumors), parietal pleura diaphragm, mediastinal pleura, phrenic nerve, parietal pericardium; or, tumor in the main bronchus less than 2 cm distal to the carina but without involvement of the carina; or, associated atelectasis or obstructive pneumonitis of the entire lung or separate tumor nodules in the same lobe.

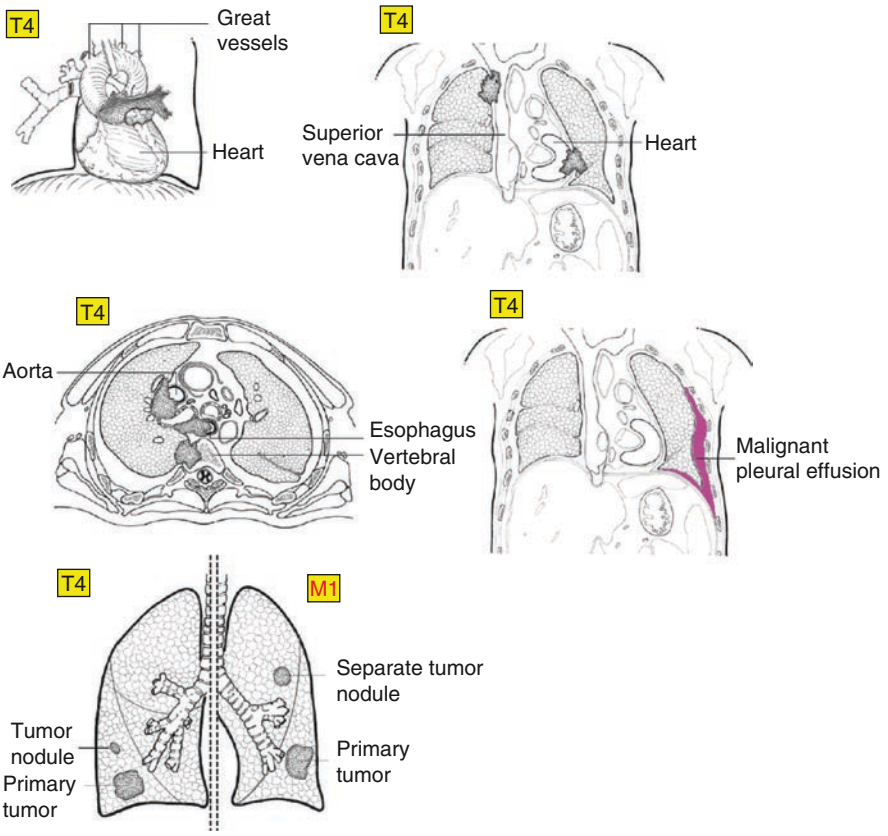

Fig. 6.5 T4 stage in lung cancer (from [17], p.170, Fig. 19.6, reproduced with the permission from the American Joint Committee on Cancer)

T4: A tumor of any size that invades any of the following (Fig. 6.5): Mediastinum, heart, great vessels, trachea, recurrent laryngeal nerve, esophagus, vertebral body, carina; or, separate tumor nodules in a different ipsilateral lobe.

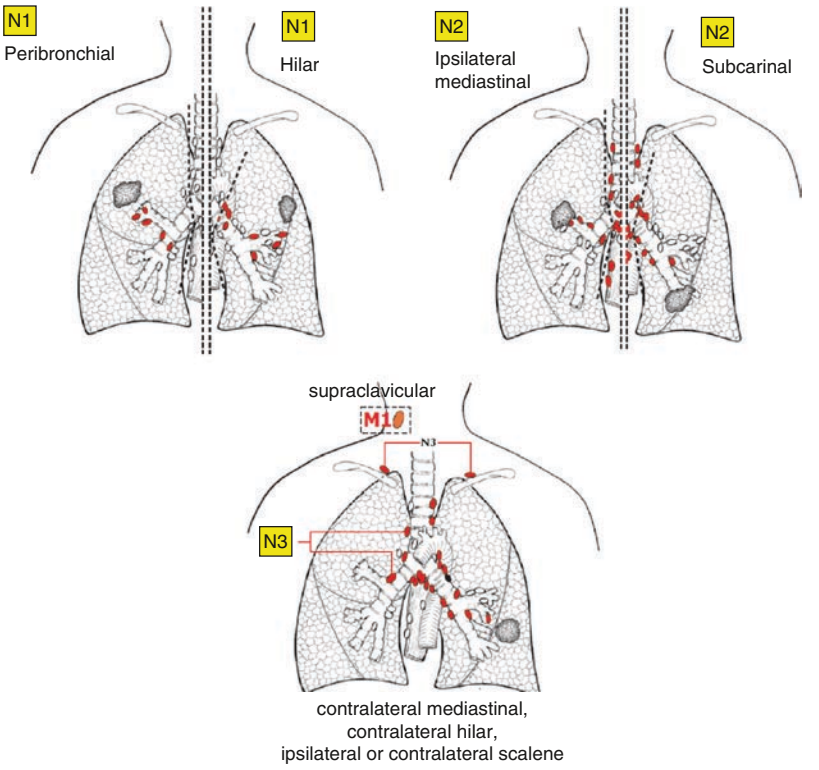

Fig. 6.6 N stages in lung cancer (from [17], p.174, Figs. 19.7–19.9, reproduced with the permission from the American Joint Committee on Cancer)

N Staging (Fig. 6.6)

N0: No regional lymph node metastasis
N1: Metastasis to ipsilateral peribronchial and/or ipsilateral hilar lymph nodes, and intrapulmonary nodes including involvement by direct extension of the primary tumor
N2: Metastasis to ipsilateral mediastinal and/or subcarinal lymph node(s)
N3: Metastasis to contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene, or supraclavicular lymph node(s)

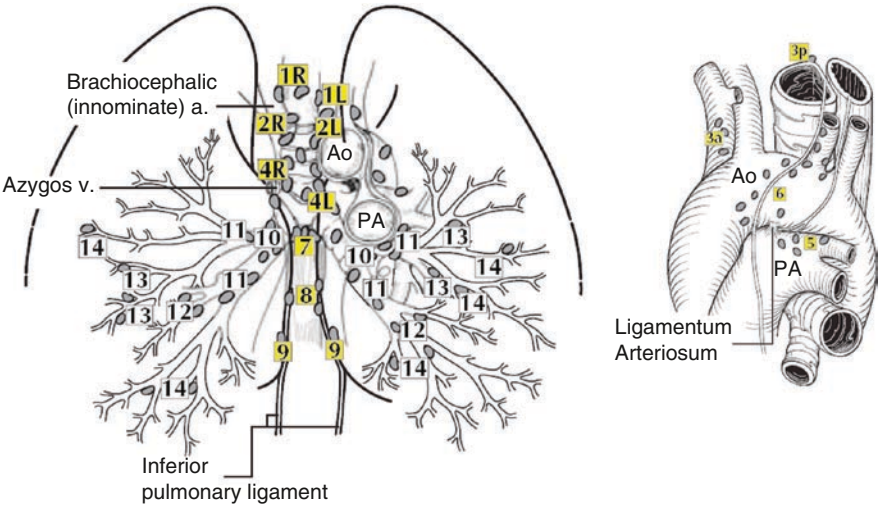

Fig. 6.7 Lymph node mapping in lung cancers (from [17], p 169, Fig. 19.2, reproduced with the permission from the American Joint Committee on Cancer)

AJCC Stage Groupings

Stage 0:	TisN0M0
Stage IA:	T1a-bN0M0
Stage IB:	T2aN0M0
Stage IIA:	T2bN0M0, T1a-bN1M0, T2aN1M0
Stage IIB:	T2bN1M0; T3N0M0
Stage IIIA:	T1N2M0; T2N2M0; T3N1M0; T3N2M0; T4N0-1M0
Stage IIIB:	Any T, N3M0; T4N2-3, M0
Stage IV:	Any T, Any N, M1

Lung Lymphatics (Figs. 6.7 and 6.8) [9]

N2 lymph nodes
1: upper mediastinal
2: upper paratracheal
3: prevascular (3a) and retrotracheal (3p)
4: lower paratracheal
5: subaortic
6: paraaortic
7: subcarinal
8: paraesophagial
9: pulmonary ligament

N1 lymph nodes
10: hilar
11: interlobar
12: lobar
13: segmental
14: subsegmental

Lymphatic drainage of lung lobes
Right upper lobe → ipsilateral mediastinum
Left upper lobe → ipsilateral and contralateral mediastinum
Right lower lobe → subcarinal lymph nodes > right upper mediastinum > right lower mediastinum
Left lower lobe → subcarinal lymph nodes > right or left upper mediastinum > right or left lower mediastinum

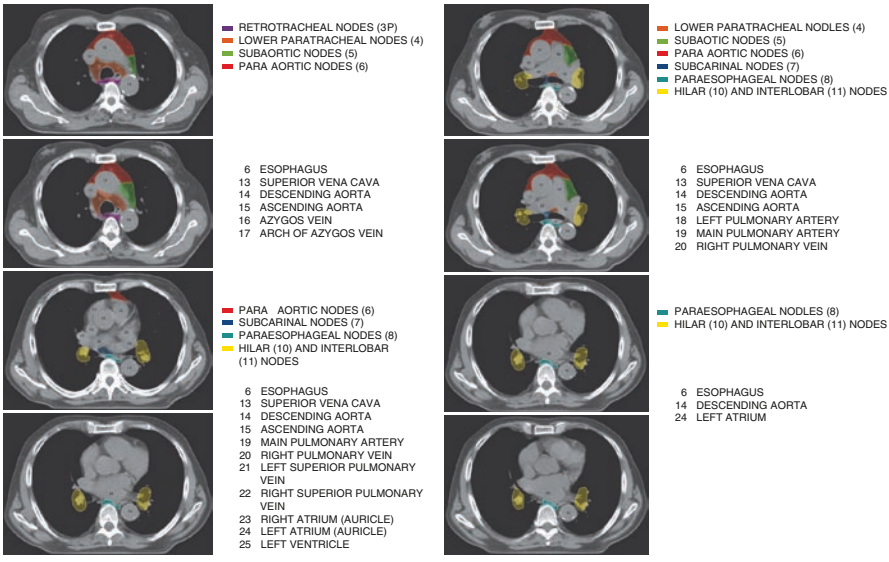

Fig. 6.8 Intrathoracic lymph nodes in serial axial CT slices

6.1.4 Treatment Algorithm

Operable stage I–II [10]

Lobectomy or pneumonectomy

Gross total resection (+), and T2N0 or T1N1
Adjuvant chemotherapy is added
Gross total resection (+) and T3N0

Adjuvant chemotherapy is added
Surgical margin (+), nodal extracapsular extension (+)
Reresection
Postoperative RT (adjuvant chemotherapy is given after RT)

Limited operable stage I–II
Preoperative chemotherapy → surgery → chemotherapy
Surgical margin (+), nodal extracapsular extension (+)
Postoperative RT (adjuvant chemotherapy is given after RT)

Inoperable stage I–II
Definitive RT (primary tumor + involved lymph nodes)
1.8–2 Gy/day, total >65 Gy (conventional fractionation)
4 Gy/day, total 48 Gy (hypofractionated regimen to primary for low KPS or peripheral tm)
IMRT >70 Gy or stereotactic radiotherapy (e.g., Cyberknife)

± Chemotherapy (neoadjuvant/concurrent/adjuvant) (if patient tolerates)

Operable stage IIIA, borderline operable stage IIIA
1. Chemotherapy → restaging → progression (−)

Surgery → chemotherapy ± RT
RT indications
Surgical margin (+) or close
Nodal extracapsular extension
N2 disease
Alternative
1. Concurrent chemoradiotherapy (45 Gy), then restaging

Progression (−): surgery +CT
Progression (+)/inoperable: RT (63 Gy)
2. Chemotherapy → restaging → progression (+)/if inoperable
Concurrent chemoradiotherapy (>60 Gy)

Inoperable stage IIIA
1. Concurrent chemoradiotherapy (>60 Gy) → chemotherapy
2. Induction chemotherapy + concurrent chemoradiotherapy (>60 Gy)

Stage IIIB (pleural effusion [−])
1. Concurrent chemoradiotherapy (>60 Gy) → chemotherapy
2. Induction chemotherapy + concurrent chemoradiotherapy (>60 Gy)

T4N0, T4N1
Surgery → CT ± RT or,
CT ± RT → surgery→ CT

Stage IIIB (pleural effusion [+])
Pleurodesis or similar approaches, then treat as stage IV disease
Stage IV
ECOG performance score = 0–2
CT ± palliative RT
ECOG performance score = 3–4
Best supportive care

Superior sulcus tumor
Operable
Concurrent chemoradiotherapy (>60 Gy) → surgery → CT, or
Surgery → CT ± RT (60–66 Gy)
(RT indications → close or surgical margin (+) or, extracapsular nodal extension)
Borderline operable
Concurrent chemoradiotherapy (45 Gy), then restaging

Progression (−) → surgery → CT
Progression (+)/inoperable → concurrent chemoradiotherapy (>60 Gy)

Inoperable
Concurrent chemoradiotherapy (>60 Gy)

6.1.5 Radiotherapy

Radiotherapy for NSCLC is given either alone or in combination with chemotherapy for curative intent, or palliatively to improve symptoms, prophylactically to prevent the occurrence of disease, as a neoadjuvant treatment to decrease tumor size in order to make it operable, or postoperatively to eradicate microscopic disease.

Simulation is performed in the supine position with T arm (arms are up over the head), regardless of the technique.

Developmental Steps in Radiotherapy Techniques for NSCLC

- *Conventional radiotherapy.* Very large fields were used; dose escalation was not possible due to large volumes of lung, heart and spinal cord. Elective nodal irradiation was used.
- *Conformal radiotherapy.* Limited fields are used, including only the primary tumor and the involved lymphatic region. Therefore, dose escalation is possible for curative approaches. Elective nodal radiotherapy is not used. However, incidental elective nodal RT was demonstrated in some trials by evaluating isodoses.

- *Stereotactic radiotherapy.* This is used for small, peripheral T1–2N0M0 tumors. It is a highly effective and curative approach with minimal toxicity. More than 100 Gy can be given to the GTV. No elective nodal RT is used.

Conventional RT field in upper lobe tumors (Fig. 6.9)
- Bilateral supraclavicular field
- Upper mediastinum
- Subcarinal field
  (Two vertebra below carina) or
  (Five to six centimeters below carina)
- Primary tumor + 2 cm
  (Two anterior–posterior parallel–opposed fields)

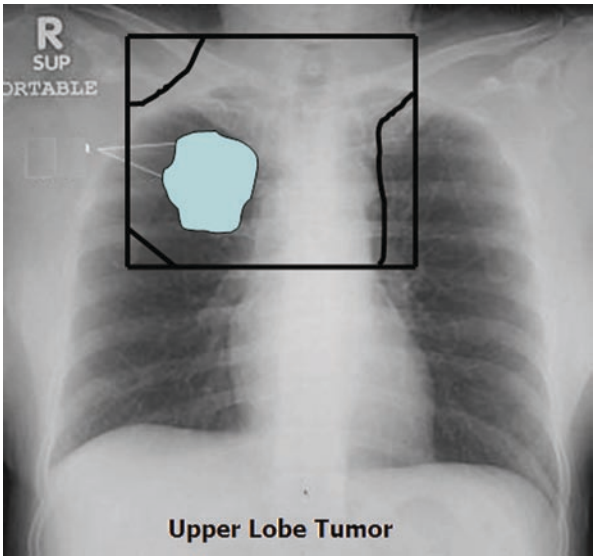

Fig. 6.9 Conventional RT field for upper lobe tumor

Conventional RT fields in hilar tumors (Fig. 6.10)
- Superior: thoracic inlet
- Inferior: 8–9 cm below carina
- Includes mediastinum
- Primary tumor +2 cm
  (Two anterior–posterior parallel–opposed fields)

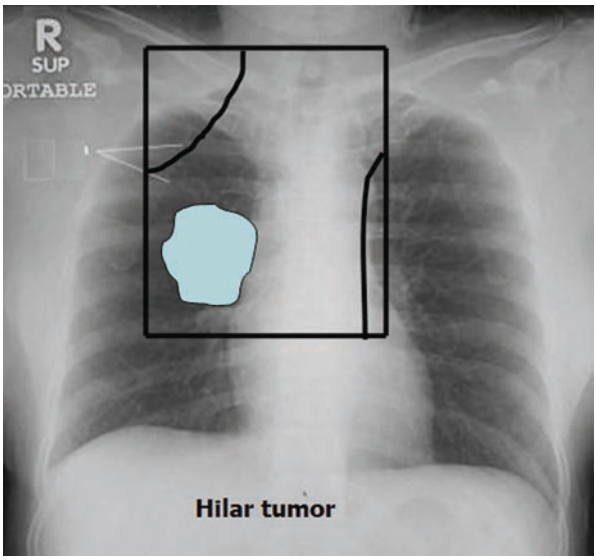

Fig. 6.10 Conventional RT field for hilar tumor

Conventional RT field in lower lobe tumors (Fig. 6.11).

- Superior: thoracic inlet.
- Inferior: 8–9 cm below carina (may be more inferior depending on whether the tumor includes the diaphragm).
- Includes mediastinum.
- Primary tumor +2 cm.
  (Two anterior–posterior parallel–opposed fields).

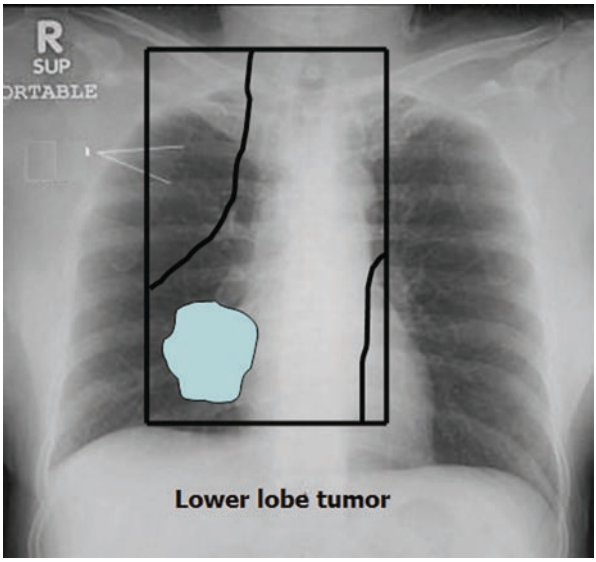

Fig. 6.11 Conventional RT field for lower lobe tumor

Conventional RT field in lower lobe tumor+gross mediastinal lymph node involvement (Fig. 6.12)

- Superior: thoracic inlet
- Inferior: 8–9 cm below carina (may be more inferior depending on the tumor localization)
- Includes supraclavicular field
- Includes mediastinum
- Primary tumor + 2 cm

(Two anterior–posterior parallel–opposed fields)

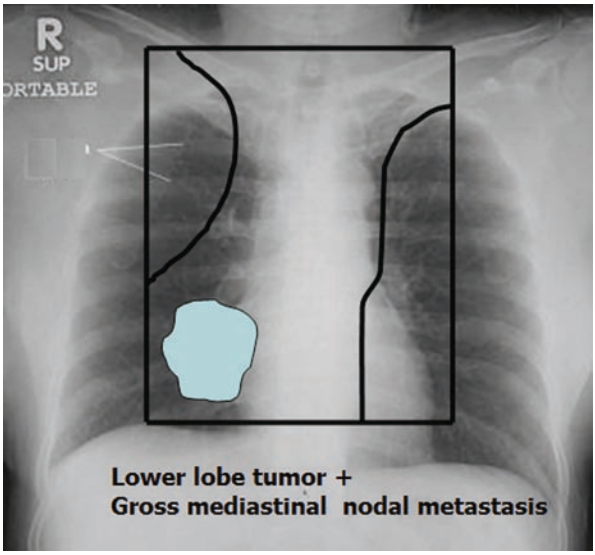

Fig. 6.12 Conventional RT field for lower lobe tumor with gross mediastinal LN involvement

Conventional Definitive RT Doses

Anterior–posterior parallel–opposed fields can be used until 46 Gy, then the spinal cord is spared and primary + involved lymphatics are given more than 60 Gy.

- Six to ten megavolt photons are recommended

Planning in postoperative cases is similar. It is indicated for a close or positive surgical margin, extracapsular nodal extension, or multiple N2 lymph nodes.

- Microscopic residual (−): 46–54 Gy (1.8–2 Gy/day)
- Microscopic residual (+): field is localized after 46 Gy, total dose 60–66 Gy (1.8–2 Gy/day)

Possible borders for postoperative RT

Mediastinum ± (microscopic residual + 2 cm)

Mediastinum → superior: thoracic inlet (superior to sternoclavicular joint); inferior: T9–10 intervertebral space; lateral: costochondral joints

(Ipsilateral lateral field is enlarged if that site is to be irradiated)

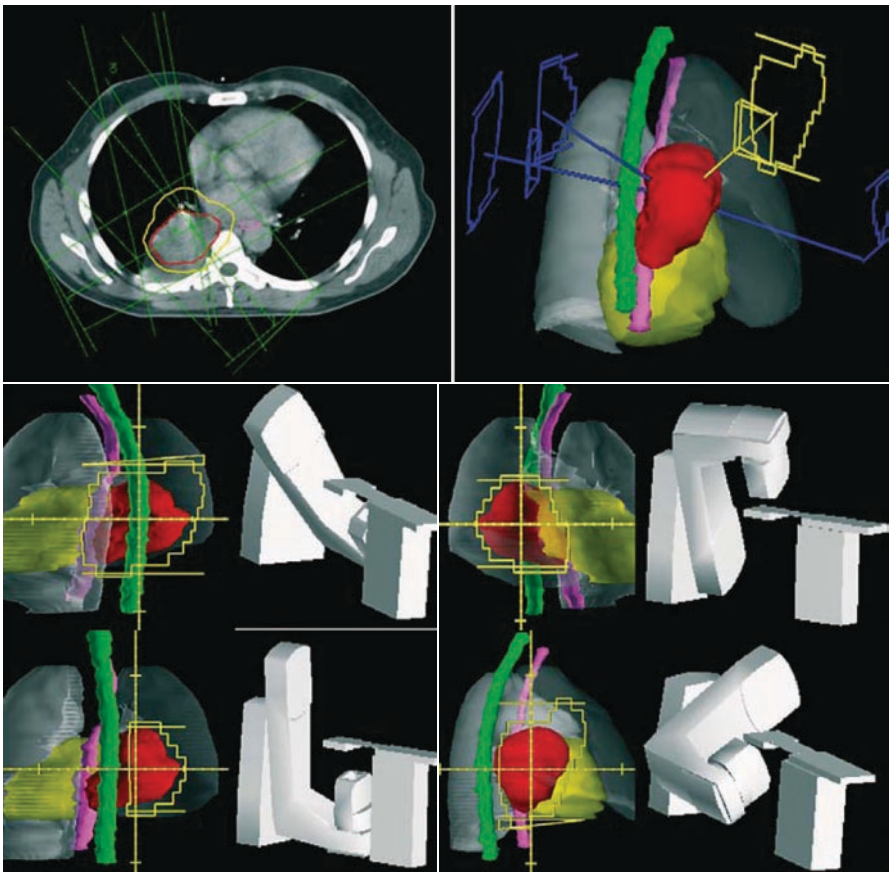

Fig. 6.13 Conformal RT fields in lung cancer

Conformal RT Volumes (Fig. 6.13) [11]

Conformal RT is the current standard RT technique for both definitive and postoperative radiotherapy. If conformal therapy facilities are available, conventional RT is not recommended due to its high toxicity and inability to escalate total radiation dose. Only the primary tumor and involved lymphatic regions are irradiated in conformal therapy.
CTV: (primary tumor and involved nodes)
SCC: 6 mm; adenocarcinoma: 8 mm; LN: 5 mm
PTV:
Upper lobes
Right–left: CTV + 1.5 cm
Anterior–posterior: CTV + 1.5–2 cm
Superior–inferior: CTV + 2 cm

Lower lobes
Right–left: CTV + 1.5 cm
Anterior–posterior: CTV + 2 cm
Superior: CTV + 2–3 cm
Inf: CTV + 3–4 cm

Critical organs for conformal radiotherapy

Lung (volume calculated by subtracting the bilateral lung volume from PTV)
Mean lung dose (MLD): <15 Gy
V20 (volume of lungs receiving 20 Gy and more):
<35% for chemoradiotherapy
<40% for definitive radiotherapy
V30 (volume of lungs receiving more than 30 Gy): <25–30%
V10 (volume of lungs receiving more than 10 Gy): <40%
V5 (volume of lungs receiving more than 5 Gy): <60%
Esophagus
V20 (volume of esophagus receiving more than 20 Gy): <45%
Mean esophageal dose (MED): <28 Gy
V50 (volume of esophagus receiving more than 50 Gy): <31 Gy
V60 (volume of esophagus receiving more than 60 Gy): <24 Gy
Maximum dose should be less than 73 Gy (D_{max} < 73 Gy)
Heart
V30 (volume of heart receiving more than 30 Gy): <46%
Mean heart dose should be less than 26 Gy
Spinal cord
<46 Gy

Stereotactic Body Radiotherapy (SBRT) (Fig. 6.14)

Patients with T1–2N0M0 NSCLC can be treated with SBRT. Lesions should be localized in peripheral regions of the lung. However some selected centralized tumors may also be treated with SBRT.
Recommended total dose: 60 Gy in three fractions (20 Gy/fraction) or 60 Gy in four fractions for centralized tumors.
Critical organs and tolerance dose: see Sect. 2.12.

Fig. 6.14 Robotic radiosurgery for a T1N0M0 peripheral non-small cell lung cancer (figure provided courtesy of Hacettepe University)

6.1.6 Selected Publications

Limited resection vs. lobectomy

North America Lung Cancer Study Group 821 (LCSG 821) 1995 (1982–88) → 247 pT1N0M0 peripheral NSCLC. Randomized to limited resection vs. lobectomy.

- Locoregional relapse: 17% in limited resection arm vs. 6% in lobectomy.
- Fatality: 39% in limited resection arm vs. 30% in lobectomy.
- Conclusion: lobectomy is recommended rather than limited excision.

Ginsberg RJ et al (1995) Randomized trial of lobectomy vs. limited resection for T1 N0 nonsmall cell lung cancer. Ann Thorac Surg 60(3):615–622

Surgery ± external RT.

Rome, 2002 (1989–1997) → 104 stage I NSCLC. Randomized to surgery vs. surgery + RT. RT dose: 54 Gy (51 cases).

- Five-year OS: 67% in combined arm vs. 58% in surgery-alone arm ($p = 0.048$).
- Five-year locoregional recurrence: 2% in combined arm vs. 23% in surgery-alone arm.
- 11% toxicity in RT arm, but no long-term toxicity.
- 37% percent radiological lung fibrosis in RT arm.
- Conclusion: adjuvant RT increases local control after surgery, and is promising in regards to increasing survival.

Trodella L (2002) Adjuvant radiotherapy in nonsmall cell lung cancer with pathological stage I: definitive results of a phase III randomized trial. Radiother Oncol 62(1):11–19

GETCB, France. 1999 (1986–1994) → 728 stage I–III NSCLC cases. Randomized after surgery to surveillance vs. 60 Gy RT.

- Five-year OS: 30% in combined arm vs. 43% in surveillance.
- Death other than NSCLC: 31% in combined arm vs. 8% in surveillance (most deaths were due to high fraction dose; subgroup analysis showed that these deaths were at stage I–II, not stage III).
- No difference in local relapse and distant metastasis.
- However, presence of N0 cases and use of Co-60, high fraction dose (>2.5 Gy) are criticized.

Dautzenberg B et al (1999) A controlled study of postoperative radiotherapy for patients with completely resected nonsmall cell lung carcinoma. Groupe d'Etude et de Traitement des Cancers Bronchiques. Cancer 86(2):265–273

Lung Cancer Study Group 773 (LCSG 773), 1986 → 230 stage II–III NSCLC cases. Randomized after surgery to RT (50 Gy, mediastinum) vs. surveillance.

- Local relapse: 1% in RT vs. 20% in surveillance
- No difference in overall survival

The Lung Cancer Study Group (1986) Effects of postoperative mediastinal radiation on completely resected stage II and stage III epidermoid cancer of the lung. N Engl J Med 315(22):1377–1381

Adjuvant chemotherapy vs. adjuvant chemoradiotherapy

CALGB 9734, 2007→ randomized. 44 stage IIIA (N2) NSCLC cases. 37 patients: adjuvant chemotherapy after surgery (carboplatin + paclitaxel) vs. RT (2–4 weeks after chemotherapy, 50 Gy RT).

- No difference in median survival.
- No difference in overall survival.
- Study was closed early.

Perry MC (2007) A phase III study of surgical resection and paclitaxel/carboplatin chemotherapy with or without adjuvant radiation therapy for resected stage III non-small-cell lung cancer: Cancer and Leukemia Group B 9734. Clin Lung Cancer 8(4):268–272

INT 0115, ECOG EST 3590/RTOG 91-05, 2000 → Randomized. 488 stage II–IIIA NSCLC cases, four cycles of cisplatin/etoposide + concurrent RT vs. RT (50.4 Gy).

- No difference in OS
- No difference in in-field relapses
- No difference in treatment-related toxicity

Keller SM et al (2000) A randomized trial of postoperative adjuvant therapy in patients with completely resected stage II or IIIA nonsmall-cell lung cancer. N Engl J Med 343(17):1217–1222

Prophylactic cranial RT (PCI) in NSCLC

Germany, 2007 (1994–2001) → Randomized. 112 operable stage IIIA (diagnosed with mediastinoscopy). Surgery + adjuvant 50–60 Gy RT vs. preoperative CT (three cycles cisplatin/etoposide) + concurrent chemoradiotherapy (cisplatin/etoposide, 2 daily fractions of 1.5 Gy, total dose 45 Gy) + surgery + PCI (30 Gy in 15 fractions).

- Study closed early due to benefit of the chemotherapy arm.
- Brain metastasis as a first site: 8% in PCI arm vs. 35% in non-PCI arm (statistically significant).
- Brain metastasis rate: 9% in PCI arm vs. 27% in non-PCI arm (statistically significant).

Pottgen C (2007) Prophylactic cranial irradiation in operable stage IIIA nonsmall-cell lung cancer treated with neoadjuvant chemoradiotherapy: results from a German multicenter randomized trial. J Clin Oncol 25(31):4987–4992

CHART, 1997 → 563 patients. CHART (continuous hyperfractionated accelerated radiotherapy) regimen, which uses 36 small fractions of 1.5 Gy given three times per day, to give 54 Gy in only 12 consecutive days. NSCLC localized to the chest with a performance status of 0 or 1. Patients were randomized to CHART or conventional radiotherapy (60/2 Gy in 6 weeks). Overall there was a 24% reduction in the relative risk of death, which is equivalent to an absolute improvement in 2-year survival of 9%, from 20 to 29% ($p = 0.004$). The largest benefit occurred in patients with squamous cell carcinomas (34% reduction in the relative risk of death; an absolute improvement at 2 years of 14% from 19 to 33%). Severe dysphagia occurred more often in the CHART group (19 vs. 3%). There were no important differences in short-term or long-term morbidity. CHART compared with conventional radiotherapy gave a significant improvement in survival of patients with NSCLC.

Saunders M et al (1997) Continuous hyperfractionated accelerated radiotherapy (CHART) vs. conventional radiotherapy in nonsmall-cell lung cancer: a randomized multicentre trial. CHART Steering Committee. Lancet 350(9072):161–165

UCSD, 1990 → Patients randomly assigned to group one received cisplatin and vinblastine and then began radiation therapy on day 50 (60 Gy over a 6-week period). Patients assigned to group two received the same radiation therapy but began it immediately and received no chemotherapy. In patients with stage III NSCLC, induction chemotherapy significantly improves median survival (by about 4 months) and doubles the number of long-term survivors as compared with radiation therapy alone.

Dillman RO et al (1990) A randomized trial of induction chemotherapy plus high-dose radiation vs. radiation alone in stage III nonsmall-cell lung cancer. N Engl J Med 323(14):940–945

Institute Gustave Roussy, 1991 → Randomized study comparing radiotherapy alone with combination of radiotherapy and chemotherapy in nonresectable squamous cell and large-cell lung carcinoma. The radiation dose was 65 Gy in each group, and chemotherapy included vindesine, cyclophosphamide, cisplatin, and lomustine. The 2-year survival rate was 14% in RT alone and 21% in the combined arm ($p = 0.08$). The distant metastasis rate was significantly lower in the combined arm ($p < 0.001$). Local control was poor in both groups (17 and 15%, respectively) and remained the major problem.

Le Chevalier T et al (1991) Radiotherapy alone vs. combined chemotherapy and radiotherapy in nonresectable nonsmall-cell lung cancer: first analysis of a randomized trial in 353 patients. J Natl Cancer Inst 83(6):417–423

The Netherlands, 1992 → 331 patients with nonmetastatic inoperable NSCLC randomized to one of three treatments: RT for 2 weeks (3 Gy given ten times, in five fractions per week), followed by a 3-week rest period and then radiotherapy for 2 more weeks (2.5 Gy given ten times, five fractions per week); RT on the same schedule, combined with cisplatin given on the first day of each treatment week; or RT on the same schedule, combined with cisplatin given daily before radiotherapy. Survival was significantly improved in the radiotherapy and daily cisplatin group as compared with the radiotherapy group ($p = 0.009$).

Schaake-Koning C et al (1992) Effects of concomitant cisplatin and radiotherapy on inoperable nonsmall-cell lung cancer. N Engl J Med 326(8):524–530

Sause, 1995 → Patients were randomly assigned to receive either 60 Gy of RT delivered at 2 Gy per fraction, 5 days a week, over a 6-week period; induction chemotherapy consisting of cisplatin (100 mg/m^2) on days 1 and 29 and 5 mg/m^2 vinblastine per week for five consecutive weeks beginning on day 1 with cisplatin, followed by standard RT starting on day 50; or 69.6 Gy delivered at 1.2 Gy per fraction twice daily (hyperfractionated radiation therapy). Induction chemotherapy followed by RT in unresectable NSCLC was superior to hyperfractionated radiation therapy or standard radiation therapy alone, yielding a statistically significant short-term survival advantage.

Sause WT et al (1995) Radiation Therapy Oncology Group (RTOG) 88–08 and Eastern Cooperative Oncology Group (ECOG) 4588: preliminary results of a phase III trial in regionally advanced, unresectable nonsmall-cell lung cancer. J Natl Cancer Inst 87(3):198–205

PORT meta-analysis → 2,128 patients from nine randomized trials (published and unpublished) were analyzed by intention to treat. There were 707 deaths among 1,056 patients assigned to postoperative radiotherapy and 661 among 1,072 assigned to surgery alone. Median follow-up was 3.9 years for surviving patients. The results show a significant adverse effect of postoperative radiotherapy on survival (hazard ratio 1.21 [95% CI 1.08–1.34]). This 21% relative increase in the risk of death is equivalent to an absolute detriment of 7% (3–11) at 2 years, reducing overall survival from 55 to 48%. Subgroup analyses suggest that this adverse effect was greatest for patients with stage I/II, N0–N1 disease, whereas for those with stage III, N2 disease there was no clear evidence of an adverse effect. Postoperative radiotherapy was detrimental to patients with early-stage completely resected NSCLC and should not be used routinely for such patients. The role of postoperative radiotherapy in the treatment of N2 tumors is not clear and may warrant further research.

PORT Meta-analysis Trialists Group (1998) Postoperative radiotherapy in nonsmall-cell lung cancer: systematic review and meta-analysis of individual patient data from nine randomized controlled trials. Lancet 352(9124):257–263

6.2 Small Cell Lung Cancer (SCLC)

Small cell lung cancer (SCLC) constitutes nearly 20% of all lung cancers. Its incidence is increasing rapidly compared to other lung cancers. SCLC has the most prominent association with cigarette smoking among all lung cancers. The probability of female cigarette smokers developing SCLC is higher than that of male cigarette smokers.

SCLC is rapidly fatal if not treated [12].

- Mean survival with a combination of chemotherapy and radiotherapy for limited-stage disease is 20 months. Two-year survival is 45%, and 5-year survival is 15–20%.
- Survival is 1–3 months in extensive-stage disease if not treated. Chemotherapy may prolong survival to 9–12 months.

6.2.1 Pathology

Tumor cells of small cell lung cancer are found in small, dense packages with limited cytoplasm. Their nuclei have finely granular chromatin, and a nucleolus cannot be seen [13].

6.2.2 General Presentation

Symptoms and findings of SCLC are similar to those for NSCLC. Since SCLC has a high tendency for distant metastasis (~60% at presentation), metastatic organ-specific signs and symptoms may be prominent at diagnosis.

Most cases die due to relapses, secondary malignancies or other reasons during late periods.

- Most recurrences are observed in the first year of therapy. Although relapses in the following years are rare, most patients die due to the disease.
- Secondary malignancies are usually NSCLC, upper airway cancers or gastrointestinal system tumors.
- SCLC patients surviving more than 5 years have a sixfold greater risk of dying from noncancer-related causes [14].

6.2.3 Staging

AJCC 7th edition is recommended for the classification of both non-small cell and small cell lung cancers. However, old staging system simply divided SCLC into limited and extensive stages.

Limited-stage SCLC [8]

- One-third of all SCLCs.
- Limited to one hemithorax, ipsilateral hilus and mediastinum (can be treated with a reasonable radiotherapy portal).
- Ipsilateral pleural effusion: extensive stage.
- Ipsilateral supraclavicular lymph node does not affect limited-stage disease.

Extensive-stage SCLC

- Beyond the limits of its origin at the hemithorax, distant metastasis, pleural effusion

(Any SCLC that cannot be treated with a reasonable radiotherapy portal.)
(Veterans Affairs Lung Study Group 1957)
The *International Lung Cancer Study Group (ILCSG)* modified this staging system as follows. Contralateral mediastinal lymph nodes that can be treated with a reasonable RT field and benign pleural effusions also are included in limited-stage disease. All circumstances other than these are accepted as extensive-stage SCLC (1997) [15].
The ILCSG has defined limited-stage SCLC as stage I–IIIb according to the TNM staging system in recent years [15]. TNM staging is the same as that of NSCLC.

6.2.4 Treatment Algorithm

SCLC is highly chemosensitive and radiosensitive, but is not chemocurable or radiocurable.

Limited-stage SCLC (stage I–IIIB) [16]
Concurrent chemoradiotherapy
(CT → cisplatin + etoposide in every 3 weeks for four cycles)
(RT → 1.8–2 Gy/day, total dose 54–56 Gy
(RT → 1.5 Gy×2/day, total 45 Gy, hyperfractionated course)
Complete response → PCI (25/2.5 or 24/2 Gy)
T1N0M0 → surgery and chemotherapy is an alternative approach
Extensive-stage SCLC (stage IV)
CT ± palliative RT

6.2.5 Radiotherapy

The radiotherapy techniques for SCLC are similar to those for NSCLC.

Possible RT portal

- GTV + 1.5 cm
- Ipsilateral hilar region, bilateral mediastinum

(Mediastinum, starts at thoracic inlet and includes subcarinal region)
(Subcarinal involvement (+), inferior border is 5 cm below carina)
No contralateral hilar region and supraclavicular lymphatics are included within RT portal if not involved.

Prophylactic cranial RT

- Helmet-type cranial RT is applied.
- Anterior border includes orbital apex beyond 2 cm of lens. Inferior border is below the C2 vertebra including the temporal lobe, and 0.5 cm below the cribriform plate.

6.2.6 Selected Publications

NCI Canada, 1993 → patients randomized to early RT received 40 Gy in 15 fractions over 3 weeks to the primary site concurrent with the first cycle of EP (week 3), and late RT patients received the same radiation concurrent with the last cycle of EP (week 15). After completion of all chemotherapy and TI, patients without progressive disease received prophylactic cranial irradiation (25 Gy in 10 fractions over 2 weeks). Progression-free survival and overall survival were superior in the early RT arm. Patients in the late RT arm had a higher risk of brain metastases. The early administration of RT in the combined modality therapy of limited-stage SCLC is superior to late or consolidative TI.

Murray N et al (1993) Importance of timing for thoracic irradiation in the combined modality treatment of limited-stage small-cell lung cancer. The National Cancer Institute of Canada Clinical Trials Group. J Clin Oncol 11(2):336–344

Pignon, 1992 → the meta-analysis included 13 trials and 2,140 patients with limited disease. The relative risk of death in the combined therapy group as compared with the chemotherapy group was 0.86 ($p = 0.001$), corresponding to a 14% reduction in the mortality rate. The benefit in terms of overall survival at 3 years was 5.4%. Thoracic radiotherapy moderately improves survival in patients with limited small-cell lung cancer who are treated with combination chemotherapy.

Pignon JP et al (1992) A meta-analysis of thoracic radiotherapy for small-cell lung cancer. N Engl J Med 327(23):1618–1624

Warde, 1992 → Meta-analysis of 11 randomized trials. The risk difference method showed that radiation therapy improved 2-year survival by 5.4%. Intrathoracic tumor

control was improved by 25.3% in RT arms. The OR for excess treatment-related deaths in the thoracic radiation-treated patients was 2.54 ($p < 0.01$). This meta-analysis demonstrated a small but significant improvement in survival and a major improvement in tumor control in the thorax in patients receiving thoracic radiation therapy. However, this was achieved at the cost of a small increase in treatment-related mortality.

Warde P, Payne D (1992) Does thoracic irradiation improve survival and local control in limited-stage small-cell carcinoma of the lung? A meta-analysis. J Clin Oncol 10(6):890–895

Takada, 2002 → 231 patients with LS-SCLC. RT consisted of 45 Gy over 3 weeks (1.5 Gy twice daily), and the patients were randomly assigned to receive either sequential or concurrent TRT. All patients received four cycles of cisplatin plus etoposide every 3 weeks (sequential arm) or 4 weeks (concurrent arm). TRT was begun on day 2 of the first cycle of chemotherapy in the concurrent arm and after the fourth cycle in the sequential arm. Concurrent radiotherapy yielded better survival than sequential radiotherapy. The two-, three-, and 5-year survival rates for patients who received sequential radiotherapy were 35.1, 20.2, and 18.3%, respectively, as opposed to 54.4, 29.8 and 23.7%, respectively, for the patients who received concurrent radiotherapy. Hematologic toxicity was more severe in the concurrent arm.

Cisplatin plus etoposide and concurrent radiotherapy was more effective for the treatment of LS-SCLC than cisplatin plus etoposide and sequential radiotherapy.

Takada M et al (2002) Phase III study of concurrent vs. sequential thoracic radiotherapy in combination with cisplatin and etoposide for limited-stage small-cell lung cancer: results of the Japan Clinical Oncology Group Study 9104. J Clin Oncol 20(14):3054–3060

EORTC 08993/22993, 2007 (2001–2006) → 286 extensive-stage SCLC. Randomized after 4–6 cycles of CT in the case of complete response to PCI (20 Gy/5 fractions or 30 Gy/12 fractions) vs. surveillance.

- One-year symptomatic brain metastasis: 15% in PCI arm vs. 40% in surveillance arm.
- One-year OS: 27% in PCI arm, 13% in surveillance arm.
- Clinically insignificant neurological side effects in PCI arm.
- PCI dose: 20 Gy/5 fractions in 60% of cases, and efficient (but long-term sequelae unknown).
- PCI is beneficial in patients with extensive-stage disease who completely respond to 4–6 cycles of chemotherapy.

Slotman B et al (2007) Prophylactic cranial irradiation in extensive small-cell lung cancer. N Engl J Med 357(7):664–672

Gustave-Roussy PCI-88, France, 1998 → 211 SCLC cases with complete response. Randomized PCI vs. surveillance. No standard RT schedule (RT dose: 24–30 Gy, fraction dose: ≤3 Gy and duration: <3 weeks). Median follow-up was 5 years.

- Trial closed early due to highly significant benefit of PCI.

Laplanche A (1998) Controlled clinical trial of prophylactic cranial irradiation for patients with small-cell lung cancer in complete remission. Lung Cancer 21(3):193–201

(Turrisi), Medical University of South Carolina, USA, 1999 → 417 SCLC cases. All patients had four cycles of cisplatin/etoposide and received concurrent 45 Gy thoracic RT, but were randomized into two groups, one receiving one fraction daily and the other two fractions daily.

- Five-year survival in hyperfractionated schedule was 26 vs. 16% in the conventional arm.
- Grade III esophagitis was significantly higher in the hyperfractionation arm.
- It was recommended that a 45 Gy hyperfractionation schedule or higher doses with conventional RT should be used.

Turrisi T et al. (1999) Twice-daily compared with once-daily thoracic radiotherapy in limited small-cell lung cancer treated concurrently with cisplatin and etoposide. N Engl J Med 340(4):265–271

(Auperin) Gustave-Roussy, France, 1999 → 7 randomized trials of PCI, including 987 cases with complete response to chemotherapy.

- Three-year survival: 20.7% in PCI arm vs. 15.3% in non-PCI arm (absolute benefit of 5%).
- PCI dose increase decreased the brain metastasis risk but not survival (8, 24–25, 30, 36–40 Gy).
- PCI should be done as early as possible after chemotherapy.
- Criticisms: number of patients in four trials <100, ~14% of cases with extensive-stage SCLC, and heterogeneous dose fractionation.

Auperin A (1999) Prophylactic cranial irradiation for patients with small-cell lung cancer in complete remission. Prophylactic Cranial Irradiation Overview Collaborative Group. N Engl J Med 341(7):476–484

Brussels, Belgium, 2001→ 12 randomized trials with 1,547 cases (PCI (+) and PCI (−)). PCI given with induction CT in five trials, or given after complete response to CT in five trials.

- PCI significantly decreased brain metastasis incidence (hazard ratio = HR = 0.48).
- PCI significantly increased OS (HR = 0.82).
- No long-term neurotoxicity.
- PCI should be given to patients with complete response to chemotherapy.

Meert AP (2001) Prophylactic cranial irradiation in small cell lung cancer: a systematic review of the literature with meta-analysis. BMC Cancer 1:5

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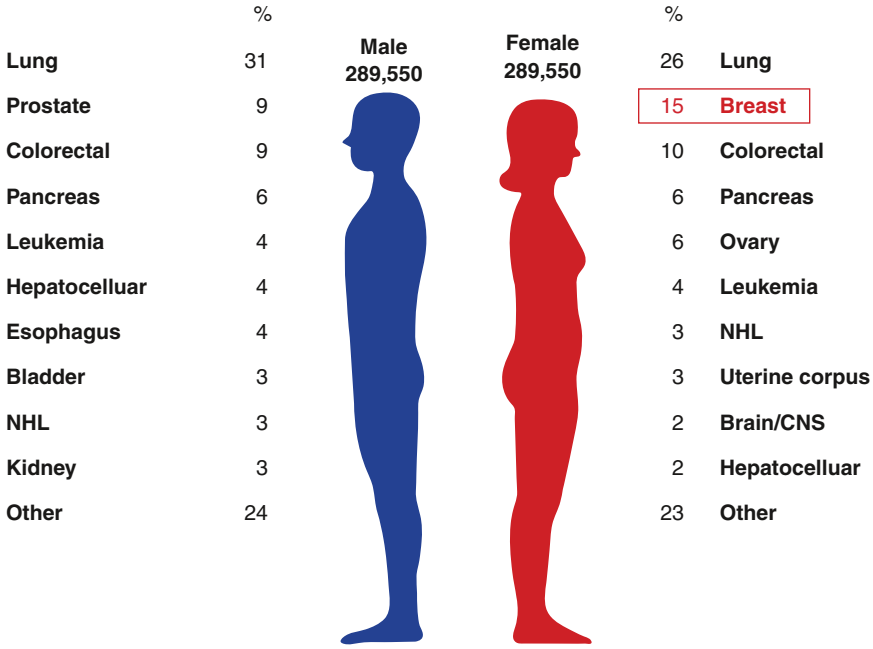
Breast Cancer

7

Gokhan Ozyigit, Murat Beyzadeoglu, and Cuneyt Ebruli

Breast cancer is the most common cancer, and the second most common cause of cancer-related death in females (Fig. 7.1). It is an important cause of morbidity and mortality despite recent developments in early diagnosis and treatment. Early diagnosis is common in developed countries due to regular screening programs [1].



Source : American Cancer Society, 2007.

Fig. 7.1 Estimated cancer mortality rates in the USA in 2007

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The female breast lies between the second and sixth costae, and consists of 15–20 sections called lobes (Fig. 7.2). Each lobe ends in lobules, which are smaller than the lobes. In turn, these lobules end in milk saccules that secrete milk. All of these structures are connected to each other by canals.

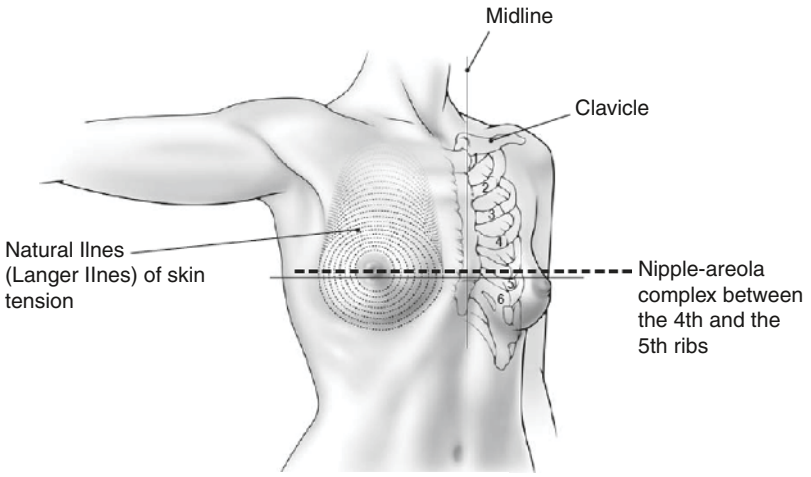

Fig. 7.2 Anatomy of the breast (from [18], p 10, Fig. 2.1)

Thin bands extending from the chest wall muscles to the breast skin divide the lobes from each other. Each lobe excretes milk through one main canal. These main canals converge and exit from the nipple. All of these breast structures are surrounded by connective fatty and fibrous tissue.

7.1 Pathology

Most breast carcinomas are of adenocarcinomas that originate from the terminal ducts of the breast (Fig. 7.3). Other tumors, such as squamous cell cancer, cystosarcoma phyllodes, sarcoma and lymphoma, constitute less than 5% of all breast malignancies [2].

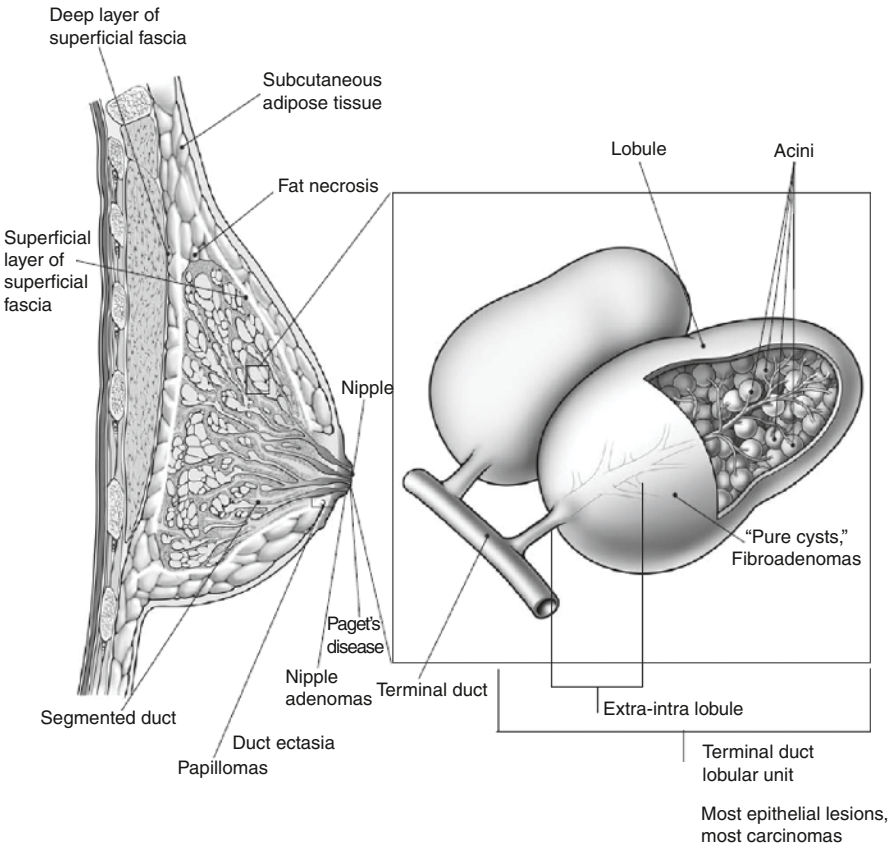

Fig. 7.3 Ductal lobular system in breast and their pathologies (from [18], p 10, Fig. 2.3, reproduced with the permission from Springer Science and Business Media)

Breast cancers are histopathologically divided into two main groups: carcinoma in situ (noninvasive breast cancer) and invasive carcinoma.

- *Carcinoma in situ*: malignant epithelial cells are limited to the basal membrane of ductus and acinus.
- *Invasive carcinoma (infiltrative cancer)*: neoplastic cells invade the basal membrane and show stromal invasion; therefore, invasive cancers may invade lymphovascular spaces, and they have the ability to metastasize to regional lymph nodes and distant organs (Table 7.1).

Table 7.1 WHO classification of breast cancer [2]

In situ carcinoma	Invasive carcinoma
Ductal carcinoma in situ (DCIS)	Invasive ductal carcinoma
Lobular carcinoma in situ (LCIS)	Invasive lobular carcinoma Tubular carcinoma Invasive cribriform carcinoma Medullary carcinoma Mucinous carcinoma Invasive papillary carcinoma Invasive micropapillary carcinoma Apocrine carcinoma Secretory (juvenile) carcinoma Adenoid cystic carcinoma Metaplastic carcinoma Neuroendocrine carcinoma Inflammatory carcinoma

Invasive ductal carcinoma (nonspecific type) [3]. This is the most commonly seen invasive cancer (70–80%), and constitutes a wide range of cancers that do not have the specific features observed in other subtypes.

- 70–80% of invasive ductal cancers are estrogen receptor (ER) positive, 60–70% are progesterone receptor (PR) positive, and 15–30% are HER-2/neu positive.

Invasive ductal cancer with extensive in situ component [4]. Here there is a >25% in situ component within the tumor or its surroundings.

- This situation may be important in relation to local relapses in patients with breast-conserving surgery.

Invasive lobular carcinoma [5]. This constitutes 5–15% of all invasive breast cancers, and is more commonly seen in females receiving hormone replacement therapy.

- It has a higher tendency for multifocality and bilaterality compared to other breast cancers.
- It also has a different metastasis pattern. Peritoneal, retroperitoneal, bone marrow, leptomeningeal, gastrointestinal, ovarian and uterine metastases are more frequent.
- Lung and pleural metastases are rare.
- Invasive lobular cancers are 70–95% ER (+), 60–70% PR (+).
- HER-2/neu is negative, except for the pleomorphic type.

Inflammatory carcinoma [6]. This is a special clinical presentation of invasive breast cancer.

- Here, lymphatic drainage is damaged due to extensive dermal lymphatic invasion. Clinical findings are characterized by skin edema, erythema, induration, sensitivity and a "peau d'orange" appearance.
- Its name derives from the fact that it resembles inflammation, although there is no inflammation microscopically.
- The underlying invasive cancer is usually a high-grade infiltrative ductal carcinoma.

Ductal carcinoma in situ (DCIS) [7]. This is a noninvasive malignant epithelial cell proliferation limited to the duct system that exhibits no basal membrane invasion.

- It may be limited to just a few terminal duct tubules, or may include several lobules or segments in a very extensive form.
- DCIS constituted only 0.8–5% of all breast cancers before the introduction of routine screening with mammography; it now constitutes 15–20% of all breast cancers.
- 6.2–22% of all DCIS cases are bilateral, while 64–80% are multicentric.
- The risk of axillary metastasis is only 1–2%.
- DCIS is seen synchronously with invasive cancer in 2–46% of cases [7].
- The risk of invasive cancer development in a woman with DCIS is 10–16 times higher than in the normal female population.

There are several prognostic indices for DCIS that can be used to standardize therapeutic approaches, the most common of which is the Van Nuys prognostic index (VPNI). Breast-conserving surgery (BCS) is recommended for patients with a low VNPI score (Table 7.2).

Total score of VNPI	**Recommended treatment**
4–6	BCS
7–9	BCS+RT
10–12	Mastectomy

Table 7.2 Updated Van Nuys prognostic Index

Parameter	1 Point	2 Points	3 Points
Size (mm)	≤15	16–40	>40
Grade	Grade I–II	Grade I–II + necrosis	Grade III
Surgical margin (mm)	≥10	1–9	<1
Age (years)	>60	40–60	<40

Important reminder: RT is currently recommended for all DCIS patients with BCS, regardless of VNPI.

Lobular carcinoma in situ (LCIS) [8]. This is a very rare lesion found in 1% of all breast biopsies. It consists of uniform proliferated cells that fill and distort terminal duct lobular units.

- They are generally not macroscopic lesions, and are diagnosed incidentally in an excised breast biopsy due to other reasons.
- They do not have a special appearance in mammography.
- LCIS is almost always observed in premenopausal women 35–55 years of age or postmenopausal women receiving hormone replacement therapy.
- Cancer develops after 15–20 years.
- There is no risk of metastasis.

Treatment of LCIS. Two treatment options are recommended to patients: bilateral mastectomy with or without reconstruction and life-long close observation (surveillance).

- Patients should be informed that bilateral mastectomy is performed only for prophylactic reasons, and that there is a 25% risk of invasive cancer development within one of the breasts during the next 25–30 years.

7.2 General Presentation

See Table 7.3.

Table 7.3 Signs and symptoms in breast cancers

Signs and symptoms	Comment
Mass	Mobile
	Painless
	Unilateral and continuous
	No clear border
	Irregular and difficult to palpate
Pain	Ninety percent painless at presentation. Pain occurs at later periods
Nipple discharge	Not frequent
	Unilateral
	Generally bloody

Table 7.3 (continued)

Signs and symptoms	Comment
Forgue sign	This is the fullness, verticality and upward position of the involved breast. Upper quadrant cancers in the breast pull the nipple towards the tumor
Skin edema over breast	Tumor cells reach superficial dermal lymphatics by passing through lymph vessels within Cooper's ligaments. Lymphatics are obstructed, lymph drainage is damaged, and a limited edema occurs on the skin
Nipple retraction or depression	This occurs as a result of tumor growth and its invasion of the nipple
Skin ulceration and erythema	Tumor cells first invade the deep fascia, and then the pectoral muscle and chest wall during the advanced stages of cancer
Axillary lymphadenopathies	–
Abnormal swelling in arm	Lymphatic drainage is damaged due to obstruction with tumor cells, resulting in lymphedema in arm
Mass	Mobile Painless Unilateral and continuous No clear border Irregular and difficult to palpate
Pain	Ninety percent painless at presentation. Pain occurs during later periods
Nipple Discharge	Not frequent Unilateral Generally bloody

7.3 Staging

T Staging (Fig. 7.4) [2]

T0: No evidence of primary tumor
Tis: Intraductal carcinoma, lobular carcinoma *in situ*, or Paget disease of the nipple with no associated invasion of normal breast tissue
Tis (DCIS): ductal carcinoma *in situ*
Tis (LCIS): lobular carcinoma *in situ*
Tis (Paget): Paget disease of the nipple with no invasive tumor (note: Paget's disease associated with a tumor is classified according to the size of the tumor)

(*continued*)

(continued)

T1: Tumor is not larger than or equal to 2.0 cm in greatest dimension
- T1mi: Microinvasion not larger than or equal to 0.1 cm in greatest dimension
- T1a: Tumor larger than 0.1 cm but not larger than or equal to 0.5 cm in greatest dimension
- T1b: Tumor larger than 0.5 cm but not larger than or equal to 1.0 cm in greatest dimension
- T1c: Tumor larger than 1.0 cm but not larger than or equal to 2.0 cm in greatest dimension

T2: Tumor larger than 2.0 cm but not larger than or equal to 5.0 cm in greatest dimension

T3: Tumor larger than 5.0 cm in greatest dimension

T4: Tumor of any size with direct extension to (a) the chest wall or (b) skin, only as described below (invasion of dermis alone is not T4)
- T4a: Extension to chest wall, not including pectoralis muscle
- T4b: Edema (including peau d'orange other than inflammatory carcinoma) or ulceration of the skin of the breast, or satellite skin nodules confined to the same breast
- T4c: Both T4a and T4b
- T4d: Inflammatory carcinoma

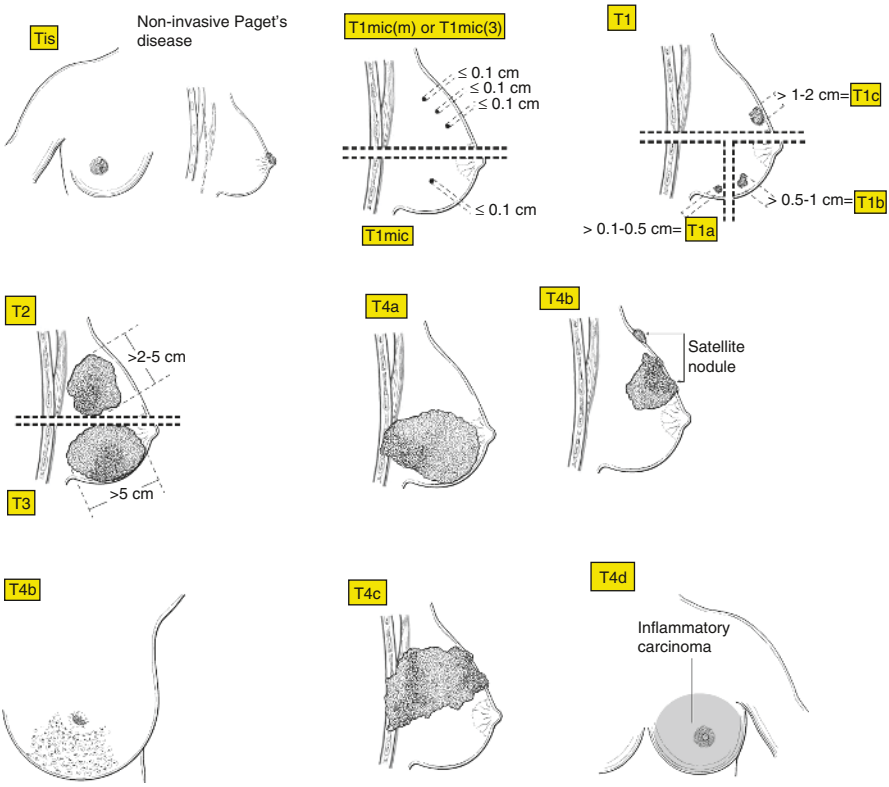

Fig. 7.4 T staging in breast cancer (from [19], pp 222–225, Figs. 25.3–25.10, reproduced with the permission from the American Joint Committee on Cancer)

Regional Lymph Nodes (N) (Fig. 7.5)

NX: Regional lymph nodes cannot be assessed (e.g., previously removed)
N0: No regional lymph node metastasis
N1: Metastasis to movable ipsilateral axillary lymph node(s)
N2: Metastasis to ipsilateral axillary lymph node(s) fixed or matted, or in clinically apparent* ipsilateral internal mammary nodes in the *absence* of clinically evident lymph node metastasis
  N2a: Metastasis in ipsilateral axillary lymph nodes fixed to one another (matted) or to other structures
  N2b: Metastasis only in clinically apparent* ipsilateral internal mammary nodes and in the *absence* of clinically evident axillary lymph node metastasis
N3: Metastasis in ipsilateral infraclavicular lymph node(s) with or without axillary lymph node involvement, or in clinically apparent* ipsilateral internal mammary lymph node(s) and in the *presence* of clinically evident axillary lymph node metastasis; or, metastasis in ipsilateral supraclavicular lymph node(s) with or without axillary or internal mammary lymph node involvement
  N3a: Metastasis in ipsilateral infraclavicular lymph node(s)
  N3b: Metastasis in ipsilateral internal mammary lymph node(s) and axillary lymph node(s)
  N3c: Metastasis in ipsilateral supraclavicular lymph node(s)

[Note: Clinically apparent is defined as detected by imaging studies (excluding lymphoscintigraphy) or by clinical examination or grossly visible pathologically].

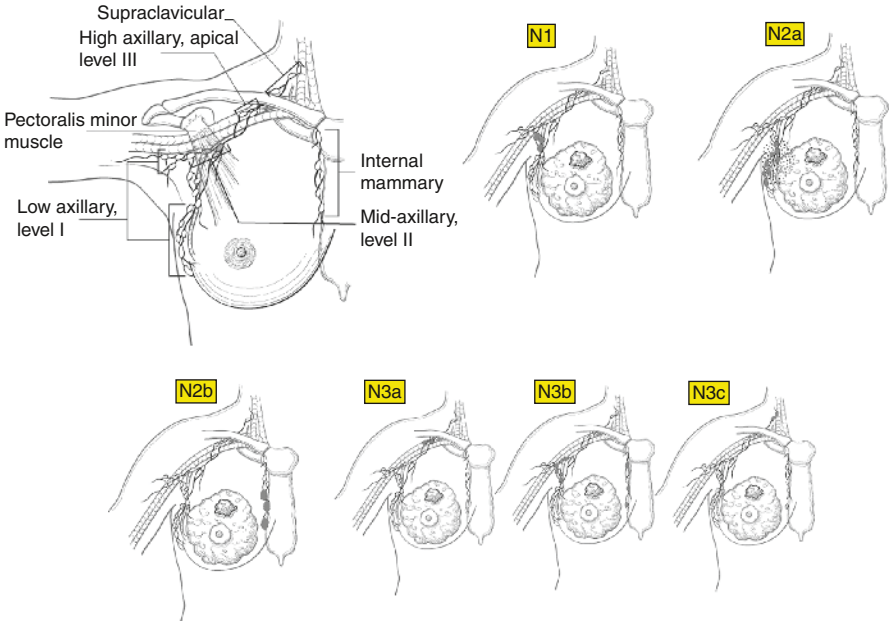

Fig. 7.5 N staging in breast cancer (from [19], pp 221, 225–227, Figs. 25.2, 25.10–25.16, reproduced with the permission from the American Joint Committee on Cancer)

Pathologic Classification (pN)*

pNX: Regional lymph nodes cannot be assessed (e.g., not removed for pathologic study or previously removed)

pN0: No regional lymph node metastasis histologically, and no additional examination for isolated tumor cells (ITC)

[Note: ITCs are defined as single tumor cells or small cell clusters that are not larger than 0.2 mm, usually detected only by immunohistochemical (IHC) or molecular methods, but that may be verified on hematoxylin and eosin (H&E) stain. ITCs do not usually show evidence of malignant activity, e.g., proliferation or stromal reaction].

pN0 (i−): No regional lymph node metastasis histologically, negative IHC

pN0 (i+): No regional lymph node metastasis histologically, positive IHC, and No IHC cluster larger than 0.2 mm

pN0 (mol−): No regional lymph node metastasis histologically, and negative molecular findings (RT-PCR)**

pN0 (mol+): No regionally lymph node metastasis histologically, and positive molecular findings (RT-PCR)**

*[Note: Classification is based on axillary lymph node dissection with or without sentinel lymph node (SLN) dissection. Classification based solely on SLN dissection without subsequent axillary lymph node dissection is designated (sn) for sentinel node, e.g., pN0(I+) (sn)].

**[Note: RT-PCR: Reverse transcriptase-polymerase chain reaction].

pN1: Metastasis in 1–3 axillary lymph nodes, and/or in internal mammary nodes with microscopic disease detected by SLN dissection but not clinically apparent**

pN1mi: Micrometastasis (larger than 0.2 mm and/or more than 200 cells, but not larger than 2.0 mm)

pN1a: Metastasis in 1–3 axillary lymph nodes

pN1b: Metastasis in internal mammary nodes with microscopic disease detected by SLN dissection but not clinically apparent**

pN1c: Metastasis in 1–3 axillary lymph nodes and in internal mammary lymph nodes with microscopic disease detected by SLN dissection but not clinically apparent** (If associated with more than three positive axillary lymph nodes, the internal mammary nodes are classified as pN3b to reflect increased tumor burden.)

pN2: Metastasis in 4–9 axillary lymph nodes, or in clinically apparent** internal mammary lymph nodes in the *absence* of axillary lymph node metastasis to ipsilateral axillary lymph node(s) fixed to each other or to other structures

pN2a: Metastasis in 4–9 axillary lymph nodes (at least one tumor deposit is larger than 2.0 mm)

pN2b: Metastasis in clinically apparent* internal mammary lymph nodes in the *absence* of axillary lymph node metastasis

pN3: Metastasis in ten or more axillary lymph nodes, or in infraclavicular lymph nodes, or in clinically apparent* ipsilateral internal mammary lymph node(s) in the

presence of one or more positive axillary lymph node(s); or, in more than three axillary lymph nodes with clinically negative microscopic metastasis in internal mammary lymph nodes; or in ipsilateral supraclavicular lymph nodes

pN3a: Metastasis in ten or more axillary lymph nodes (at least one tumor deposit larger than 2.0 mm); or metastasis to the infraclavicular lymph nodes

pN3b: Metastasis in clinically apparent* ipsilateral internal mammary lymph nodes in the *presence* of one or more positive axillary lymph node(s); or in more than three axillary lymph nodes and in internal mammary lymph nodes with microscopic disease detected by sentinel lymph node dissection but not being clinically apparent**

pN3c: Metastasis in ipsilateral supraclavicular lymph nodes

*[Note: Clinically apparent is defined as detected by imaging studies (excluding lymphoscintigraphy) or by clinical examination].

**[Note: Not clinically apparent is defined as not detected by imaging studies (excluding lymphoscintigraphy) or by clinical examination].

Stage may change after surgery if distant metastasis is detected with radiological modalities.

New TNM system seems to be more complex. However, there is no important change other than new stage IIIC according to stage evaluation.

AJCC Stage Group

Stage 0: $T_{is}N0M0$
Stage IA: T1*N0M0
Stage IB: T0N1miM0, T1*N1miM0
Stage IIA: T0N1M0; T1*N1M0; T2N0M0
Stage IIB: T2N1M0; T3N0M0
Stage IIIA: T0N2M0; T1*N2M0; T2N2M0; T3N1M0; T3N2M0
Stage IIIB: T4N0M0; T4N1M0; T4N2M0
Stage IIIC**: Any TN3M0
Stage IV: Any T, Any N, M1
*T1 includes T1mi.
**Stage IIIC breast cancer includes patients with any T stage who have pN3 disease. Patients with pN3a and pN3b disease are considered operable and are managed as described in the section on Stage I, II, IIIA, and operable IIIC breast cancer. Patients with pN3c disease are considered inoperable and are managed as described in the section on ınoperable stage IIIB or IIIC or inflammatory breast cancer.

7.4 Treatment Algorithm

DCIS [9]

1. BCS+RT.
   - RT, decreases local recurrences
2. Total mastectomy (no axillary dissection)
   - Indications:

   Diffuse microcalcifications
   Multicentricity
   Permanent surgical margin (+) despite re-excisions
   Patient request
   Adjuvant tamoxifen if ER (+)

LCIS [9]

1. Lifelong surveillance ± tamoxifen (presence of high risk).
2. Young age, family history or genetic predisposition: prophylactic bilateral mastectomy may be considered.

Stage I–IIA (T1–2, N0–1) (early-stage breast cancer)
BCS + axillary sentinel lymph node dissection (SLND) + RT

- RT may not be needed; age >70 years and adjuvant hormonal therapy is given.
- *Contraindications for BCS:*
  - Multicentricity
  - Tumor size/breast size is too large
  - Diffuse microcalcification
  - Permanent surgical margin (+) despite re-excisions
  - Previous history of breast cancer
  - Pregnancy
  - Collagen vascular disease
  - Previous history of RT to breast

Alternative → modified radical mastectomy (MRM) ± RT ± CT ± hormonal treatment (HT)

Stage IIB (T3N0), Stage IIIA
Neoadjuvant CT + surgery (BCS+AD or MRM) + RT ± HT ± CT
Alternative → MRM + RT ± HT ± CT

Stage IIIB, Stage IIIC
Neoadjuvant CT + surgery (BCS + AD or MRM) + RT ± HT ± CT

Stage IV
CT/HT
Biphosphonates in bone metastases
± Palliative RT
± Targeted therapies (e.g., herceptin, lapatinib)

Special Circumstances [9]

Isolated axillary lymph node metastasis (TxN(+)M0)

Neoadjuvant CT+ axillary dissection + RT (RT; breast + axilla ± supraclavicular field)

Alternative → MRM ± RT ± HT ± CT

Breast cancer in pregnancy

First trimester → discuss termination of pregnancy

- If not: MRM ± CT, and after birth or at the second trimester ± RT ± HT

Second to third trimester → surgery (BCS+AD or MRM) ± CT, and after birth ± RT ± HT

Post-mastectomy RT (PMRT) indications [10]:

- Involvement of four or more axillary lymph nodes
- T3 (>5 cm tumor), T4 (skin/chest wall invasion) or stage III tumor
- Positive surgical margin
- Gross extracapsular invasion in axilla
- Gross residual disease
- Invasion of pectoral muscle fascia
- Inadequate axillary dissection (<6 or <10 lymph nodes excised)

Late side effects of PMRT: lymphatic edema, brachial plexopathy, radiation pneumonitis, costal fractures, cardiac toxicity and secondary malignancies due to radiation; modern RT (if indicated) should be recommended, regardless of its side effects.

Relative PMRT indications [10]:

- Involvement of 1–3 axillary lymph nodes
- Close surgical margin (<1 mm)
- Multiple primary tumors (multicentricity)

Patients with complete (I–III) or level I–II axillary dissection (adequate axillary dissection) are not routinely recommended for radiotherapy to all fields if no axillary metastasis is detected.

Supraclavicular lymph node radiotherapy is recommended for patients with four or more axillary lymph node metastases, since the risk of recurrence in this region is very high.

Internal mammary lymph node radiotherapy is a highly controversial issue. One should consider the high risk of cardiotoxicity regardless of technique, since coronary arteries are very close to the high-dose region, particularly in left-sided breast cancers.

Adjuvant chemotherapy indications [11]:

- Tumor >1 cm or lymph node (+) (adjuvant CT decreases distant metastases as well as local relapses after surgery ± RT).

Neoadjuvant chemotherapy indications [12]:
Locally advanced breast cancer
Initial therapy in stage IIIB–IIIC
Inoperable stage IIB–IIIA (neoadjuvant CT increases probability of BCS in 20–30% of cases)

Breast-conserving surgery [13]. This is the excision of the tumor together with a specific amount of surrounding healthy breast tissue (wide local excision, lumpectomy, quadrantectomy) (± axillary SLND or axillary lymph node dissection).

- It is frequently used in the management of early-stage breast cancer, since it provides good cosmesis with the preservation of the breast as well as good psychosocial effects on the patient's social life.

Modified radical mastectomy [14]. The entire breast, areola, nipple, pectoral muscle fascia, and pectoralis minor muscle are excised, and axillary dissection (to at least level I–II) is performed. MRM alone already includes AD, so it is not correct terminology to use MRM + AD in the patient's chart.

7.5 Radiotherapy

Radiotherapy for breast cancer decreases the locoregional relapse rate, increases survival and palliates symptoms according to stage. Radiotherapy after BCS is an essential component of treatment for early-stage breast cancer [15]. Adjuvant radiotherapy during more advanced stages increases locoregional control and increases survival, particularly in patients with axillary lymph node metastases [16].

A breast board should be used in breast cancer radiotherapy, and the patient should put her arms up in a comfortable position at a fixed location (Fig. 7.6).

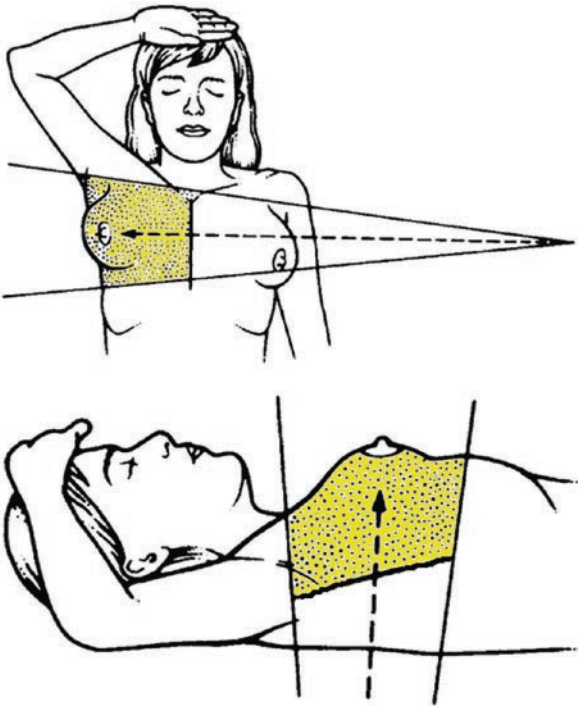

Fig. 7.6 Arm positions in breast radiotherapy in the absence of a breast board

Breast RT After BCS and Chest Wall RT After MRM (Figs. 7.7 and 7.8)

Superior border: superior to breast with a margin of at least 2 cm (usually the first intercostal space, may be reach up to the clavicle according to breast size).

- The superior border is the inferior border of the supraclavicular fossa (SCF) if the SCF is irradiated, and is usually at the second intercostal space.

Inferior border: 2 cm below the inframammary sulcus (determined according to the contralateral breast in the case of MRM).
Lateral border: midaxillary line or 2 cm lateral to palpable breast tissue.
Medial border: midline (midsternum).

- Medial border may be 1 cm lateral to the midline in the case of internal mammary lymph node RT.

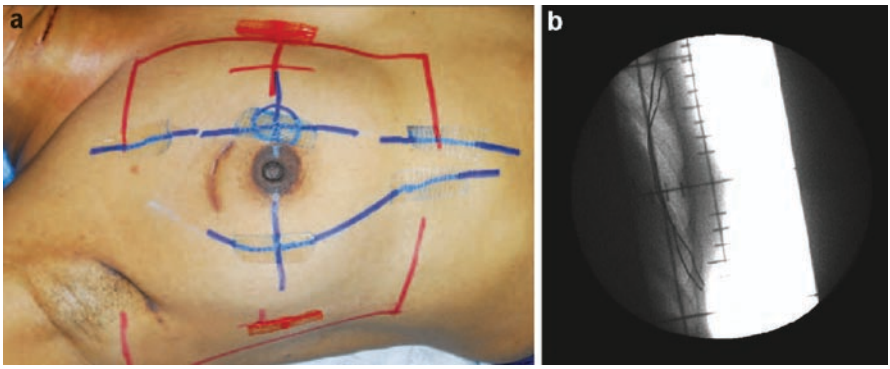

Fig. 7.7 Conventional breast RT field and simulation film after breast-conserving surgery

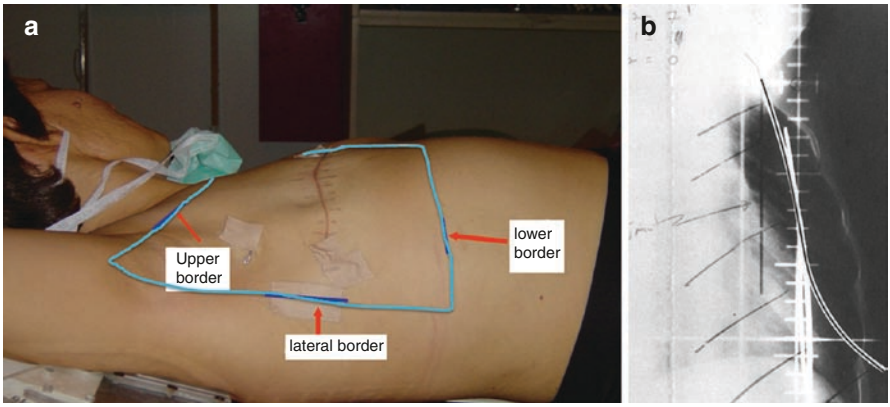

Fig. 7.8 Conventional chest wall RT field and simulation film after mastectomy

Medial and lateral borders and the midline contour should be marked with wires so that they are visible in the simulation film.

BCS or MRM scars and drain sites should also be marked with wires to make them visible in the film.

Boost Field

The boost field is determined by the surgical scar, and clips that should be put into the tumor bed during surgery.

- A 2–3 cm margin should be introduced between the surgical clips and scar. The nipple–areola complex should be spared if possible for cosmetic reasons.

Central lung distance (CLD): a maximum of 1.5–2 cm CLD (lung tissue) should be included within tangential fields.

- Most local relapses occur within or close to scar tissue. Thus, the entire mastectomy or incision scar should be irradiated. Additional electron fields can be used. It is not recommended to increase tangential fields to include all scars due to the increased risk of lung and cardiac toxicity.
- A breast board is a simple sloped plane that makes the chest wall parallel to the ground plane. It therefore prevents the lungs from receiving higher doses, simplifies setup and enables dose homogeneity.

Peripheral Lymphatic Field I: Supraclavicular Field (Fig. 7.9)

Superior border: superior to acromioclavicular joint, including the SCF.
Inferior border: superior to breast/chest wall field.
Medial border: midline in simulation film.

- One centimeter lateral to the suprasternal notch

Lateral border: the coracoid process, by passing one-third lateral to the head of the humerus head (which is spared).

- A single anterior field is used with the SSD technique (100 cm for linac, 80–100 cm for Co-60) (prescription depth is usually 3 cm). A lateral gantry angle of 10–15° is used to protect spinal cord and esophagus.

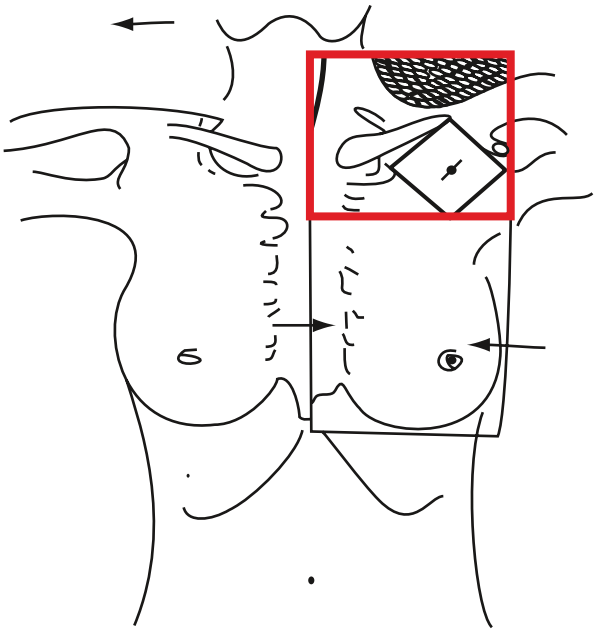

Fig. 7.9 SCF field

The SCF field and the chest wall or breast fields are orthogonal fields. Therefore, there is always an abutment problem. Half-block, asymmetrical collimation or divergence adjustment techniques should be used to prevent hot or cold spots in this abutment region.

Peripheral Lymphatic Field II: Axillary Field (Fig. 7.10)

Superior border: parallel to clavicle
Inferior border: inferior border of SCF
Medial border: includes 1.5–2 cm lung tissue
Lateral border: includes half of the head of the humerus

- The axilla is marked on the skin anteriorly, but it is irradiated as a single posterior field.
- The dose to be delivered to the axilla is calculated on the basis of the dose coming from the anterior SCF and the proper dose deficiency can be complemented from posterior axillary field irradiation.

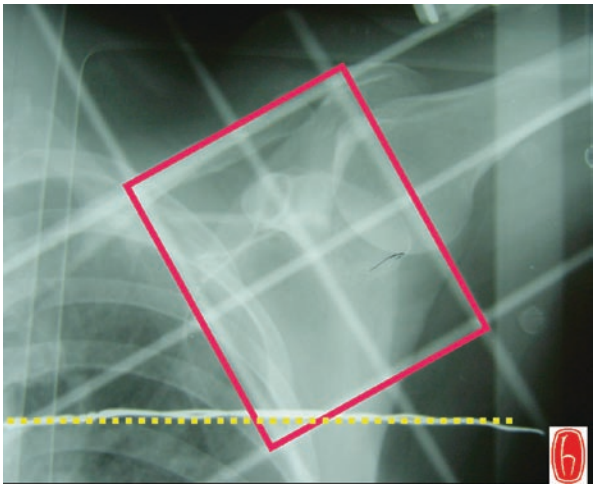

Fig. 7.10 Posterior axillary RT field

Peripheral Lymphatic Field III: Internal Mammary Field

Superior border: inferior border of SCF.
Inferior border: sixth intercostal space.
Medial border: 4–5 cm from the midline towards the involved breast.
Lateral border: 1 cm from the midline towards the normal breast (avoid irradiating the contralateral breast tissue).

It can also be irradiated by wide tangential fields, but the dose should be checked during planning.

- Superior and inferior borders are not determined in this case, since they depend on the borders of the tangential fields.
- Internal mammary lymph nodes should be irradiated with suitable (established during treatment planning) electron–photon energies due to the high risk of cardiac toxicity or even mortality.
- The dose calculation is based on the depth found during planning CT (usually a depth of 3 cm).

Contouring procedure (Fig. 7.11):

Contours should show the lateral and vertical positions of the entrances of both tangential beams.

- Outer and inner entry points are connected by a line on the contour paper.
- A vertical line from the middle of the previous dorsal line is drawn, which divides the treatment volume in half.
- On this vertical line, the midpoint of the field height is marked and denoted the pseudoisocenter.
- From the contours, the vertical depth (d) and the lateral distance of the pseudoisocenter (X) are determined.
- In practice, the SSD distance (the inner site at midpoint) is adjusted to ($100 - d$), and if the couch is moved x cm laterally, the pseudoisocenter is adequately found in the vertical position.
- Finally, if the couch is shifted cranially by a distance Z, the X mark on the central axis will be the field abutment line. This point is denoted the real isocenter and SSD is recorded.
- The couch and collimator angles are zero during simulation.

Fig. 7.11 Contouring procedure in breast RT and isodose distribution

Dose Fractionation Energy

- Fraction dose: 1.8–2 Gy
- Total dose:

Breast after BCS: 50 Gy entire breast + 10 Gy boost to tumor bed (use linac 4–6 MV in BCS for cosmetic purposes, since the skin dose is very high with Co-60).

- Surgical margin (+) and no re-excision is possible; boost dose 14–16 Gy.
- Boost: 9–18 MeV electron energy, depending on the depth of the tumor bed. Normalization is done to 80–85% isodose so that a steep dose gradient can be used after these isodoses to spare underlying lung tissue.
- Photon energies used in treatment planning can be used to give a boost dose if there are no electron energies.
- The boost can be delivered by tangential fields when there is a deeply seated tumor bed.
- *Chest wall after MRM:* 46–50 Gy. (Co-60/linac 4–6 MV, with scheduled bolus use to increase skin dose).
- Incision scars outside tangential fields should be irradiated with 6 MeV electron energy, giving a margin of at least 2 cm (30 Gy in ten fractions).
- *Peripheral lymphatics:* 50 Gy (Co-60/linac 4–6 MV).

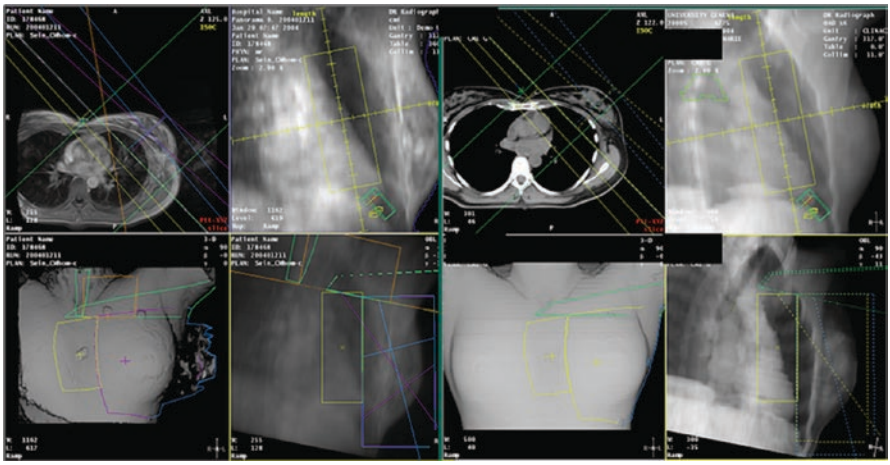

Fig. 7.12 Conformal RT fields in breast cancer

Conformal RT Volumes (Fig. 7.12) [17]

CTV 1 (tumor bed): include surgical clips
CTV 2: entire breast tissue or chest wall
CTV 3: SCF ± axillary lymph nodes ± internal mammary lymph nodes
PTV: CTV + 1.5 cm

RTOG Consensus Guidelines for Target Delineation in Breast Cancer (www.rtog.org) (Fig. 7.13)

Breast and Chestwall Contour: Anatomical Boundaries

Breast

Cranial: Clinical reference+Second rib insertion
Caudal: Clinical reference+loss of CT apparent breast
Anterior: skin
Posterior: Ecludes pectoralis muscles, chestwall muscles, ribs
Lateral: Clinical reference+Midaxillary line typically, ecludes latissimus dorsi muscle
Medial: Sternal-rib junction

Breast+Chestwall

Cranial: same as breast
Caudal: same as breast
Anterior: same as breast
Posterior: includes pectoralis muscles, chestwall muscles, ribs
Lateral: same as breast
Medial: same as breast

Chestwall

Cranial: Caudal border of the clavicle head
Caudal: Clinical reference+loss of CT apparent contralateral breast
Anterior: skin
Posterior: rib-pleural interface (includes pectoralis muscles, chestwall muscles, ribs)
Lateral: clinical reference/mid axillary line typically, excludes latissimus dorsi muscle
Medial: Sternal rib junction

Regional Nodal Contours: Anatomical Boundaries

Supraclavicular

Cranial: Caudal to the cricoid cartilage
Caudal: Junction of brachiocephaxillary veins/caudal edge clavicle head
Anterior: Sternocleidomastoid (SCM) muscle
Posterior: Anterior aspect of the scalene muscles
Lateral: lateral edge of SCM cranially, and junction of 1st rib-clavicle caudally
Medial: Excludes thyroid and trachea

Axilla Level I

Cranial: Axillary vessels cross lateral edge of pectoral minor muscle
Caudal: pectoralis major muscle insertion into ribs
Anterior: plane defined by anterior surface of pectoralis major and latissimus dorsi muscles
Posterior: anterior surface subscapularis muscle
Lateral: medial border of latissimus dorsi muscle
Medial: lateral border of pectoralis minor muscle

Axilla Level II

Cranial: Axillary vessels cross medial edge of pectoral minor muscle
Caudal: Axillary vessels cross lateral edge of pectoral minor muscle

Anterior: anterior surface pectoralis muscle
Posterior: ribs and intercostal muscles
Lateral: lateral border of latissimus dorsi muscle
Medial: medial border of pectoralis minor muscle

Axilla Level III

Cranial: pectoral minor muscle insertion on cricoid
Caudal: Axillary vessels cross medial edge of pectoral minor muscle
Anterior: posterior surface pectoralis muscle
Posterior: ribs and intercostal muscles
Lateral: medial border of latissimus dorsi muscle
Medial: thoracic inlet

Internal mammary (IM)

Cranial: superior aspect of the medial 1st rib
Caudal: cranial aspect of the 4th rib
Other borders of IM nodes encompass the internal mammary/thoracic vessels

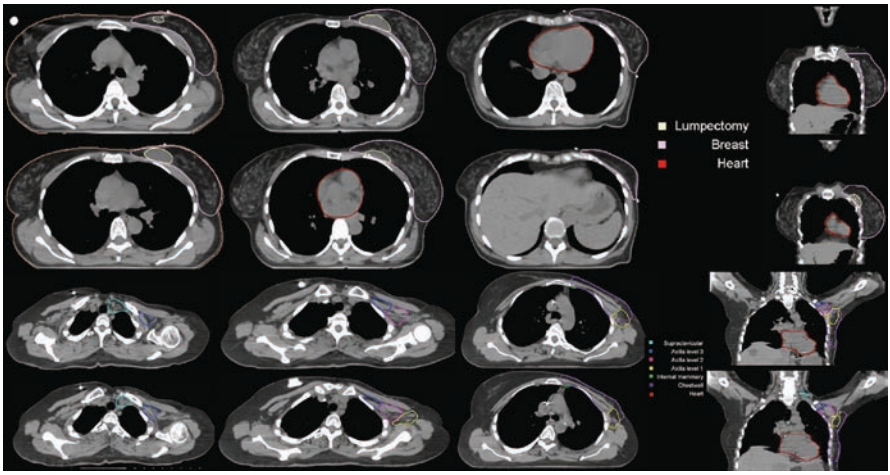

Fig. 7.13 RTOG Consensus target delineation guidelines for breast cancer (ref: www.rtog.org)

7.6 Selected Publications

Breast cancer prevention

NSABP P-1 → randomized. More than 13,000 cases. Placebo vs. tamoxifen (TMX) 20 mg for 5 years.

TMX:

- 49% decrease in invasive cancer risk
- 56% decrease in LCIS
- 86% decrease in atypical ductal hyperplasia
- 56% decrease in noninvasive breast cancer
- RR = 2.53 for endometrial cancer
- No increase in ischemic heart disease
- Decrease in fracture risk due to osteoporosis

Fisher B et al (1998) Tamoxifen for prevention of breast cancer: report of the National Surgical Adjuvant Breast and Bowel Project P-1 Study. J Natl Cancer Inst 90(18):1371–1388

Updated in 2005 with 7 years of median follow-up:

- 43% decrease in invasive breast cancer risk
- 37% decrease in noninvasive breast cancer risk
- 32% decrease in osteoporotic fracture risk

Fisher B et al (2005) Tamoxifen for the prevention of breast cancer: current status of the National Surgical Adjuvant Breast and Bowel Project P-1 study. J Natl Cancer Inst 97(22):1652–1662

NSABP P-2 (STAR: Study of Tamoxifen and Raloxifen) → randomized. 22,000 cases. No premenopausal women. TMX 20 mg vs. raloxifene (RLX) 60 mg for 5 years.

Raloxifene arm:

- More successful than TMX in decreasing invasive breast cancer risk.
- No difference in noninvasive cancer risk.
- Thromboembolic events and cataracts are decreased.
- Similar for risks of LCIS, atypical ductal hyperplasia, osteoporotic fracture.

Vogel VG et al (2006) Effects of tamoxifen vs raloxifene on the risk of developing invasive breast cancer and other disease outcomes: the NSABP Study of Tamoxifen and Raloxifene (STAR) P-2 Trial. JAMA 295:2727–2741

IBIS-1 International Breast Cancer Intervention study, 2002 → randomized. 7152 cases. Placebo vs. TMX 20 mg for 5 years. Median follow-up 50 months.
TMX arm:

- 32% decrease in noninvasive and invasive breast cancer risk
- Nonsignificant increase in endometrial cancer risk

Cuzick J et al (2002) First results from the International Breast Cancer Intervention Study (IBIS-I): a randomised prevention trial. Lancet 360(9336):817–824

DCIS

Harvard, *2006* → prospective nonrandomized. 158 DCIS cases. DCIS ≤2.5 cm, grade 1–2, necrosis (+) and TMX (−). Surgical margin ≥1 cm. Median follow-up 40 months.

- Local relapse: 2.4%/year, and 12% at 5 years.
- 69% DCIS relapse, 31% invasive breast cancer development.
- Conclusion: radiotherapy should be given to prevent locoregional relapses, even in the presence of good prognostic factors.

Wong JS et al (2006) Prospective study of wide excision alone for ductal carcinoma in situ of the breast. J Clin Oncol 24(7):1031–1036

NSABP B-17 → randomized. 818 DCIS cases. Lumpectomy vs. lumpectomy + RT. Surgical margin (±). RT: 50 Gy, boost (−).

1993 results with 43 months of follow-up:

- Five-year event free survival: 74 vs. 84% in RT arm ($p < 0.05$)
- Five-year ipsilateral invasive breast cancer development: 10.5 vs. 2.9% in RT arm
- Five-year ipsilateral noninvasive breast cancer development: 10.4 vs. 7.5% in RT arm

Updated in 1998:

- Eight-year ipsilateral breast cancer development: 13.4 vs. 3.9% in RT arm
- Five-year ipsilateral noninvasive breast cancer development: 13.4 vs. 8.2% in RT arm

Updated in 2000:

- Ten-year ipsilateral breast cancer development: 16.4 vs. 7.1% in RT arm (62% decrease in breast cancer risk)
- Ten-year ipsilateral breast cancer development: 16.4 vs. 7.1% in RT arm (62% decrease in breast cancer risk)
- Ten-year ipsilateral noninvasive breast cancer development: 30.8 vs. 14.9% in RT arm (57% decrease in breast cancer risk)
- Similar rates of distant metastases and contralateral breast cancer

Predictive factors for ipsilateral recurrences: comedonecrosis and unknown or positive surgical margin.

Fisher B (2001) Prevention of invasive breast cancer in women with ductal carcinoma in situ: an update of the national surgical adjuvant breast and bowel project experience. Semin Oncol 28(4):400–418

EORTC 10853 → randomized. 1010 DCIS cases. DCIS ≤5 cm. Lumpectomy vs. lumpectomy + RT. Surgical margin (−); re-excision if surgical margin (+) intraoperatively. RT dose: 50 Gy, no boost dose.

RT arm:

- Four-year local relapse-free survival: 84% in no-RT arm vs. 91% in RT arm
- Invasive cancer risk: 8 vs. 4%
- DCIS risk: 8 vs. 5%
- Four-year distant metastasis-free period: 98 vs. 99%

Updated in 2006:

- Ten-year local relapse: 26% in no RT arm vs. 15% in RT arm
- 47% decrease in risk, valid for all subgroups
- 42% decrease in invasive breast cancer risk
- 48% decrease in DCIS risk
- Local relapse risk increase: age <40 years, grade 2–3, cribriform or solid growth pattern, suspicious surgical margin or wide local excision only
- No prognostic significance of DCIS size
- No difference in overall survival and distant metastasis

Bijker N (2006) Breast-conserving treatment with or without radiotherapy in ductal carcinoma in situ: 10-year results of the European Organisation for Research and Treatment of Cancer Randomized Phase III Trial 10853—a study by the EORTC Breast Cancer Cooperative Group and EORTC Radiotherapy Group. J Clin Oncol 24(21):3381–3387

UKCCCR, 2003 → randomized. 1701 DCIS cases. 2 × 2 trial; after BCS: (1) arm surveillance, (2) arm RT, (3) arm TMX, (4) arm RT + TMX. RT dose: 50 Gy with no boost, and TMX: 20 mg/5 years.

- No effect of TMX on ipsilateral invasive breast cancer risk, but prevents ipsilateral DCIS risk (HR = 0.68).
- RT is beneficial for decreasing both ipsilateral invasive and noninvasive breast cancer risk (new event in ipsilateral breast risk: 16 vs. 7% in RT arms.
- No synergistic effect of RT+TMX.

Houghton J (2003) Radiotherapy and tamoxifen in women with completely excised ductal carcinoma in situ of the breast in the UK, Australia, and New Zealand: randomised controlled trial. Lancet 362(9378):95–102

Mastectomy + RT in early-stage breast cancer

NSABP B-04 → a total of 1,079 women with clinically negative axillary nodes underwent radical mastectomy, total mastectomy without axillary dissection but with postoperative irradiation, or total mastectomy plus axillary dissection only if their nodes became positive. A total of 586 women with clinically positive axillary nodes underwent either radical mastectomy or total mastectomy without axillary dissection but with postoperative irradiation.

- Ten-year results (1985): no survival difference between locoregional therapies.
- Twenty-five-year results (2000): no differences in DFS, RFS, distant metastasis and OS between treatment arms.
- Conclusion: radical mastectomy had no advantage; surgery and RT for occult (+) axillary lymph nodes also had no survival advantage.

Fisher B (2002) Twenty-five-year follow-up of a randomized trial comparing radical mastectomy, total mastectomy, and total mastectomy followed by irradiation. N Engl J Med 347(8):567–575

Denmark, 1992 → randomized. 908 early-stage breast cancer patients. Mastectomy vs. BCS + RT. Axillary dissection performed in all cases. Median follow-up: 3.3 years.

Six-year results:

- DFS: 66 vs. 70% in RT arm.
- OS: 82 vs. 79% in RT arm.
- Conclusion: CRT+BCS is as effective as mastectomy in the management of early-stage breast cancer.

Blichert-Toft M (1992) Danish randomized trial comparing breast conservation therapy with mastectomy: six years of life-table analysis. Danish Breast Cancer Cooperative Group. J Natl Cancer Inst Monogr (11):19–25

Milan, *2002* → randomized. 701 cases of breast cancer with $T \leq 2$ cm. 25% axillary LN (+). Radical mastectomy vs. quadrantectomy + RT. RT: 50 + 10 Gy boost. Adjuvant CMF chemotherapy after 1976 in cases of axillary LN (+).

Twenty-year results in 2002:

- Ipsilateral relapse: 2 vs. 9% in RT arm ($p < 0.05$).
- No difference in secondary malignancy and distant metastasis.
- No difference in 20-year OS and cancer-specific survival.
- Conclusion: BCS + RT is an effective modality for the management of early-stage breast cancer that does not result in any significant increase in contralateral breast cancer.

Veronesi U (2002) Twenty-year follow-up of a randomized study comparing breast-conserving surgery with radical mastectomy for early breast cancer. N Engl J Med 347(16): 1227–1232

NSABP B-06, *2002* → randomized. 1851 stage I–II, $T < 4$ cm, axillary LN (±). Lumpectomy vs. lumpectomy + RT vs. total mastectomy. Axillary dissection in all cases. RT: 50 Gy ± boost with no axillary RT. Melphalan + 5-FU chemotherapy for axillary LN (+). 10% surgical margin (+) in lumpectomy arm.

Twenty-year results in 2002:

- Ipsilateral breast cancer recurrence: 39.3% in lumpectomy vs. 14.3% in lumpectomy + RT.
- Relapses after lumpectomy: 73% in 5 years, 18% in 5–10 years, 8% after 10 years.

- Relapses after lumpectomy + RT: 39% in 5 years, 29% in 5–10 years, 30% after 10 years.
- All other events other than local recurrences were similar between the three arms.
- Twenty-year DFS: 35% in lumpectomy vs. 35% lumpectomy + RT vs. 36% in mastectomy.
- Twenty-year DMFS: 45% in lumpectomy vs. 46% lumpectomy + RT vs. 49% in mastectomy.
- Twenty-year OS: 46% in lumpectomy vs. 46% lumpectomy + RT vs. 47% in mastectomy.
- Conclusion: all three modalities were similar in terms of DFS, DMFS and OS; late relapses were common in the RT arm, particularly after 5 years of therapy.

Fisher B et al (2002) Twenty-year follow-up of a randomized trial comparing total mastectomy, lumpectomy, and lumpectomy plus irradiation for the treatment of invasive breast cancer. N Engl J Med 347(16):1233–1241

Other randomized trials in early stage breast cancer → EORTC 10801 (1980–1986), NCI (1979–1987), Gustave-Roussy (1972–1980).

General conclusion: there is no survival difference between mastectomy and BCS + RT (Table 7.4).

Table 7.4 Selected randomized trials of BCS ± RT in early-stage breast cancer

Study	Surgery	Chemotherapy	RT dose	LR, RT (–) (%)	LR, RT (+) (%)
NSABP B-06	Lumpectomy	CT for N (+)	50	39	14
Milan	Quadrantectomy	N (+) high-risk: CT N (+) low-risk: TMX	50 + 10	23	6
NSABP B-21	Lumpectomy	TMX	50 ± boost	16	3
Finland	Lumpectomy	–	50	18	7
Sweden	Sector resection	9% (+)	48–54	14	4
Canada	BCS	TMX	40/16 + 12.5/5	8	1
CALGB 9343	Lumpectomy	TMX	45 + 14	4	1

RT radiotherapy; *CT* chemotherapy; *TMX* tamoxifen; *N* node

General conclusion. Ipsilateral breast relapse risk is 75% less in patients receiving RT in addition to BCS. This effect is more prominent in young women and node (+) patients

Meta-analyses in early-stage breast cancer

Early Breast Cancer Trialists' Collaborative Group Meta-analysis → 1995 results:

- Local recurrences and OS rates are similar.
- Ten-year breast cancer-related mortality was 5% less in the RT arm.
- Nonbreast cancer-related mortality was 25% more in the RT arm.
- Most mortalities occurred after 60 years of age.

Anon (1995) Effects of radiotherapy and surgery in early breast cancer. An overview of the randomized trials. N Eng J Med 333(22):1444–1455

2000 results:

- Included 40 randomized trials.
- 50% of deaths were in LN (+) patients.
- Local recurrence risk decreased from 27 to 8.8% in patients receiving RT.
- Breast cancer-related mortality decreased.
- Nonbreast cancer-related mortality increased.
- Twenty-year OS: 37.1% in RT vs. 35.9% in surgery ($p = 0.06$).
- Cardiac dose was higher in older studies with old RT techniques.

Early Breast Cancer Trialists' Collaborative Group (2000) Favorable and unfavorable effects on long-term survival of radiotherapy for early breast cancer: an overview of the randomized trials. Lancet 355(9217):1757–1770

2005 results:

- Included 78 randomized trials with 42,000 cases
- Five-year local recurrence after BCS: 7% in RT (+) vs. 26% in RT (−) ($p < 0.05$)
- Five-year breast cancer-related mortality 30.5% in RT (+) vs. 35.9% in RT (−) ($p < 0.05$)

Clark M et al (2005) Effects of radiotherapy and of differences in the extent of surgery for early breast cancer on local recurrence and 15-year survival: an overview of the randomized trials. Lancet 366(9503):2087–2106

Other meta-analyses

BCS Project, 2004 → 15 randomized BCS ± RT trials.

- Conclusion: RT decreases the risk of ipsilateral breast cancer development with minimal effect on mortality.

Vinh-Hung V (2004) Breast-conserving surgery with or without radiotherapy: pooled-analysis for risks of ipsilateral breast tumor recurrence and mortality. J Natl Cancer Inst 96(2):115–121

McMaster University, 2000 → 18 randomized trials of BCS+RT or MRM.

Conclusion: RT decreased local recurrence (OR = 0.25) and mortality (OR = 0.83).

Whelan TJ et al (2000) Does loco regional radiation therapy improve survival in breast cancer? A meta-analysis. J Clin Oncol 18(6):1220–1229

BCS+TMX±RT in early-stage breast cancer

Austrian ABCSG 8A, 2007 → randomized. 869 early-stage breast cancers (tm<3 cm, G1–2, N0, ER or PR [+]). Anastrozole or TMX after lumpectomy: RT (50±10 Gy boost) vs. RT (−)

2005 results with median 3.5 years of follow-up:

- Local recurrence: 0.2% in RT arm vs. 3.1% in no-RT arm
- Locoregional recurrences: 4.4% in RT arm vs. 6.7% in no-RT arm

2007 results:

- Five-year local recurrence: 0.4% in RT arm vs. 5.1% in no-RT arm.
- Five-year locoregional recurrence: 2.1% in RT arm vs. 6.1% in no-RT arm.
- No difference in terms of distant metastasis and overall survival.
- Conclusion: radiotherapy is highly effective for decreasing local and regional recurrences.

Potter R (2007) Lumpectomy plus tamoxifen or anastrozole with or without whole breast irradiation in women with favorable early breast cancer. Int J Radiat Oncol Biol Phys 68(2):334–340

Intergroup (CALGB 9343, RTOG 97-02, ECOG), 2004 → randomized: ≥70 years 638 T1N0, ER (+) cases. TMX after BCS: randomized to RT vs. no-RT. Axilla dissection in 37% of cases. RT dose: 45 + 14 Gy boost.

Five-year results:

- Local recurrence 4% in TMX arm vs. 1% in TMX+RT arm ($p < 0.05$).
- No difference in salvage mastectomy, distant metastasis and overall survival.
- No difference in side effects and cosmesis after 4 years.
- Conclusion: lumpectomy plus adjuvant therapy with tamoxifen alone can be an alternative approach for the treatment of women 70 years of age or older who have early, estrogen receptor positive breast cancer.

Hughes KS et al (2004) Lumpectomy plus tamoxifen with or without irradiation in women 70 years of age or older with early breast cancer. N Engl J Med 351(10):971–977

Other randomized trials:

Canada multi-institutional, 2004

- TMX+RT decreased locoregional recurrences significantly.

Fyles AW et al (2004) Tamoxifen with or without breast irradiation in women 50 years of age or older with early breast cancer. N Engl J Med 351(10):963–970

NSABP B-21, 2002

- TMX + RT should be considered for a tumor size of ≤1 cm.

Fisher B (2002) Tamoxifen, radiation therapy, or both for prevention of ipsilateral breast tumor recurrence after lumpectomy in women with invasive breast cancers of one centimeter or less. J Clin Oncol 20(20):4141–4149

Radiotherapy boost trials in early-stage breast cancer

EORTC 22881/10882 (boost vs. no-boost) → stage I–II. 5,318 cases with BCS + axilla dissection + RT (50 Gy). 21% LN (+). Surgical margin (−). Randomized: 16 Gy boost vs. no-boost. Boost field: scar + 1.5 cm. Adjuvant chemotherapy in 28% of cases.
Cosmesis results in 1999:

- Excellent/good cosmesis: 71% in boost arm vs. 86% in no boost arm.
- Conclusion: boost caused bad cosmesis.

Updated in 2001:

- Five-year locoregional control: 4.3 vs. 7.3% in no-boost
- Decrease in recurrence risk: 40%; age < 40 years (10 vs. 20%), age > 60 years (2.5 vs. 4%)

Updated in 2007:

- Ten-year local recurrence: 6 vs. 10% in no-boost ($p < 0.05$).
- Local relapses were significantly decreased with the boost in all age groups.
- Conclusion: a boost should be given to all age groups to increase local control.

Bartelink H (2007) Impact of a higher radiation dose on local control and survival in breast-conserving therapy of early breast cancer: 10-year results of the Randomized Boost Versus No Boost EORTC 22881–10882 Trial. J Clin Oncol 25(22):3259–3265

Other randomized trials:

Lyon, 1997, (1986–1992)

Romestaing P et al (1997) Role of a 10-Gy boost in the conservative treatment of early breast cancer: results of a randomized clinical trial in Lyon, France. J Clin Oncol 15(3):963–968

Netherlands, 2006, (ongoing)

Hurkmans CW (2006) High-dose simultaneously integrated breast boost using intensity-modulated radiotherapy and inverse optimization. Int J Radiat Oncol Biol Phys 66(3):923–930

Hypofractionation trials in breast cancer

MRC START A&B (England), 2008 (1999–2002) → two parallel randomized trials.

START-A: 2,236 women with early breast cancer (pT1–3a pN0–1 M0) were randomly assigned after primary surgery to receive 50 Gy in 25 fractions of 2.0 vs. 41.6 or 39 Gy in 13 fractions of 3.2 or 3.0 Gy over 5 weeks. After a median follow-up of 5.1 years, the rate of locoregional tumor relapse at 5 years was 3.6% after 50 Gy, 3.5% after 41.6 Gy, and 5.2% after 39 Gy. Photographic and patient self-assessments suggested lower rates of late adverse effects after 39 Gy than with 50 Gy. A lower total dose in a smaller number of fractions could offer similar rates of tumor control and normal tissue damage to the international standard fractionation schedule of 50 Gy in 25 fractions.

START Trialists' Group (2008) The UK Standardisation of Breast Radiotherapy (START) Trial A of radiotherapy hypofractionation for treatment of early breast cancer: a randomised trial. Lancet Oncol 9(4):331–341

START-B: 2,215 women with early breast cancer (pT1–3a pN0–1 M0) were randomly assigned after primary surgery to receive 50 Gy in 25 fractions of 2.0 Gy over 5 weeks or 40 Gy in 15 fractions of 2.67 Gy over 3 weeks. After a median follow-up of 6.0 years, the rate of locoregional tumor relapse at 5 years was 2.2% in the 40 Gy group and 3.3% in the 50 Gy group. Photographic and patient self-assessments indicated lower rates of late adverse effects after 40 Gy than after 50 Gy. A radiation schedule delivering 40 Gy in 15 fractions seems to offer rates of locoregional tumor relapse and late adverse effects that are at least as favorable as the standard schedule of 50 Gy in 25 fractions.

START Trialists' Group (2008) The UK Standardisation of Breast Radiotherapy (START) Trial B of radiotherapy hypofractionation for treatment of early breast cancer: a randomised trial. Lancet 371(9618):1098–1107.

Other randomized fractionation trials:

Canada, 2002

Whelan T et al (2002) Randomized trial of breast irradiation schedules after lumpectomy for women with lymph node-negative breast cancer. J Natl Cancer Inst 94(15): 1143–1150

Royal Marsden, 2006

Owen JR (2006) Effect of radiotherapy fraction size on tumour control in patients with early-stage breast cancer after local tumour excision: long-term results of a randomised trial. Lancet Oncol 7(6):467–471

Egypt NCI, 2004

Taher AN (2004) Hypofractionation versus conventional fractionation radiotherapy after conservative treatment of breast cancer: early skin reactions and cosmetic results. J Egypt Natl Canc Inst 16(3):178–187

Axilla dissection vs. RT in early-stage breast cancer

NSABP B-04 (Fisher) → randomized. 1,665 operable cases. Clinical axilla (+): radical mastectomy vs. total mastectomy + RT with no axilla dissection. Clinical axilla (−): radical mastectomy vs. total mastectomy vs. total mastectomy + RT. RT: chest wall and lymphatics (50 Gy/25 fractions) and 10–20 Gy boost for LN (+). Lymphatics: axilla/SCF/internal mammary 45 Gy. No chemotherapy.

Twenty-five year results:

- 82% of events were due to breast cancer: mostly recurrences and metastases.
- 57% of the events were in LN (+) vs. 33% in LN (−) patients; mostly distant metastases.
- Distant metastases: 42% in LN (+) vs. 30% in LN (−).
- Recurrences in LN (+): 5% local and 4% regional.
- Other most common events: nonbreast cancer-related mortality (25%), secondary primary cancer and contralateral breast cancer (6%).
- No difference between disease and relapse-free survival between arms.
- No benefit of axilla dissection clinically in LN(−) cases.

The 10-year results of this trial in 1985 were the basis for the Fisher hypothesis: that breast cancer is a systemic not a locoregional disease.

Fisher B et al (2002) Twenty-five-year follow-up of a randomized trial comparing radical mastectomy, total mastectomy, and total mastectomy followed by irradiation. N Engl J Med 347(8):567–575.

Institute Curie, 2004 → clinical N0, $T<3$cm, 685 cases; randomized to BCS + axilla dissection vs. BCS + axilla RT. RT: 50 + 10–15 Gy boost. Chemotherapy and hormone therapy in some LN (+) cases.

Fifteen-year results:

- No difference in OS and DFS.
- Five-year distant metastasis: 10% in surgery vs. 12% in RT.
- Fifteen-year distant metastasis: 25% in both arms.
- Ipsilateral breast recurrences: 7% in 5 years, 12% in 10 years, and 17% in 15 years.
- Fifteen-year isolated axilla recurrences: 1% in surgery vs. 3% in RT ($p=0.04$).
- Conclusion: axilla dissection significantly decreased isolated axilla relapses compared to RT.

Louis-Sylvestre C et al (2004) Axillary treatment in conservative management of operable breast cancer: dissection or radiotherapy? Results of a randomized study with 15 years of follow-up. J Clin Oncol 22(1):97–101

Conventional RT vs. IMRT

Canada, 2008→ randomized. 331 early-stage breast cancer cases with BCS. Standard conventional RT vs. IMRT (optional 16 Gy electron boost).

- Less wet desquamation, particularly on the inframammary fold, in the IMRT arm: 26 vs. 43%.
- Less wet desquamation on the entire breast in the IMRT arm: 31 vs. 48%.
- V95 (dose received by 95% of the breast volume) was related to acute skin toxicity.
- IMRT had a better dose distribution.
- No differences in breast pain and quality of life.

Pignol JP (2008) A multicenter randomized trial of breast intensity-modulated radiation therapy to reduce acute radiation dermatitis. J Clin Oncol 26:2085–2092

Royal Marsden, 2007 → randomized. 306 early-stage breast cancer. RT: 50 + 11.1 Gy. IMRT vs. conventional RT. Median follow-up: 5 years.

- Photographic change in breast cosmesis: 40% in IMRT vs. 58% in non-IMRT.
- Less palpable breast induration in IMRT arm.
- No difference in breast pain and quality of life.
- Late side effects decreased with minimal inhomogeneity.

Donovan E (2007) Randomized trial of standard 2D radiotherapy (RT) versus intensity modulated radiotherapy (IMRT) in patients prescribed breast radiotherapy. Radiother Oncol 82(3):254–264

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Genitourinary System Cancers

8

Gokhan Ozyigit, Murat Beyzadeoglu, and Cuneyt Ebruli

8.1 Prostate Cancer

Prostate cancer is the most common cancer in men and the second most common cause of cancer-related mortality in males [1]. Ninety-five percent of prostate cancer cases are diagnosed between 45 and 89 years of age (mean: 72 years). The incidence of prostate cancer increases with age, and the risk of developing it is 1/10,000 before 40 years of age, 1/103 between 40 and 59 years of age, 1/8 between 60 and 79 years of age [2]. The risk of prostate cancer in a man over the course of his lifetime is nearly 10%.

Prostate is the largest accessory gland of the male genital system. It is located in the pelvis, with its base superior and its apex inferior (Fig. 8.1). It is a conical organ that surrounds the prostatic urethra.

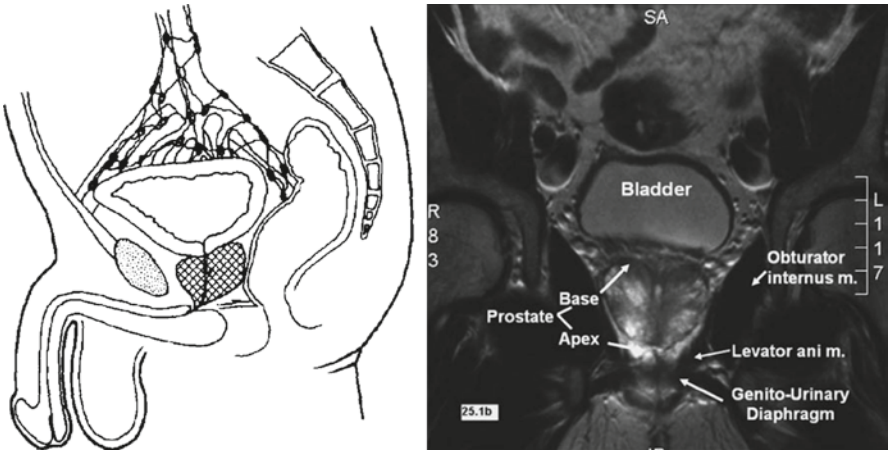

Fig. 8.1 Anatomy of the prostate (Fig. 28.1, p 688 from [36])

M. Beyzadeoglu et al. *Basic Radiation Oncology*,
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The base of the prostate base is continuous with the bladder neck, while its apex is continuous with the membranous urethra.

The prostate has four surfaces: anterior, posterior and two inferolateral surfaces.

- The anterior is convex and narrow, and 2 cm from the pubic symphysis, with the space between being filled with a rich venous plexus (Santorini's plexus) and loose connective tissue. The anterior surface is connected to the pubic symphysis via two puboprostatic ligaments, while the inferolateral surfaces neighbor the levator and muscle. Between them is another rich venous plexus surrounded by prostatic sheaths (the lateral plexus).
- The posterior surface is separated from the rectal ampulla by the prostatic capsule and Denonvillier's fascia, and it neighbors both of the seminal vesicles and the ampulla of ductus deferens.
- The cavernous sinus originating from the pelvic plexus (PP) is located within the periprostatic sheath, but outside of the prostate capsule, and is posterolateral to the prostate at the 5 and 7 o'clock positions. The membranous urethra perforates the urogenital diaphragm at the 3 and 9 o'clock positions, and enters the corpus cavernousum. These nerves exhibit branching along their paths.
  - Nerve entries into the prostate have a low resistance to tumor extension.
  - Vascular structures are found with the nerves, resulting in a neurovascular bundle. The distance between the capsule and the neurovascular bundle is shortest at the prostatic apex.
- The prostate is also surrounded by a thin sheath that includes rich venous plexus. This prostatic sheath is also continuous with the puboprostatic ligament anteriorly and the deep fascia of the transverse perineal muscle inferiorly.

Peripheral region [3]. This is the largest section of the prostate, and it surrounds the apical, lateral and posterior regions of the prostate (Fig. 8.2). It constitutes 75% of the entire glandular tissue. Seventy-five to eighty percent of all prostate cancers arise from this region. The prostate capsule is very thin at the apex of the prostate, and this area is a weak point for prostate cancer invasion.

Neurovascular bundle [4]. The relation of the cavernous nerves to the prostate is important for surgery. The cavernous nerves pass from the prostatic plexus and advance within the neurovascular bundle along with the prostate vessels. This bundle is located within retroperitoneal connective tissue posterolateral to the prostate and medial to the endopelvic fascia.

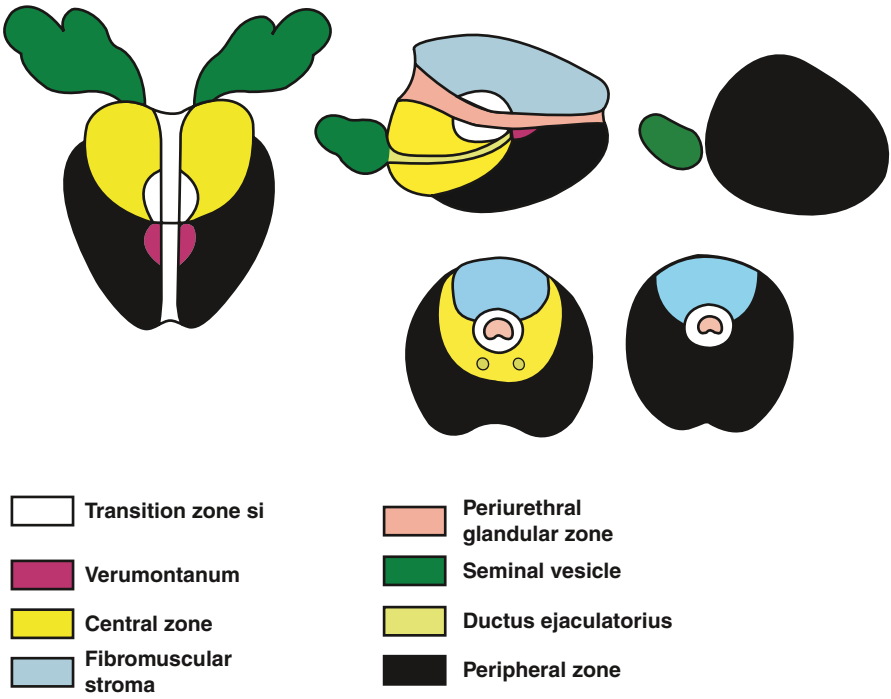

Fig. 8.2 Prostate zonal anatomy

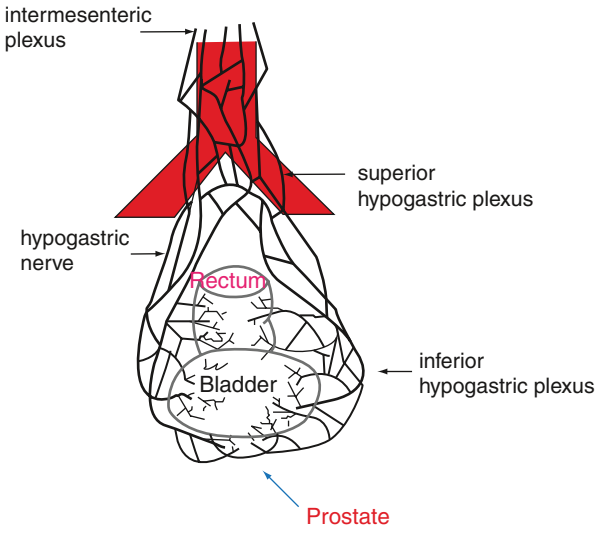

Fig. 8.3 Neurovascular bundle

Pelvic plexus (PP) (Fig. 8.3) [5]. The pelvic nerves originate at the S4–S3 and S2 levels as several anterior roots. These pelvic parasympathetic nerves combine with the sympathetic nerves originating from the hypogastric nerve.

- The upper part of the PP is called the vesical, and the lower part is the prostatic plexus

PP branches:

1. *Anterior branch*: advances within the inferolateral surface of bladder and the lateral surface of the seminal vesicles
2. *Anterior–inferior branch*: advances transversely with the lateral surface of the prostate and provides branches to the prostatovesical anastomosis
3. *Inferior branch*: advances between the posterolateral prostate surface and the rectum, and this branch is known as the neurovascular bundle of the prostate.

8.1.1 Pathology

More than 95% of prostate cancers are adenocarcinomas, and ~4% are transitional cell cancers [6]. Others are neuroendocrine carcinomas (small cell) and sarcomas. Prostatic intraepithelial neoplasia (PIN) is a precursor lesion.

- PIN is cytologically similar to prostate cancer, but is differentiated from cancer by the presence of an intact basal membrane layer.
- PIN is generally classified into either high-grade PIN (HGPIN) or low-grade PIN (LGPIN) [7].
- The clinical importance of this distinction is that HGPIN is associated with cancer in 80% of cases, while this ratio is 20% for LGPIN.
- Prostate cancer develops from the peripheral zone in 70% of cases, from the central zone in 15–20% for central zone, and from the transitional zone in 5–10%.
- Most prostate cancers are multifocal, and can be found in different zones of prostate with various grades.

Grading. The most commonly used histological grading system is that of Gleason, which evaluates major growth patterns and glandular differentiation [8].

- The Gleason grade varies between 1 and 5. The most commonly seen major pattern is combined with the secondary pattern, and the total is used to derive the Gleason score.
- The Gleason score varies between 2 and 10. Grade 1 is similar to normal, while grade 5 corresponds to no glandular pattern.
- *Gleason score:* 2–6 = well-differentiated; 7 = moderately differentiated; 8–10 = poorly differentiated.

8.1.2 General Presentation

Most patients are asymptomatic in the early stages, and the presence of symptoms is generally the sign of locally advanced or metastatic disease.

- The extension of the tumor towards the urethra or neck of the bladder or direct invasion of the trigone causes irritative or obstructive symptoms and hematuria.
- Metastatic disease causes anorexia, weight loss, pathologic fractures, and bone pain as a result of metastatic bone disease. It may also cause spinal cord compression and related symptoms of sensory loss, incontinence and motor loss.
- Uremic symptoms may occur resulting from ureteral obstruction or retroperitoneal lymph node (LN) metastases.
- Hematospermia due to seminal vesicle invasion, lower extremity edema due to LN metastasis, and erectile dysfunction due to cavernous nerve invasion may also be seen in the advanced stages.

Findings. A firm and irregular prostate in a digital rectal exam (DRE) is typical of cancer, but cancer foci may be found in a normal prostate. Cachexia, globe vesicale, lower extremity lymphedema, deep venous thrombosis, spasticity, motor weakness and supraclavicular lymphadenopathy may be observed during routine physical examination.

Laboratory findings. Anemia may be seen due to metastatic disease. Bilateral ureter obstruction causes azotemia. Alkaline phosphatase in bone metastasis and acid phosphatase in extraprostatic extension may increase.

Prostate-specific antigen [9]. PSA is 33 kD in weight, and consists of a single glycoprotein chain of 237 amino acids and four carbohydrate side-chains, including sulfide bonds. It displays chymotrypsin-like features, and is homologous with proteases in the family of human glandular kallikrein 3 (hK-3). It also exhibits 80% homology with the other prostate cancer marker, human glandular kallikrein 2 (hK-2). Human glandular kallikrein 1 (hK-1), mainly found in the pancreas and in renal tissue, has 73–84% homology with PSA.

- PSA is a neutral serine protease that liquifies seminal coagulate by hydrolyzing seminogelin I and II, which are seminal vesicle proteins.
- Only a small portion of the PSA is found in its free form, termed free-PSA (f-PSA), as most of it is bound to alpha 2-macroglobulin (AMG) and alpha 1-antichymotrypsin (ACT).
- The half-life of PSA is around 2.2–3.2 days, and reaches its lowest level 2–3 weeks after radical prostatectomy (RP).

The upper limit for serum prostate-specific antigen (PSA) is accepted to be 4.0 ng/mL. However, 20% of prostate cancer cases have PSA levels of below 4.0 ng/mL, and only 25% of cases with serum PSA levels of 4–10 ng/mL have prostate cancer in their biopsies.

Therefore, new methods like age- and race-specific PSA, PSA density, PSA velocity, and free and complex PSA are being developed.

Age- and race-specific PSA. This may be useful for diagnosing organ-confined prostate cancer in young males that can be cured totally with radical therapy, and may prevent unnecessary treatment of clinically insignificant small tumors in older patients. The reference intervals for age- and race-specific PSA values according to the best practice policy of the American Urology Society for PSA use and prostate biopsy indications are summarized in Table 8.1 [10].

An 8% increase in positive biopsy rates and diagnoses of organ-confined disease under 59 years can be obtained compared to when age-specific PSA values are used with the standard 4 ng/mL upper limit.

Table 8.1 Age- and race-specific reference PSA levels

Age interval (years)	Asian	African American	White
40–49	0–2	0–2	0–2.5
50–59	0–3	0–4	0–3.5
60–69	0–4	0–4.5	0–0.4.5
70–79	0–5	0–5.5	0–6.5

PSA density (PSAD). More than 80% of men with high serum PSA levels have values of between 4 and 10 ng/mL. These high PSA levels are usually due to a high prevalence of benign prostate hyperplasia (BPH). The PSAD was introduced particularly for men with normal DRE and PSA levels of 4–10 ng/mL in order to differentiate between BPH and prostate cancer.

- The PSAD is calculated by dividing the serum PSA level by the prostate volume, as measured by TRUS.
- The threshold level of 0.15 or above indicates prostate cancer, while 0.15 or below indicates benign disease.
- The prostate cancer diagnosis rate increases in patients with PSA levels of 4–10 ng/mL when this PSAD threshold is applied.
- The main problems with the PSAD are errors in prostate volume measurement using TRUS, changes in the epithelial–stromal ratio of the prostate, and changes in PSA with age.

PSA velocity (PSAV). This is the change in PSA level over time. This change may be due to either an increase in prostate volume or prostate cancer.

- The concept of the PSAV was developed to aid the early diagnosis of nonpalpable organ-confined cancer, since such cases show high PSA changes in a short period of time (i.e., increased PSAV).
- The PSAV is calculated using a formula that incorporates at least three PSA levels measured at 6 month (or more) intervals.

$$PSAV = 1/2 \times \left[\frac{(PSA2 - PSA1)}{Time} + \frac{(PSA3 - PSA2)}{Time} \right] \tag{8.1}$$

- The upper limit for the PSAV is taken to be 0.75 ng/mL/year; a value above this limit is considered to be a tumor-specific marker.
- The PSAV should be measured according to certain rules (measurement interval, number of measurements).

Roach formulae. The risk of invasion is calculated using these formulae via the PSA level and the Gleason score:

$$\text{Capsule Invasion Risk} = \left(\frac{3}{2} \right) \times PSA + [(GS - 3) \times 10] \tag{8.2}$$

$$\text{Seminal Vesicle Invasion Risk} = PSA + [(GS - 6) \times 10] \tag{8.3}$$

$$\text{Lymph Node Metastasis Risk} = \left(\frac{2}{3} \right) \times PSA + [(GS - 6) \times 10] \tag{8.4}$$

PSA Bounce Phenomenon

The PSA bounce is a temporary rise in PSA level after radiation therapy. Recent trials demonstrated that patients that show a PSA bounce are not at an increased risk of relapse compared to those who do not show a temporary rise. Between a third and a half of patients experience a PSA bounce regardless of the technique applied (i.e., external radiotherapy or brachytherapy), and it may occur anywhere between about 1 and 3 years after treatment. The magnitude of the bounce lies in the range 0.5–2 ng/mL and may last from a few months to around a year. The reason for the bounce is not known. Testosterone recovery after hormonal treatment may cause a PSA bounce in patients receiving androgen ablation therapy along with radiotherapy [11].

8.1.3 Staging

T Staging (Fig. 8.4) [12]

T0: No evidence of primary tumor
T1: Clinically inapparent tumor not palpable nor visible by imaging
- T1a: Tumor incidental histologic finding in 5% or less of tissue resected
- T1b: Tumor incidental histologic finding in more than 5% of tissue resected
- T1c: Tumor identified by needle biopsy (e.g., because of elevated PSA)

T2: Tumor confined within prostate*
- T2a: Tumor involves 50% or less of one lobe
- T2b: Tumor involves more than 50% of one lobe but not both lobes
- T2c: Tumor involves both lobes

T3: tumor extends through the prostate capsule**
- T3a: Extracapsular extension (unilateral or bilateral)
- T3b: Tumor invades seminal vesicle(s)
- T4: Tumor is fixed or invades adjacent structures other than seminal vesicles: bladder neck, external sphincter, rectum, levator muscles, and/or pelvic wall

*Tumor that is found in one or both lobes by needle biopsy but is not palpable or reliably visible by imaging is classified as T1c.
**Invasion into the prostatic apex or into (but not beyond) the prostatic capsule is classified as T2 not T3.

N Staging (Fig. 8.5)

NX: Regional lymph nodes were not assessed
N0: No regional lymph nodes metastasis
N1: Metastasis in regional lymph nodes(s)

Regional lymph nodes (N) (Fig. 8.5)

Regional lymph nodes are the pelvic nodes below the bifurcation of the common iliac arteries.
- Pelvic
- Hypogastric
- Obturator
- Iliac (internal, external)
- Sacral (lateral, presacral, promontory)

Distant lymph nodes are outside the confines of the true pelvis.
- Aortic (para-aortic, periaortic, or lumbar)
- Common iliac

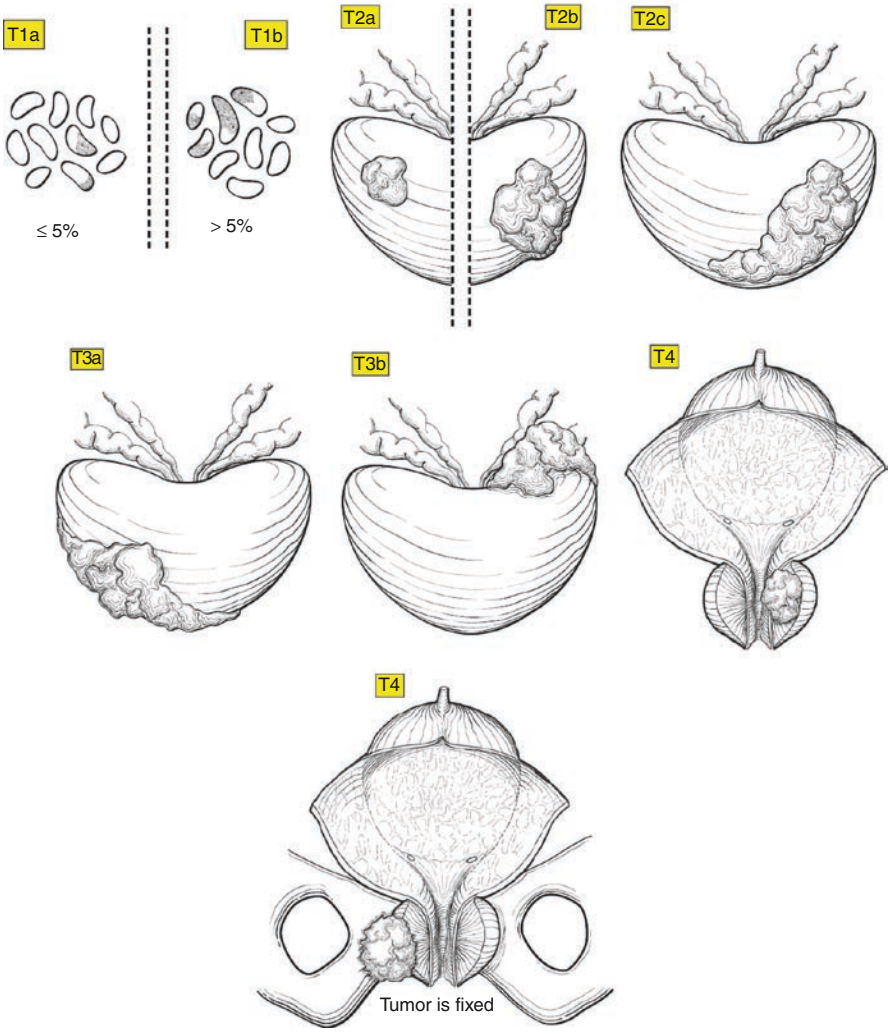

Fig. 8.4 T staging in prostate cancer (from [37], p 295–298, Figs. 34.3–34.8, reproduced with the permission from the American Joint Committee on Cancer)

Inguinal (deep)
Superficial inguinal (femoral)
Supraclavicular
Cervical
Scalene
Retroperitoneal

Involvement of distant LNs is classified M1a.

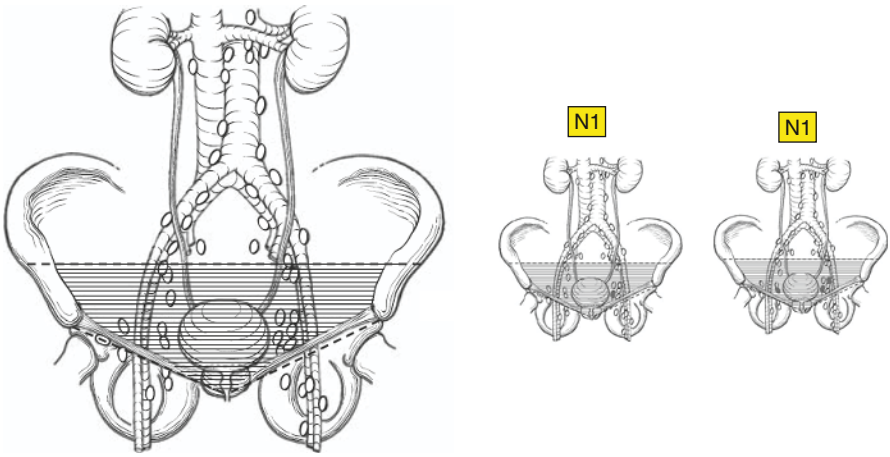

Fig. 8.5 Prostate lymphatics and N staging (from [37], p 294, 299, Figs. 34.2 and 34.9, reproduced with the permission from the American Joint Committee on Cancer)

Distant metastasis (M)

MX: Distant metastasis cannot be assessed (not evaluated by any modality)

M0: No distant metastasis

M1: Distant metastasis

- M1a: Nonregional lymph node(s)
- M1b: Bone(s)
- M1c: Other site(s) with or without bone disease

Histopathologic grade (G)

GX: Gleason score cannot be assessed

Gleason ≤ 6: Well differentiated (slight anaplasia)

Gleason 7: Moderately differentiated (moderate anaplasia)

Gleason 8–10: Poorly differentiated or undifferentiated (marked anaplasia)

AJCC Stage Groups

Group	T	N	M	PSA	Gleason
Stage I	1a-c	0	0	<10	≤6
	2a	0	0	<10	≤6
	1, 2a	0	0	X	X
Stage IIA	1a-c	0	0	<20	7
	1a-c	0	0	10-20	≤6
	2a	0	0	<20	≤7
	2b	0	0	<20	≤7
	2b	0	0	X	X
Stage IIB	2c	0	0	Any	Any
	1-2	0	0	≥20	Any
	1-2	0	0	Any	≥8

Stage III	3a-b	0	0	Any	Any
Stage IV	T4	0	0	Any	Any
	Any	1	0	Any	Any
	Any	Any	0	Any	Any

Extension and invasion [13–15]. This is related to extraprostatic extension, seminal vesicle invasion, distant metastasis, and Gleason score.

- Small and well-differentiated tumors (grade 1 and 2) are generally organ-confined, while large (>4 cm^3) and undifferentiated tumors (grade 4 and 5) are generally locally advanced or metastatic (LN/bone).
- Capsule penetration usually occurs from the perineural space.
- The trigone may be invaded in locally advanced prostate cancer, causing ureter obstruction.
- Rectal invasion is very rare, due to a barrier called Denonvillier's fascia, located between the prostate and rectum.
- Lymphatic metastasis usually occurs in obturator LNs, as well as in presacral and periaortic LNs.
- Distant metastasis via the valveless Batson's venous plexus is commonly seen in the axial skeleton, particularly the lumbar vertebrae, followed by proximal femur, pelvis, thoracic vertebrae, costae, sternum, skull and humerus.
- Bone metastasis of prostate cancer is typically osteoblastic. The involvement of long bones may cause fractures, and vertebral metastases may cause spinal cord compression.
- Visceral metastasis is usually to lungs, liver and adrenal glands. Brain metastases are very rare, and generally occur by direct metastatic extension of skull bones.

8.1.4 Treatment Algorithm

Treatment Algorithm for Prostate Cancer [16]

Low risk
Survival estimate <10 years
- Surveillance
- Definitive RT

Survival estimate ≥10 years
- Definitive RT
- RP ± pelvic LN dissection
- Surveillance

Moderate risk
Survival estimate <10 years
- Surveillance
- Definitive RT + short-term HT (4–6 months)

(*continued*)

(continued)

Survival estimate ≥10 years
RT + short term HT (4–6 months)
Definitive RT
RP ± pelvic LN dissection

- Surgical margin (+) after RP; adjuvant RT or surveillance
- LN (+) after RP; androgen ablation ± RT or surveillance

High risk
RT + long-term HT (>2 years)
Lymph node (+)
RT + long-term HT (>2 years)
Metastatic
Androgen ablation ± palliative RT ± bisphosphonates
If hormone resistant → CT (docetaxel + prednisone or estramustine)
Residual disease or recurrence after RP
Persistent local disease or high-risk local residual disease: RT ± HT
No evidence of persistent local disease or metastasis: HT or surveillance ± RT
Residual disease or recurrence after radiotherapy
Biopsy (+) and no metastasis or low-risk group: surgery or salvage brachytherapy
If systemic or local therapies are not suitable: androgen ablation or surveillance
Risk groups
Low risk: PSA ≤10 ng/mL, GS≤6, T1–T2a
Moderate risk: PSA 10–20 ng/mL, GS 7, T2b
High risk: PSA>20 ng/mL, GS 8–10, T2c–T3

Androgen ablation [10]. Several prostate cancers are hormone dependent, and it is well known that 70–80% of men with metastatic prostate cancer may respond to androgen ablation. Androgen ablation may be performed at different levels of the hypophyseal–testis axis by a variety of methods and agents (Table 8.2).

Table 8.2 Drugs used for androgen ablation

Level	Agent	Administration route	Dose (mg)	Usage frequency
Hypophysis	Diethylstilbestrol	PO	1–3	Daily
	Goserelin	SC	10.8	Every 3 months
	Goserelin	SC	3.6	Monthly
	Leuprolide	IM/SC	11.25	Every 3 months
	Leuprolide	IM/SC	7.5	Monthly
Surrenal gland	Ketoconazole	PO	400	Daily
	Aminoglutethimide	PO	250	Four times daily
Testis	Orchiectomy	–	–	–

Table 8.2 (continued)

Level	Agent	Administration route	Dose (mg)	Usage frequency
Prostate	Bicalutamide	PO	50/150	Daily
	Flutamide	PO	250	Three times daily
	Nilutamide	PO	150	Daily

Radical prostatectomy. Performed mainly by two approaches.

- The first and more popular is *radical retropubic prostatectomy* [17]. Here, the surgeon makes an incision 2 cm above the penis and 2–3 cm below the umbilicus and excises the prostate with its surrounding tissues from this incision. Pelvic LNs are dissected first with this technique, and the prostate is dissected if the LNs are not involved. These LNs are examined by frozen section, and the prostate is not usually dissected if they are positive for cancer. Another advantage of this technique is that the neurovascular bundle can be spared for erectile functions by nerve-sparing prostate surgery.
- The other technique, the *transperineal approach* [18], is usually not preferred for prostate cancer. The incision is performed between the anus and testicles. There is less bleeding in this approach, and it is easier to perform than radical retropubic prostatectomy in obese men. However, the nerves are not spared and the LNs cannot be dissected with this surgical approach. Therefore, the perineal technique is not usually preferred for the management of prostate cancer.

8.1.5 Radiotherapy

Whole-pelvis radiotherapy [19]
Relative indications:

- T4 tumor
- LN (+)
- Seminal vesicle invasion (+)
- LN risk >15% according to the Roach formula
- High-risk group

Anterior–posterior fields (Fig. 8.6):
Superior border: L5–S1 intervertebral space

- If LN (+): L4–L5 intervertebral space

Inferior border: below ischial tuberosities
Lateral borders: include 1–1.5 cm of bony pelvis (femur and iliac wings are shielded)
Lateral fields (Fig. 8.7):
Superior and inferior borders: same as anterior–posterior fields
Anterior border: anterior to pubic symphysis
Posterior border: S2–S3 intervertebral space (small intestines, posterior soft tissues of sacrum and rectum [without protecting prostate!] are shielded)

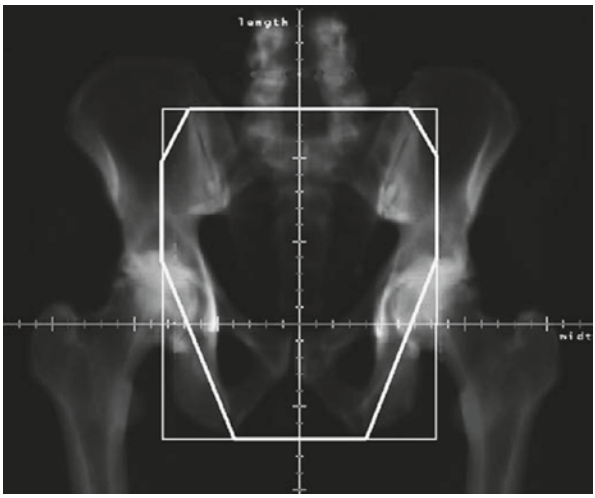

Fig. 8.6 Anterior pelvis field in prostate cancer (Fig, 28.4a, p 697 from [36])

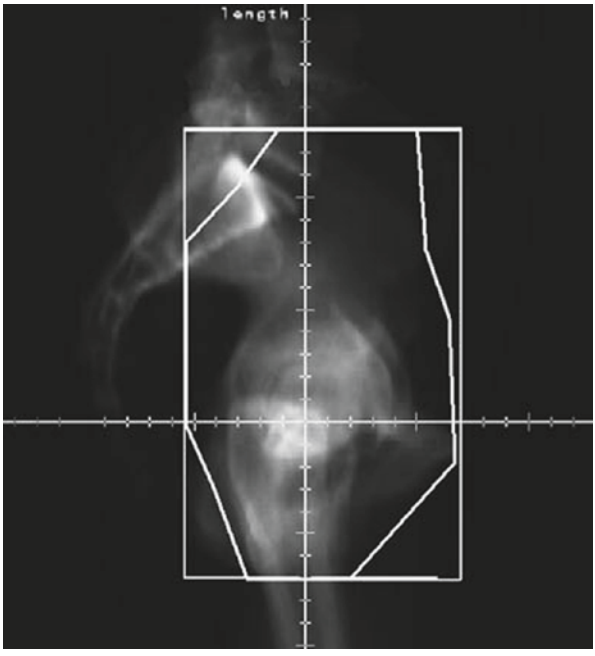

Fig. 8.7 Lateral pelvis field in prostate cancer (Fig. 28.4b, p 697 from [36])

Localized Prostate Field [19]

Indications

- T1–T2 tumor (early stage)
- LN (−)
- Seminal vesicle invasion (−)
- LN involvement risk <15% according to the Roach formula
- Low- to moderate-risk patients
- High-risk patients receiving long-term androgen ablation therapy

Conformal therapy is used for localized prostate fields. Therefore, no bony markers are available for localized prostate radiotherapy (Figs. 8.8 and 8.9).

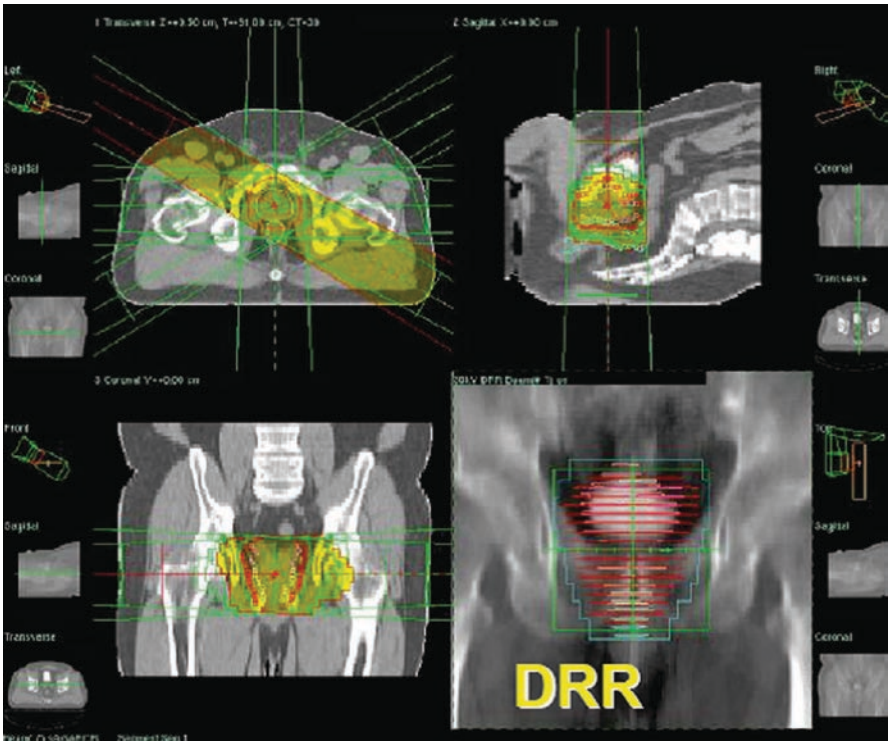

Fig. 8.8 Anterior localized field in prostate cancer

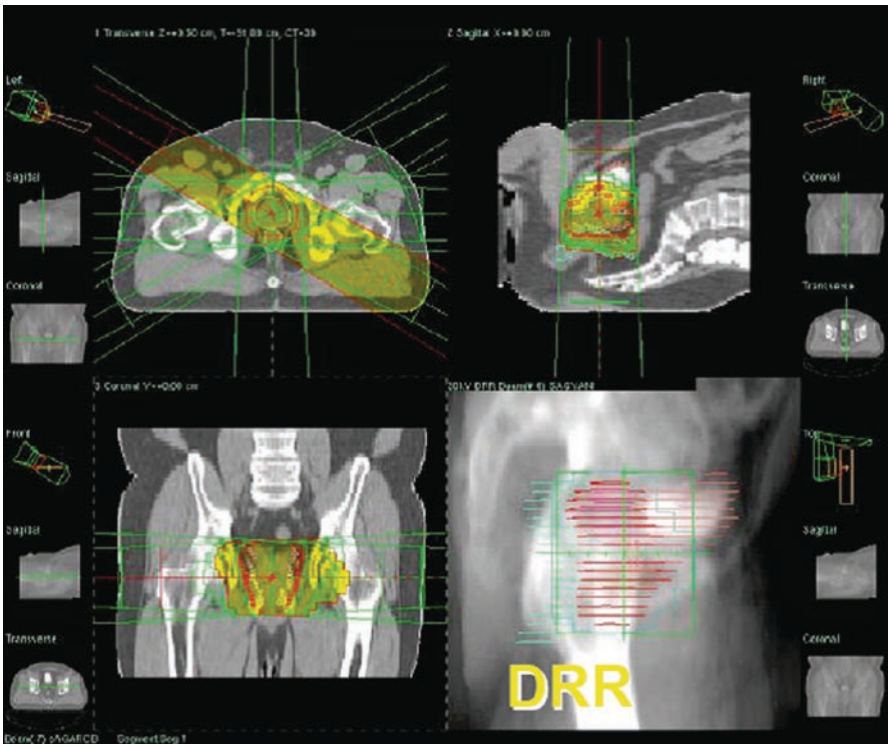

Fig. 8.9 Lateral localized field in prostate cancer

Simulation:

- Simulation is usually performed in the supine position. Some centers prefer the prone position in order to decrease the volume of the small intestine. Knee support may be used in the supine position for the same purpose.
- The bladder is visualized with a small amount of IV contrast material (40–50 cm^3) to differentiate the base of the prostate from the neck of the bladder.

Conformal RT Volumes (Fig. 8.10) [20]

GTV: nodule if visible, otherwise the GTV is not delineated; it is adequate to delineate the CTV as described below.
CTV: entire prostate gland (usually includes one-third of SV)±SV (depends on SV invasion risk).
PTV: CTV+ 1 cm in all directions, except 8 mm at posterior border.
CTV volumes are similar in IMRT.
Critical organ dose for 3D-conformal RT

Rectum

Less than 5–10% grade III–IV rectal toxicity
V50 (volume of rectum receiving more than 50 Gy): 60–65%
V60 (volume of rectum receiving more than 60 Gy): 45–50%
V70 (volume of rectum receiving more than 70 Gy): 25–30%

Bladder

Entire bladder <65 Gy
Partial volume 75–80 Gy
Three percent of bladder volume should receive less than 78 Gy

Femoral heads

Mean dose for femoral heads should be less than 50 Gy

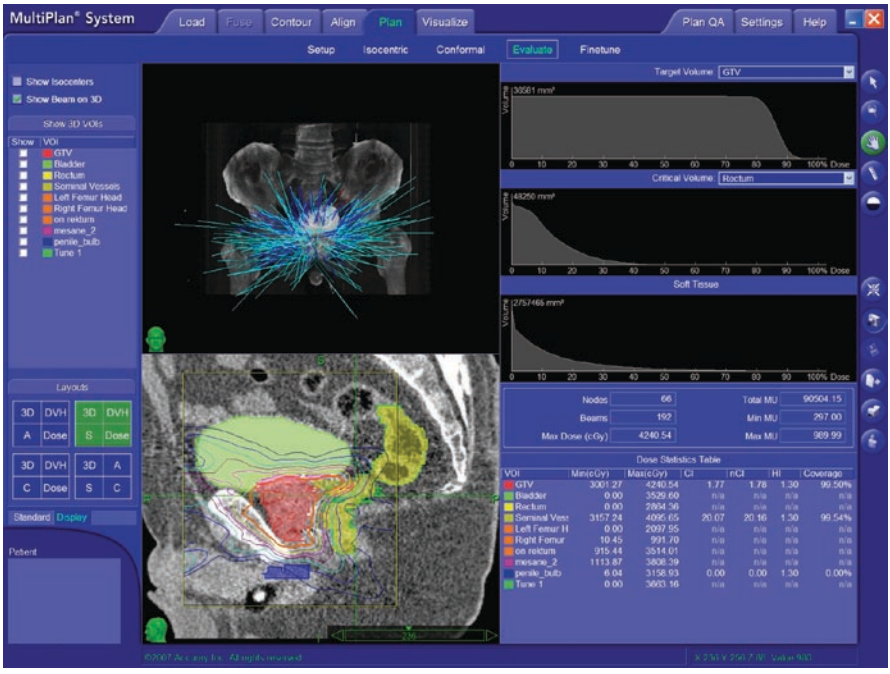

Fig. 8.10 Robotic radiosurgery planning for a patient with low-risk prostate cancer

Dose/Energy

- 1.8–2 Gy daily fractions with a suitable X-ray energy according to patient thickness (6–18 MV):

  Whole pelvis (if indicated): 45–50 Gy
  Prostate field: >70 Gy for definitive
  Prostate bed: 64–66 Gy for postoperative (at least 70 Gy for macroscopic disease)

8.1.6 Selected Publications

PSA relapse definition after RT

ASTRO consensus → three consecutive increases in PSA is the definition of biochemical failure after radiation therapy. The date of failure should be the midpoint between the post-RT nadir PSA and the first of the three consecutive rises.

- Biochemical failure is not a justification to initiate additional treatment. It is not equivalent to clinical failure. It is an appropriate early end-point for clinical trials.

Anon (1997) Consensus statement: guidelines for PSA following radiation therapy. American Society for Therapeutic Radiology and Oncology Consensus Panel. Int J Radiat Oncol Biol Phys 37(5):1035–1041

Phoenix definition → (1) a rise by 2 ng/mL or more above the nadir PSA should be considered the standard definition for biochemical failure after external RT with or without hormonal treatment; (2) the date of failure should be determined "at call" (not backdated).

- Investigators are allowed to use the ASTRO Consensus Definition after RT alone (no hormonal therapy) with strict adherence to guidelines regarding "adequate follow-up".
- The reported date of control should be listed as 2 years short of the median follow-up.

Roach M III et al (2006) Defining biochemical failure following radiotherapy with or without hormonal therapy in men with clinically localized prostate cancer: recommendations of the RTOG-ASTRO Phoenix Consensus Conference. Int J Radiat Oncol Biol Phys 65(4):965–974

Dose escalation

MRC RT01, 2007 → 843 men with localized prostate cancer who were randomly assigned to standard-dose CFRT or escalated-dose CFRT, both with neoadjuvant androgen suppression. Escalated-dose CFRT with neoadjuvant androgen suppression was clinically worthwhile in terms of biochemical control, and decreased use of salvage androgen suppression. This additional efficacy was offset by an increased incidence of longer-term adverse events.

Dearnaley DP (2007) Escalated-dose versus standard-dose conformal radiotherapy in prostate cancer: first results from the MRC RT01 randomised controlled trial. Lancet Oncol 8(6):475–487

Dutch trial, 2006 → 664 stage T1b–4 prostate cancer patients were enrolled onto a randomized trial comparing 68 Gy with 78 Gy. The primary end-point was freedom from failure (FFF). Median follow-up time was 51 months. Hormone therapy was prescribed for 143 patients. FFF was significantly better in the 78 Gy arm compared with the 68 Gy arm (64 vs. 54%, $p = 0.02$). There was no difference in late genitourinary toxicity of RTOG and EORTC grade 2 or more and a slightly higher nonsignificant incidence of late gastrointestinal toxicity of grade 2 or more.

Peeters ST (2006) Dose-response in radiotherapy for localized prostate cancer: results of the Dutch multicenter randomized phase III trial comparing 68 Gy of radiotherapy with 78 Gy. J Clin Oncol 24(13):1990–1996

Altered fractionation

NCI Canada, 2005 → 66 Gy/33 fractions (2 Gy/fractions) vs. 52.5 Gy/20 fractions (2.62 Gy/fractions), 936 T1–T2, PSA <40 cases with no hormone therapy. Median follow-up: 5.7 years.

- Five-year DFS: 40% in hypofractionated arm vs. 47% in standard arm (NS).
- No difference in OS.
- Late grade III toxicity: 3.2% in both arms.

Lukka H (2005) Randomized trial comparing two fractionation schedules for patients with localized prostate cancer. J Clin Oncol 23(25):6132–6138

Pelvic field RT

RTOG 94-13, 2007 → this trial was designed to test the hypothesis that total androgen suppression and whole pelvic radiotherapy (WPRT) followed by a prostate boost improves progression-free survival (PFS) compared with total androgen suppression and prostate-only RT (PORT). This trial was also designed to test the hypothesis that neoadjuvant hormonal therapy (NHT) followed by concurrent total androgen suppression and RT improves PFS compared with RT followed by adjuvant hormonal therapy (AHT). It involved 1,323 localized prostate cancer cases with an elevated PSA ≤100 ng/mL and an estimated risk of LN involvement of 15%. The difference in overall survival for the four arms was statistically significant ($p = 0.027$). However, no significant differences were found in PFS or overall survival between NHT vs. AHT and WPRT compared with PORT. A trend towards a difference was found in PFS ($p = 0.065$) in favor of the WPRT + NHT arm compared with the PORT + NHT and WPRT + AHT arms.

Lawton CA (2007) An update of the phase III trial comparing whole pelvic to prostate-only radiotherapy and neoadjuvant to adjuvant total androgen suppression: updated analysis of RTOG 94-13, with emphasis on unexpected hormone/radiation interactions. Int J Radiat Oncol Biol Phys 69(3):646–655

GETUG-01, France, 2007 → 444 patients with T1b–T3, N0 pNx, M0 prostate carcinoma were randomly assigned to either pelvic and prostate radiotherapy or prostate radiotherapy only. Short-term 6-month neoadjuvant and concomitant hormonal therapy was given to patients in the high-risk group. The pelvic dose was 46 Gy. The total dose recommended to the prostate was 66–70 Gy. With a 42.1-month median follow-up time, the 5-year PFS and overall survival were similar in the two treatment arms for the whole series and for each stratified group. Pelvic node irradiation was well tolerated but did not improve PFS.

Pommier P et al (2007) Is there a role for pelvic irradiation in localized prostate adenocarcinoma? Preliminary results of GETUG-01. J Clin Oncol 25(34):5366–5373

Hormonal therapy + radiotherapy

RTOG 85-31, 2005 → 977 palpable primary tumor cases extending beyond the prostate (clinical stage T3) or those with regional lymphatic involvement. Patients who had

undergone prostatectomy were eligible if penetration through the prostatic capsule to the margin of resection and/or seminal vesicle involvement was documented histologically. Patients were randomized to either RT and adjuvant goserelin (arm I) or RT alone followed by observation and the application of goserelin at relapse (arm II). In arm I, the drug was to be started during the last week of RT and was to be continued indefinitely or until signs of progression. Median follow-up was 7.6 years.

- Ten-year survival rate was significantly greater for the adjuvant arm than for the control arm: 49 vs. 39%, respectively ($p = 0.002$).
- Ten-year local failure rate for the adjuvant arm was 23 vs. 38% for the control arm ($p < 0.0001$).
- Ten-year rates for the incidence of distant metastases and disease-specific mortality were 24 vs. 39% ($p < 0.001$) and 16 vs. 22% ($p = 0.0052$), respectively.
- In patients with carcinoma of the prostate with an unfavorable prognosis, androgen suppression applied as an adjuvant after definitive RT was associated not only with a reduction in disease progression but with a statistically significant improvement in absolute survival. The improvement in survival appeared preferentially in patients with Gleason scores of 7–10.

Pilepich MV (2005) Androgen suppression adjuvant to definitive radiotherapy in prostate carcinoma—long-term results of Phase III RTOG 85-31. Int J Radiat Oncol Biol Phys 61(5):1285–1290

Harvard, 2008 → 206 men with localized but unfavorable-risk prostate cancer were randomized to receive RT alone or RT and hormone therapy. Median follow-up: 7.6 years.

- A significant increase in the risk of all-cause mortality (44 vs. 30 deaths; $p = 0.01$) was observed in men randomized to RT compared with RT and AST.
- The increased risk in all-cause mortality appeared to apply only to men randomized to RT with no or minimal comorbidity (31 vs. 11 deaths; $p < 0.001$).
- Among men with moderate or severe comorbidity, those randomized to RT alone vs. RT and AST did not have an increased risk of all-cause mortality (13 vs. 19 deaths; $p = 0.08$).
- The addition of 6 months of hormonotherapy to RT resulted in increased overall survival in men with localized but unfavorable-risk prostate cancer.

D'Amico AV (2008) Androgen suppression and radiation vs radiation alone for prostate cancer: a randomized trial. JAMA 299(3):289–295

RTOG 86-10, 2008 → 456 patients with bulky (5 × 5 cm) tumors (T2–4) with or without pelvic LN involvement. Patients received combined hormone therapy that consisted of goserelin 3.6 mg every 4 weeks and flutamide 250 mg t.i.d. for 2 months before and concurrent with RT, or they received RT alone.

- Ten-year OS (43 vs. 34%) and median survival times (8.7 vs. 7.3 years) favored hormone therapy and RT, respectively ($p = 0.12$).
- There was a statistically significant improvement in 10-year disease-specific mortality (23 vs. 36%; $p = 0.01$), distant metastasis (35 vs. 47%; $p = 0.006$), DFS (11 vs. 3%;

$p < 0.0001$), and biochemical failure (65 vs. 80%; $p < 0.0001$) with the addition of hormone therapy.
- No differences were observed in the risk of fatal cardiac events.
- The addition of 4 months of ADT to EBRT appears to have a dramatic impact on clinically meaningful end-points in men with locally advanced disease, with no statistically significant impact on the risk of fatal cardiac events.

Roach M et al (2008) Short-term neoadjuvant androgen deprivation therapy and external-beam radiotherapy for locally advanced prostate cancer: long-term results of RTOG 8610 J clin Oncol 26(4):585–591

RTOG 92-02, 2008 → 1,554 patients with T2c–T4 prostate cancer with no extra pelvic LN involvement and PSA less than 150 ng/mL. All patients received 4 months of goserelin and flutamide before and during RT. They were randomized to no further ADT (short-term ADT [STAD] + RT) or 24 months of goserelin (long-term ADT [LTAD] + RT). RT was 45 Gy to the pelvic nodes and 65–70 Gy to the prostate.

- At 10 years, the LTAD + RT group showed significant improvement over the STAD + RT group for all end-points except overall survival: disease-free survival (13.2 vs. 22.5%; $p < 0.0001$), disease-specific survival (83.9 vs. 88.7%; $p = 0.0042$), local progression (22.2 vs. 12.3%; $p < 0.0001$), distant metastasis (22.8 vs. 14.8%; $p < .0001$), biochemical failure (68.1 vs. 51.9%; $p \leq 0.0001$), and overall survival (51.6 vs. 53.9%, $p = 0.36$).
- A difference in overall survival was observed in patients with a Gleason score of 8–10 (31.9 vs. 45.1%; $p = 0.0061$).
- LTAD as delivered in this study for the treatment of locally advanced prostate cancer was superior to STAD for all end-points except survival.
- The survival advantage for LTAD + RT in the treatment of locally advanced tumors with a Gleason score of 8–10 suggests that this should be the standard of treatment for these high-risk patients.

Horwitz EM et al (2008) Ten-year follow-up of radiation therapy oncology group protocol 92-02: a phase III trial of the duration of elective androgen deprivation in locally advanced prostate cancer. J Clin Oncol 26(15):2497–2504

Prostatectomy ± RT

EORTC 22911, 2005 (1992–2001) → EORTC Trial 22911 demonstrated that immediate postoperative irradiation significantly improved biochemical failure-free survival (BPFS) compared to wait-and-see (W and S) until relapse in patients with pT2–3 tumors and pathological risk factors (cancer extending beyond the capsule and/or involvement of seminal vesicles or positive surgical margins) after RP.

- Postoperative irradiation improved biochemical PFS in all patient groups.

Bolla M et al (2005) Postoperative radiotherapy after radical prostatectomy: a randomised controlled trial (EORTC Trial 22911). Lancet 366(9485):572–578

Collette L et al (2005) Patients at high risk of progression after radical prostatectomy: do they all benefit from immediate post-operative irradiation? (EORTC Trial 22911). Eur J Cancer 41(17):2662–2672

RTOG 90-19/SWOG-8794 Intergroup → 425 patients with stage pT3 N0 M0 prostate cancer. Men were randomly assigned to receive 60–64 Gy of external beam radiotherapy delivered to the prostatic fossa or observation. Median follow-up was 10.6 years.

- There were no significant between-group differences for overall survival.
- PSA relapse (median PSA relapse-free survival, 10.3 years for RT vs. 3.1 years for observation; $p<0.001$) and disease recurrence (median recurrence-free survival, 13.8 years for RT vs. 9.9 years for observation; $p=0.001$) were both significantly reduced with radiotherapy.
- Adverse effects were more common with radiotherapy vs. observation (23.8 vs. 11.9%), including rectal complications (3.3 vs. 0%), urethral strictures (17.8 vs. 9.5%), and total urinary incontinence (6.5 vs. 2.8%).

Thompson IM Jr et al (2006) Adjuvant radiotherapy for pathologically advanced prostate cancer: a randomized clinical trial. JAMA 296(19):2329–2335

Swanson GP (2007) Predominant treatment failure in postprostatectomy patients is local: analysis of patterns of treatment failure in SWOG 8794. J Clin Oncol 25(16): 2225–2229

IMRT

MSKCC, 2008 → 478 patients were treated with 86.4 Gy using a five- to seven-field IMRT technique. The mean D95 and V100 for the planning target volume were 83 Gy and 87%, respectively. The median follow-up was 53 months. There was no acute grade 3 or 4 GI toxicity. Three patients (0.6%) had grade 3 GU toxicity. There was no acute grade 4 GU toxicity. Sixteen patients (3%) developed late grade 2 GI toxicity and two patients (<1%) developed late grade 3 GI toxicity. Sixty patients (13%) had late grade 2 GU toxicity and 12 (<3%) experienced late grade 3 GU toxicity. The 5-year actuarial PSA relapse-free survivals according to the nadir plus 2 ng/mL definition were 98, 85 and 70% for the low-, intermediate-, and high-risk NCCN prognostic groups.

Cahlon O et al (2008) Ultra-high dose (86.4 Gy) IMRT for localized prostate cancer: toxicity and biochemical outcomes. Int J Radiat Oncol Biol Phys 71(2):330–337

Surveillance vs. prostatectomy

Scandinavian Prostate Cancer Group Study-4, 2005 (1989–1999) → 695 cases of early-stage T1–T2 prostate cancer. Surveillance vs. prostatectomy. Follow-up with PSA and DRE. Median follow-up: 8.2 years.

Mortality due to prostate cancer:
14.4% in surveillance vs. 8.6% in prostatectomy
After 10 years: 5% in survival difference (relative risk = 0.74)

Conclusion: prostate cancer mortality was less in treated patients.
Bill-Axelson A et al (2005) Radical prostatectomy versus watchful waiting in early prostate cancer. N Engl J Med 352(19):1977–1984

8.2 Testicular Cancer

Testicular cancers constitute 1% of all cancers. A previous history of testicular cancer, cryptorchidism, Klinefelter's syndrome (47XXY) and other testicular feminizing syndromes are possible etiological factors for the development of these cancers [21].

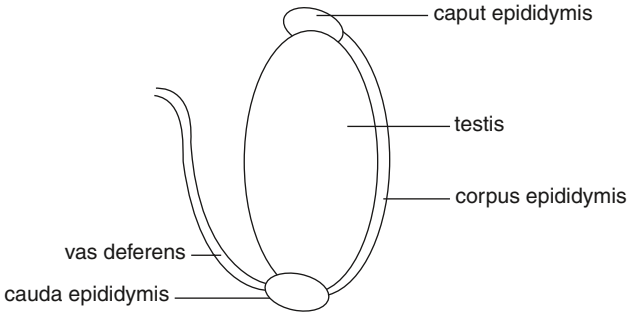

Fig. 8.11 Testis anatomy [38, p 42, Fig. 2]

Testis Anatomy (Fig. 8.11)

Scrotum. This includes the testicles, epididymis and part of the spermatic cord. The tunica dartos layer sticks to the scrotal skin, and consists of superficial and deep layers of superficial fascia. It contains smooth muscle fibers called the dartos muscle. This muscle is an important factor in the temperature regulation of the testes. This layer contains little fat tissue but is rich in elastic leaves.
Layers of the scrotum. These layers are located under the skin and tunica dartos:

1. *External spermatic fascia*. This is continuous with the fascia of the external abdominal oblique muscle.
2. *Cremasteric fascia and cremaster muscle*. This is formed by leaves of internal abdominal oblique muscle and (partially) transverse abdominal muscle. The

(*continued*)

(continued)

innervation of this layer is provided by the right femoral branch of the genitofemoral nerve, and a clinically important reflex pathway is formed called the cremaster reflex (the excitation of medial part of the femoral region causes the cremaster muscle to contract, and the testicles to be pulled up to the lower part of the abdomen).

3. *Internal spermatic fascia*. This is formed by the continuation of the transversalis fascia. This fascia is loosely attached to the parietal layer of the tunica vaginalis. It also surrounds the spermatic cord, testis and epididymis.

Testis. These are two ovoid glands that produce sperm and testosterone and are located within the scrotum. They are 4–5 cm in height, 2.5–3 cm in width, 2–3 cm thick, and 10–14 g in weight.

- A strong membrane called the tunica albuginea, located in the inner visceral layer of the tunica vaginalis, surrounds the testicles.

8.2.1 Pathology

Malignant testicular germ cell cancers consist of a single cell line in 50% of cases, and 50% of those are seminomas [22]. Other malignant testicular germ cell cancers are formed by the combination of more than one clonogenic cell type. This histological structure is important for metastases, and responds to chemotherapy. Polyembryoma is a rare histological pattern and can be classified as a single histological type, although it is also considered a mixed tumor.

1. Intratubular germ cell neoplasms, unclassified (old term: carcinoma in situ or CIS)
2. Malignant pure germ cell tumor (includes the single-cell type):
   Seminoma (34–55%)
   Embryonal carcinoma (23–34%)
   Teratoma (1–9%; locally invasive)
   Choriocarcinoma (1–4%; hematogenous spread)
   Yolk sac tumor (most frequent testicular tumor in childhood)
3. Malignant mixed germ cell tumor (includes more than one cell type):
   Embryonal carcinoma and teratoma (may additionally include seminoma or not)
   Embryonal carcinoma and yolk sac tumor (may additionally include seminoma or not)
   Embryonal carcinoma and seminoma
   Yolk sac tumor and teratoma (may additionally include seminoma or not)
   Choriocarcinoma and any of the other types
4. Polyembryoma

Testicular cancers are rare tumors. However, they are the most common cancers in males aged between 20 and 35 years [23].

8.2.1.1 General Presentation

The most common symptom is painless scrotal mass. There is hydrocele in 20% of cases. Bilateral gynecomastia, back pain due to retroperitoneal adenopathies, abdominal pain, nausea, vomiting and constipation may also be seen. Signs and symptoms change according to the area of involvement in patients with extensive metastases.

Physical examination, ultrasonography, serum levels of beta human chorionic gonadotropin (β-hCG), α-fetoprotein (AFP) and lactate dehydrogenase (LDH) are used for the diagnosis of testicular cancers [24].

- AFP and β-hCG increase in 80–85% of extensive germ cell tumors
- Pure seminomas have increased β-hCG but no increase in AFP in 15% of cases
- β-hCG may cause false positivity in hypogonadism
- AFP may increase in liver diseases and hepatitis
- Testicular biopsy is not recommended in cases with suspected cancer

Half-life of β-hCG is 24 h; that of AFP is 5 days.

8.2.1.2 Staging

Primary Tumor (T) (Fig. 8.12) [25]

The extent of the primary tumor is classified after radical orchiectomy, so a pathologic stage is assigned.
pTX: Primary tumor cannot be assessed*
pT0: No evidence of primary tumor (e.g., histologic scar in testis)
pTis: Intratubular germ cell neoplasia (carcinoma)
pT1: Tumor limited to the testis and epididymis without lymphatic/vascular invasion; tumor may invade the tunica albuginea but not the tunica vaginalis
pT2: Tumor limited to the testis and epididymis with vascular/lymphatic invasion, or tumor extending through the tunica albuginea with involvement of the tunica vaginalis
pT3: Tumor invades the spermatic cord with or without vascular/lymphatic invasion
pT4: Tumor invades the scrotum with or without vascular/lymphatic invasion

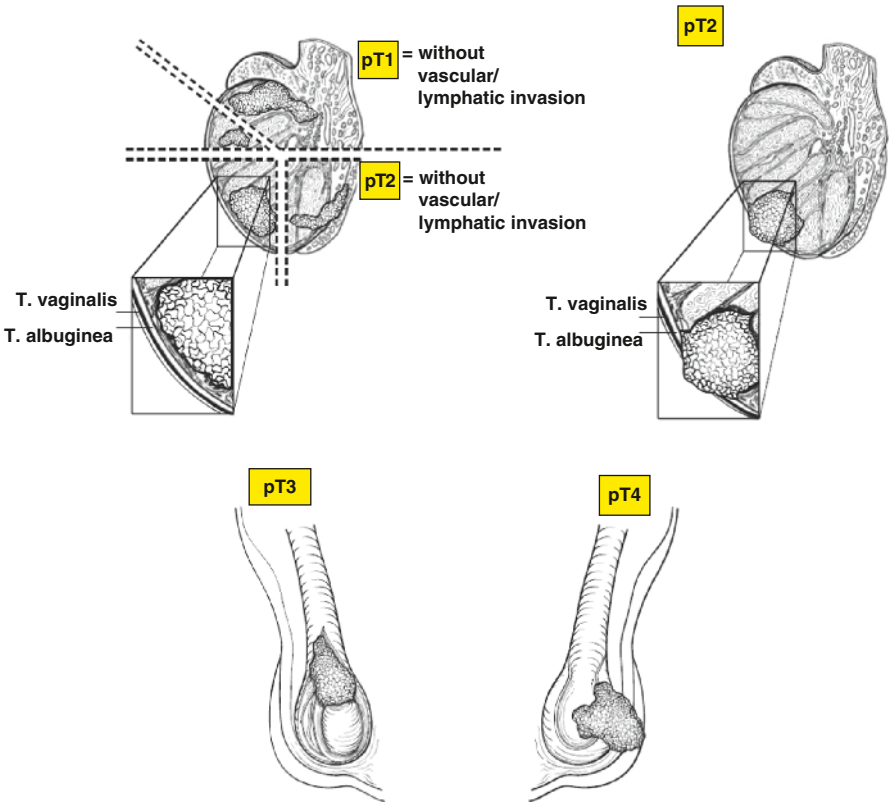

Fig. 8.12 T staging in testicular cancer (from [37], p 306, Figs. 35.3–35.5, reproduced with the permission from the American Joint Committee on Cancer)

Regional Lymph Nodes (N) (Fig. 8.13)

NX: Regional lymph nodes cannot be assessed
N0: No regional lymph node metastasis
N1: Metastasis with a single lymph node mass 2 cm or less in greatest dimension; or multiple lymph nodes, 2 cm or less in greatest dimension
N2: Metastasis with a single lymph node mass larger than 2 cm but no more than 5 cm in greatest dimension; or multiple lymph nodes, no more than 5 cm in greatest dimension
N3: Metastasis with a lymph node mass 5 cm or more in greatest dimension

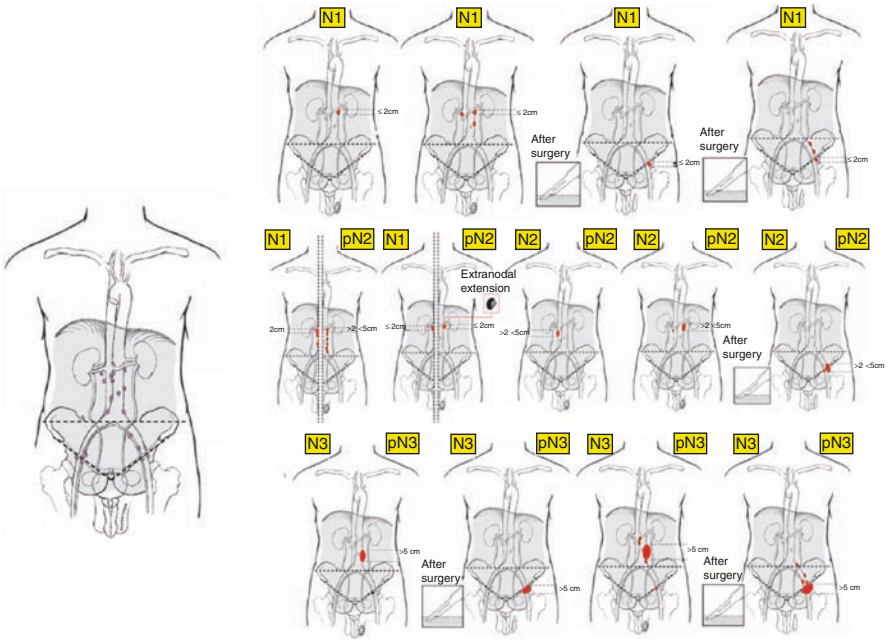

Fig. 8.13 N staging in testicular cancer (from [37], p 309–312, Figs. 35.6–35.8, reproduced with the permission from the American Joint Committee on Cancer)

Testicular lymphatics (Fig. 8.14) [25]: interaortocaval, paraaortic (periaortic), paracaval, preaortic, precaval, retroaortic, retrocaval.
Right testicular lymphatics generally drain into bilateral paraaortic lymph nodes, whereas left testicular lymphatics first drain into left paraaortic lymph nodes.

Distant Metastasis (M)

MX: Presence of distant metastasis cannot be assessed
M0: No distant metastasis
M1: Distant metastasis
M1a: Nonregional nodal or pulmonary metastasis
M1b: Distant metastasis other than to nonregional lymph nodes and lungs

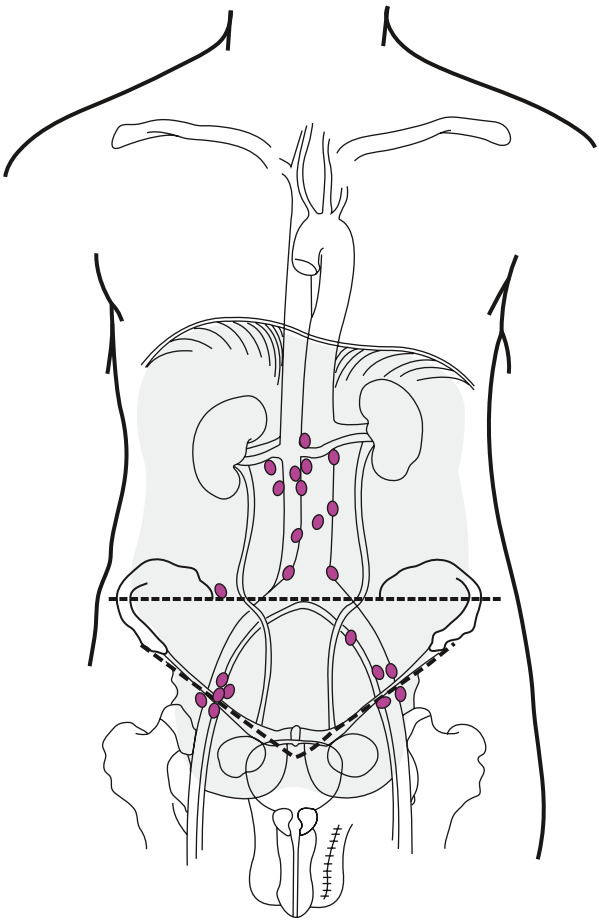

Fig. 8.14 Testicular lymphatics (from [37], p 304, Fig. 35.2, reproduced with the permission of the American Joint Committee on Cancer)

Serum tumor markers (S)
SX: Marker studies not available or not performed
S0: Marker study levels within normal limits
S1: Lactate dehydrogenase (LDH) less than 1.5 × N*, and
Human chorionic gonadotropin (hCG) less than 5,000 (mIU/mL), and
Alpha-fetoprotein (AFP) less than 1,000 (ng/mL)
S2: LDH 1.5–10 × N* or
hCG 5,000–50,000 (mIU/mL), or
AFP 1,000–10,000 (ng/mL)
S3: LDH more than 10 × N*, or
hCG more than 50,000 (mIU/mL), or
AFP more than 10,000 (ng/mL)
* [Note: N indicates the upper limit of normal for the LDH assay.]

AJCC Stage Groups

Stage 0: pTisN0M0, S0
Stage I: pT1–4N0M0, SX
Stage IA: pT1N0M0, S0
Stage IB: pT2N0M0, S0; pT3N0M0, S0; pT4N0M0, S0
Stage IS: Any pT/TxN0M0, S1–3
Stage II: Any pT/TxN1–3M0, SX
Stage IIA: Any pT/TxN1M0, S0; Any pT/TxN1M0, S1
Stage IIB: Any pT/TxN2M0S0; Any pT/TxN2M0, S1
Stage IIC: Any pT/TxN3M0, S0; Any pT/TxN3M0, S1
Stage III: Any pT/Tx, any NM1, SX
Stage IIIA: Any pT/Tx, any NM1a, S0; Any pT/Tx, any NM1a, S1
Stage IIIB: Any pT/TxN1–3M0, S2; Any pT/Tx, any NM1a, S2
Stage IIIC: Any pT/Tx, N1–3, M0, S3; Any pT/Tx, any N, M1a, S3; Any pT/Tx, Any N, M1b, Any S

8.2.2 Treatment Algorithm

The treatment algorithm changes according to the histology of the testicular cancer (seminoma or nonseminoma) [26]. Seminoma is particularly sensitive to radiation. An international germ cell prognostic classification has been derived based on retrospective analyses. The most important property that all of these patients have in common is that all receive either a carboplatin- or a cisplatin-based chemotherapy regimen as the first line treatment.

Testis cancer with good prognosis [27]
Nonseminoma
Testicular or retroperitoneal origin
Lung metastasis (−)
Marker levels normal

- LDH <1.5 times of upper limit
- β-HCG (mIU/mL) <5,000
- AFP (ng/mL) <1,000

Fifty-six percent of nonseminomas
Five-year PFS 89%, 5-year survival 92%
Seminoma
Any origin

(*continued*)

(continued)

Lung metastasis (−)
Marker levels normal
Ninety percent of seminomas
Five-year PFS 82%, 5-year survival 86%

Testis cancer with moderate prognosis [27]
Nonseminoma
Testicular or retroperitoneal origin
Lung metastasis (−)
Marker levels moderately increased

- LDH 1.5–10 times
- β-HCG (mIU/mL): 5,000–50,000
- AFP (ng/mL): 1,000–10,000

Twenty-eight percent of nonseminomas
Five-year PFS 75%, 5-year survival 80%

Seminoma
Any origin
Lung metastasis (+)
Marker levels are normal
Ten percent of seminomas
Five-year PFS 67%, 5-year survival 72%

Testis cancers with poor prognosis [27]
Nonseminoma
Mediastinal origin
Lung metastasis (+)
Marker levels are too high

- LDH >10 times
- β-HCG (mIU/mL) >50,000
- AFP (ng/mL) >10,000

Sixteen percent of nonseminomas
Five-year PFS 41%, 5-year survival 48%

There is no poor prognostic group in seminoma.

The first step in the treatment of testicular tumors is surgery: orchiectomy (which should be performed by inguinal approach, not scrotal).

Treatment of Seminoma [27]

Stage 0 (ITGCN) (TIN)
RT (to testis) (2 Gy/day, 16 Gy)
Stage I
After orchiectomy
Surveillance (recurrence rate ~16%)

RT (pararaortic LN ± pelvic LN) (total 20–26 Gy) (fraction dose 1.8–2 Gy)
Chemotherapy (1–2 cycles of carboplatin)

Stage IIA–IIB
After orchiectomy
RT (pararaortic LN + pelvic LN)

- 24–26 Gy and boost to gross disease
- Stage IIA boost 4 Gy
- Stage IIB boost 10 Gy

Stage IIC–III
After orchiectomy
Chemotherapy (2–3 cycles)

- Etoposide + cisplatin ± bleomycin

Treatment in nonseminomatous testis cancers [26]:

- After orchiectomy: chemotherapy ± LN dissection (selected cases).

8.2.3 Radiotherapy

Paraaortic Field (Fig. 8.15)

Superior: below T10
Inferior: L5–S1 intervertebral space
Lateral: includes transverse processes of lumbar vertebrae

- Renal hilar LNs are included
- Left renal hilar lymphatics should be included, particularly in left-sided testis cancers (left spermatic vein drains directly into left renal vein)
- Both kidneys should be spared, and maximum care should be taken to check for the presence of a horse-shoe kidney, which is a contraindication for radiotherapy

Pelvic + Inguinal Field (Fig. 8.16)

Superior: lower border of paraaortic field (a gap is given)
Inferior: middle obturator foramen
Medial: includes transverse processes of lumbar vertebrae
Lateral: includes inguinal field

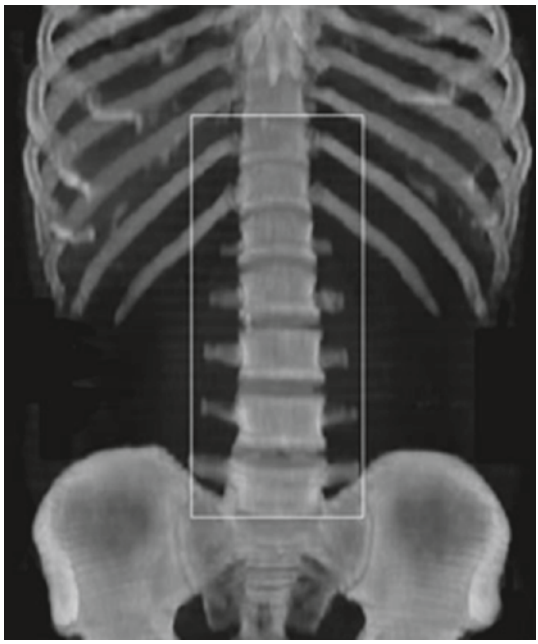

Fig. 8.15 Paraaortic region (from [39], p 744, Fig. 29.3a, reproduced with the permission from Springer Science and Business Media)

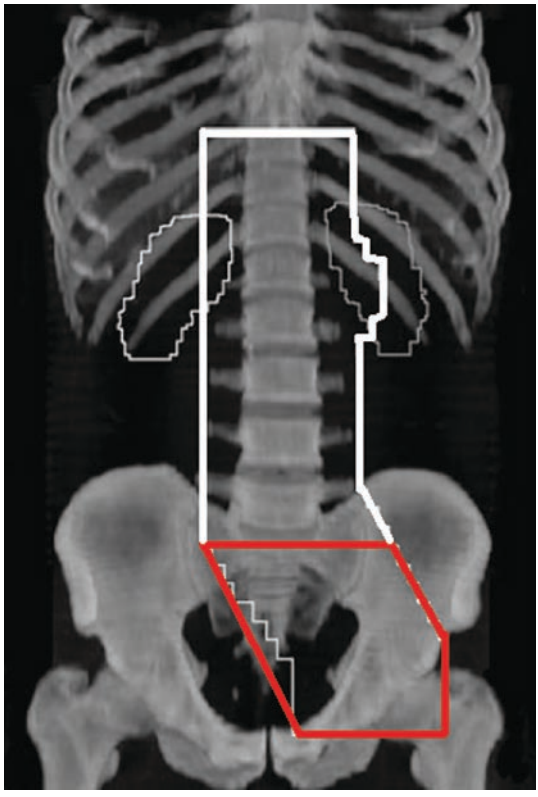

Fig. 8.16 Pelvic and inguinal RT field (from [39], p 744, Fig 29.3b, reproduced with the permission from Springer Science and Business Media)

RT Field in Stage II Seminoma (Fig. 8.17)

- Paraaortic field + pelvic + inguinal field + contralateral inguinal field at the involved ipsilateral testicular site

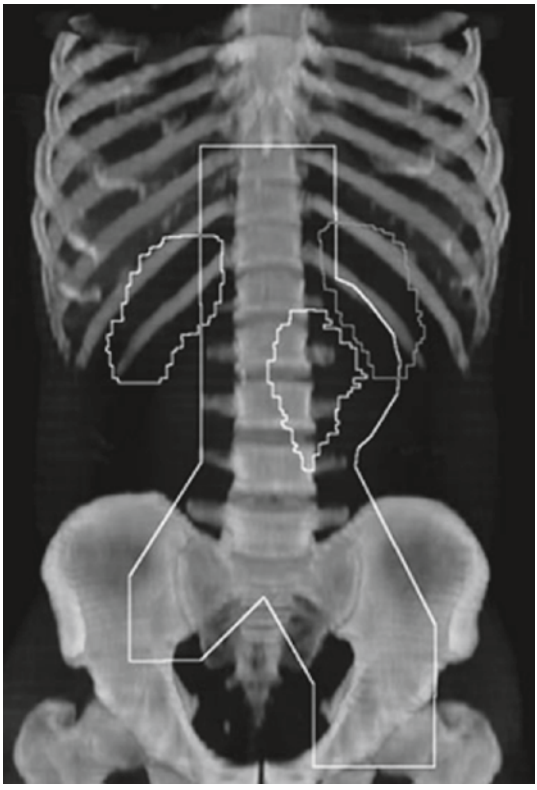

Fig. 8.17 RT field in stage II seminoma (from [39], p 744, Fig. 29.4, reproduced with the permission from Springer Science and Business Media)

- Stage I seminoma: only paraaortic RT can be used
- RT to ipsilateral iliac lymphatics is given in patients with a history of pelvic surgery
- Inguinal lymphatics and scrotum are irradiated in patients with scrotal orchiectomy

The testis is a very radiosensitive organ [28].

- 1 Gy oligospermia, 6 Gy sterility
- Sperm count may decrease due to scattered radiation
- Testicular shielding decreases these effects
- Spermatids and spermatozoa are more radioresistant than spermatogonia

8.2.3.1 Selected Publications

Surveillance, 2000 → 303 men with stage I testicular germ cell tumors. Median follow-up was 5.1 years.

- Only three deaths (one from disease, one from neutropenic sepsis and one from secondary leukemia).
- 52/183 (28%) patients with NSGCT and 18/120 (15%) patients with seminoma relapsed.
- The relapse-free survivals at 5 years were 82% for seminoma and 69% for NSGCT.
- Surveillance for stage I testicular germ cell tumors (both NSGCT and seminoma) was associated with a low mortality rate (3/303, 1%).

Francis R, Bower M, Brunström G et al (2000) Surveillance for stage I testicular germ cell tumours: results and cost benefit analysis of management options. Eur J Cancer 36(15):1925–1932

Surveillance, 2005 → prospective, single-arm study. 88 patients with stage I seminoma.

- The actuarial relapse-free rates were 83, 80, and 80% at 5, 10, and 15 years, respectively.
- Fifteen of seventeen relapses were below the diaphragm.
- Only one had a second relapse and was further salvaged by chemotherapy.
- All 17 relapsed patients remained free of recurrence after salvage treatment; none died of seminoma.
- Surveillance was found to be a safe alternative to postoperative adjuvant therapy for stage I testicular seminoma.

Choo R, Thomas G, Woo T et al (2005) Long-term outcome of postorchiectomy surveillance for stage I testicular seminoma. Int J Radiat Oncol Biol Phys 61(3):736–740

Carboplatin vs. RT, 2005 → 1,477 patients were randomly assigned to receive radiotherapy (paraaortic strip or dog-leg field) or one injection of carboplatin (dose based on the formula 7× [glomerular filtration rate + 25] mg.

- With a median follow-up of 4 years, relapse-free survival rates for radiotherapy and carboplatin were similar (96.7 vs. 97.7% at 2 years; 95.9 vs. 94.8% at 3 years, respectively).
- Patients given carboplatin were less lethargic and less likely to take time off work than those given radiotherapy.
- New, second primary testicular germ cell tumors were reported in ten patients allocated irradiation (all after paraaortic strip field) and in two allocated carboplatin (5-year event rate 1.96 vs. 0.54%, $p = 0.04$).
- One seminoma-related death occurred after radiotherapy, and none after carboplatin.
- This trial has shown the noninferiority of carboplatin to radiotherapy in the treatment of stage I seminoma.

Oliver RT, Mason MD, Mead GM et al (2005) Radiotherapy versus single-dose carboplatin in adjuvant treatment of stage I seminoma: a randomised trial. Lancet 366(9482):293–300

EORTC 30942, 2005 → 625 patients were randomly assigned 20 Gy/10 fractions over 2 weeks or 30 Gy/15 fractions during 3 weeks after orchiectomy.

- Four weeks after starting radiotherapy, significantly more patients receiving 30 Gy reported moderate or severe lethargy (20 vs. 5%) and an inability to carry out their normal work (46 vs. 28%). However, by 12 weeks, the levels in both groups were similar.
- With a median follow-up of 61 months, 10 and 11 relapses, respectively, were reported in the 30 and 20 Gy groups.
- Only one patient had died from seminoma (allocated to the 20 Gy treatment group).
- Treatment with 20 Gy in ten fractions was unlikely to produce relapse rates that were more than 3% higher than that for standard 30 Gy radiation therapy.

Jones WG, Fossa SD, Mead GM et al (2005) Randomized trial of 30 versus 20 Gy in the adjuvant treatment of stage I testicular seminoma: a report on Medical Research Council Trial TE18, European Organisation for the Research and Treatment of Cancer Trial 30942. J Clin Oncol 23(6):1200–1208

MRC, PA vs. dog-leg field, 1999 → 478 men with testicular seminoma stage I (T1–T3; no ipsilateral inguinoscrotal operation before orchiectomy) were randomized to paraaortic (PA) vs. dog-leg RT fields. Median follow-up time was 4.5 years.

- Eighteen relapses, nine in each treatment group, had occurred 4–35 months after radiotherapy; among these, four were pelvic relapses, all occurring after PA radiotherapy.
- The 3-year relapse-free survivals were 96% after PA radiotherapy and 96.6% after DL.
- One patient (PA field) had died from seminoma.
- Survivals at 3 years were 99.3% for PA and 100% for DL radiotherapy.
- Acute toxicity (nausea, vomiting, leukopenia) was less frequent and less pronounced in patients in the PA arm.
- Within the first 18 months of follow-up, the sperm counts were significantly higher after PA than after DL irradiation.
- Patients with testicular seminoma stage I (T1–T3), undisturbed lymphatic drainage, and adjuvant radiotherapy confined to the PA LNs were associated with reduced hematologic, gastrointestinal, and gonadal toxicities, but they had a higher risk of pelvic recurrence compared with DL radiotherapy. The recurrence rate was low with either treatment. PA radiotherapy is recommended as the standard treatment in these patients.

Fossa SD et al (1999) Optimal planning target volume for stage I testicular seminoma: A Medical Research Council randomized trial. Medical Research Council Testicular Tumor Working Group. J Clin Oncol 17(4):1146

8.3 Bladder Cancer

Bladder cancer is the fourth most common cancer in men, following prostate, lung and colon cancers, and it is the eighth most common cancer in women. It constitutes 5–10% of all cancers in men [29]. The risk of developing bladder cancer up to 75 years of age is

2–5% in males and 0.5–1% in females. Risk factors are aniline dyes, cigarette smoking, pelvic radiotherapy, cyclophosphamide, phenacetin use and *Schistosoma haematobium* infections (in African and Middle Eastern countries). Aromatic amines and 2-naphthylamine, benzidine, and 4-aminobiphenyl (used in leather production) are also well-known carcinogenic agents for the bladder.

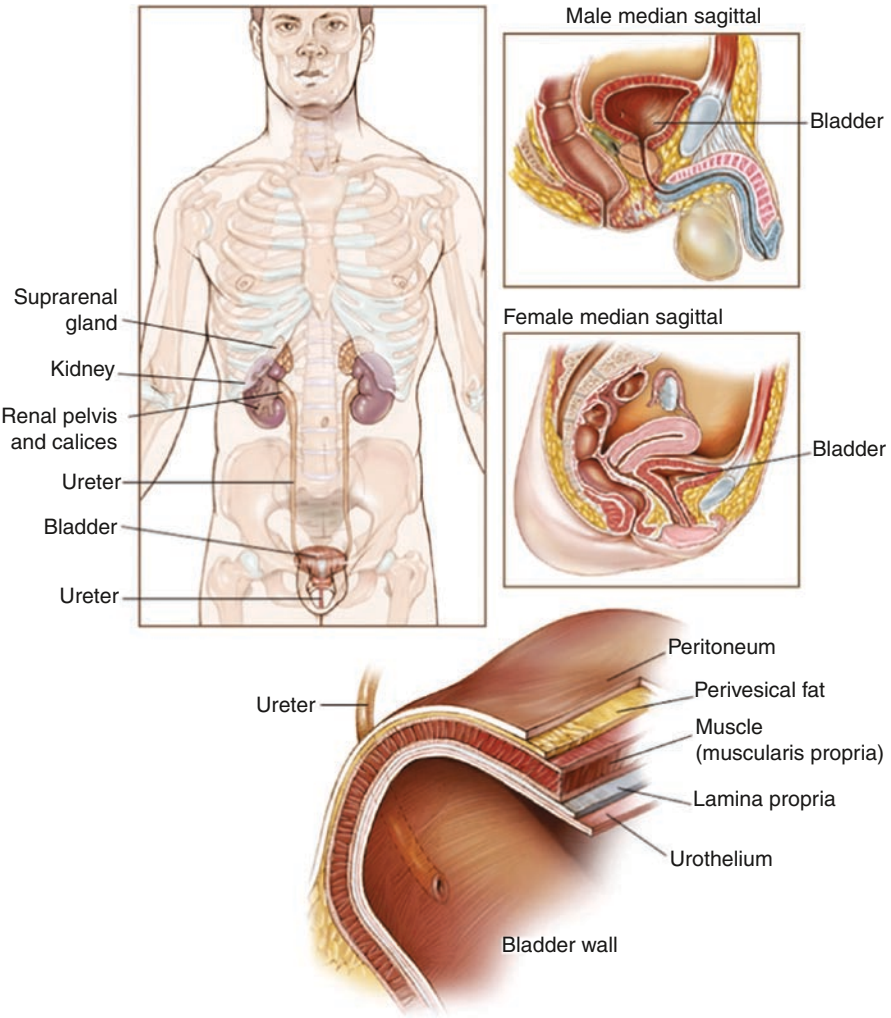

Fig. 8.18 Anatomy of the bladder

The bladder is a depot organ for urine collection with a capacity of 350–450 mL (Fig. 8.18). It is under the pubic symphysis when empty. It consists of the detrusor muscle (endodermal origin) and the trigone at its base (mesodermal origin).

- The bladder is positioned next to the seminal vesicles and the ampulla of the vas deferens posteriorly, as well as the lower tips of the ureters and the rectum
- It is next to the uterus and vagina in females
- The superior portion of the bladder is covered with peritoneum and is close to the small intestines by this peritoneum
- The base of the bladder is next to the prostate in males

The inner surface of the bladder mucosa is covered with transient cells (urothelium). A submucosal consisting of elastic and connective tissue lies beneath a mucosal layer called the lamina propria. A smooth muscle layer composed of longitudinal, circular and spiral leaves, as well as the serosa (adventitia), consisting of fibrous tissue, are found under the subserosa.

Medial umbilical ligament extending from the umbilicus to the top of the bladder is the remnant of the urachal canal, which has atrophied.

8.3.1 Pathology

Transitional cell carcinoma is responsible for 90% of all bladder cancers in developed countries. These type of cells can be papillary and superficial (70–75%) or solid and invasive (20–25%) [30].

- CIS (intraepithelial carcinoma) is another subtype seen in 10% of cases; this exhibits frequent mitoses.

Squamous cell cancers comprise 5–10% of all bladder cancers. They display a nodular and infiltrative pattern, and constitute 70% of all bladder tumors in regions where schistosomiasis is endemic, like Egypt.

- It can also be related to suprapubic catheterization, chronic infection and inflammation.

Adenocarcinoma is a rare form and comprises 2% of all bladder tumors [30]. Thirty to thirty-five percent of them originate from the urachal region, and the rest are related to bladder exstrophy and are of nonurachal origin.

Undifferentiated carcinomas have a high nucleus/cytoplasm ratio and generally form cell layers or clusters. They behave like small cell cancers and have a poor prognosis.

8.3.2 General Presentation

- Painless gross hematuria in 90% of cases.
- Polyuria, dysuria, pollakiuria are commonly seen.
- Pain under umbilicus in bladder region.
- Pain and leg edema in advanced stages.

8.3.3 Staging

Primary Tumor (T) (Fig. 8.19) [31]

TX: Primary tumor cannot be assessed
T0: No evidence of primary tumor
Ta: Noninvasive papillary carcinoma
Tis: Carcinoma in situ (i.e., flat tumor)
T1: Tumor invades subepithelial connective tissue
T2: Tumor invades muscle
pT2a: Tumor invades superficial muscle (inner half)
pT2b: Tumor invades deep muscle (outer half)
T3: Tumor invades perivesical tissue
pT3a: Microscopically
pT3b: Macroscopically (extravesical mass)
T4: Tumor invades any of the following: prostatic stroma, seminal vesicles, uterus, vagina, pelvic wall, or abdominal wall
T4a: Tumor invades the prostatic stroma, uterus, vagina
T4b: Tumor invades the pelvic wall, abdominal wall

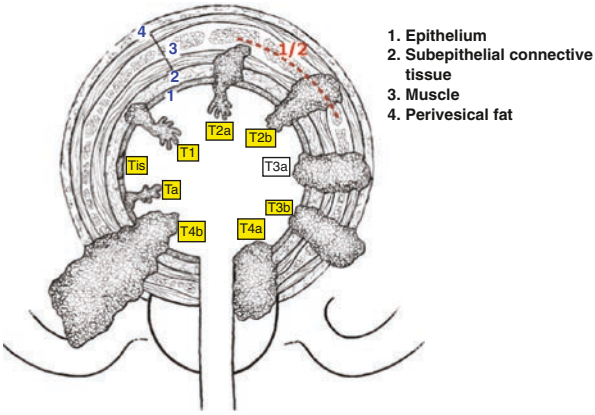

Fig. 8.19 T staging for bladder cancer (from [37], p 331, Fig. 38.3, reproduced with the permission from the American Joint Committee on Cancer)

Regional Lymph Nodes (N) (Fig. 8.20)

NX: Regional lymph nodes cannot be assessed
N0: No regional lymph node metastasis
N1: Single regional lymph node metastasis in the true pelvis (hypogastric, obturator, external iliac, or presacral lymph node)
N2: Multiple regional lymph node metastasis in the true pelvis
N3: Lymph node metastasis to the common iliac lymph nodes

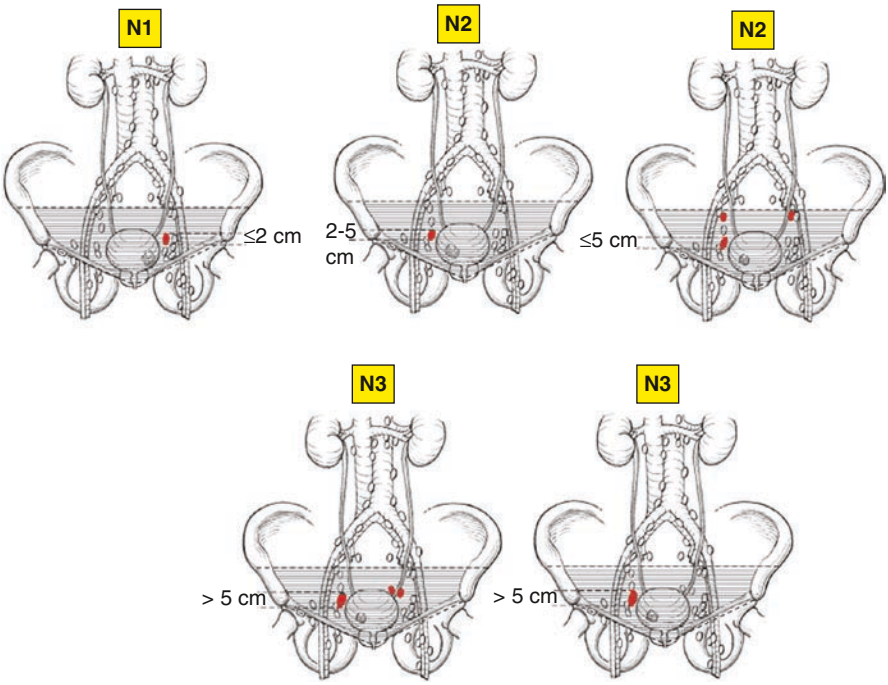

Fig. 8.20 N staging in bladder cancer (from [37], p 332–334, Figs. 38.4–38.6, reproduced with the permission from the American Joint Committee on Cancer)

AJCC Stage Groups

Stage 0a: TaN0M0
Stage 0is: TisN0M0
Stage I: T1N0M0
Stage II: T2aN0M0; T2bN0M0
Stage III: T3aN0M0; T3bN0M0; T4aN0M0
Stage IV: T4bN0M0; Any TN1M0; Any T, N2M0; Any T, N3M0; Any T, Any NM1

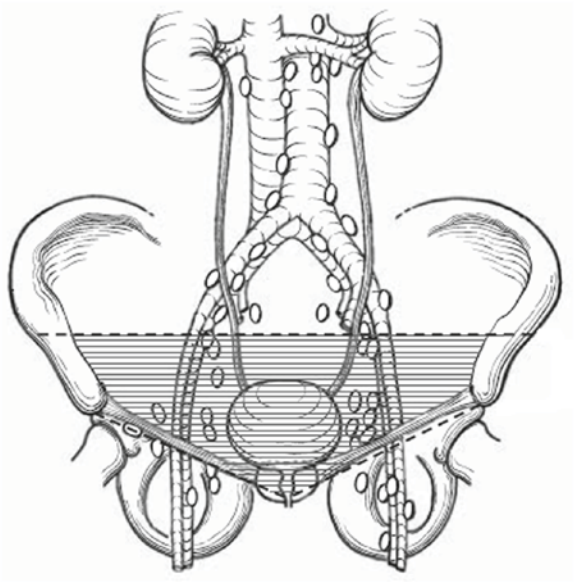

Fig. 8.21 Bladder lymphatics (from [37], p 330, Fig. 38.2, reproduced with the permission from the American Joint Committee on Cancer)

Bladder Lymphatics (Fig. 8.21) [31]

Iliac (external, internal), perivesical, pelvic, sacral [lateral, sacral promontorium (Gerota)].
Common iliac LNs are accepted as distant metastases (M1).

Bladder tumors are classified into three categories: superficial, invasive and metastatic.

1. Superficial bladder tumors: limited to the epithelium (urothelium) → Ta, Tis, T1 (Tis is high grade and known as a flat tumor)
2. Invasive bladder tumors: invade the detrusor muscle and perivesical tissues beyond the uroepithelium (T2–T4)
3. Metastatic bladder tumors:

- Seventy percent of all bladder tumors are superficial at diagnosis
- However, 15–30% of all superficial tumors transform into invasive tumors
- Superficial tumors are seen singly in 70% and as multiple lesions in 30%

There is a strong correlation between tumor grade and stage.

- Well-differentiated (grade I) and moderately differentiated tumors (grade II) are usually superficial, while undifferentiated (grade III) tumors are usually muscle invasive at diagnosis

Papilloma [31]. This is a grade 0 bladder tumor. It is a papillary lesion with normal bladder mucosa around a thin fibrovascular nucleus.

- This lesion is very rarely seen, and almost never presents a relapse after total excision. If it is seen alone, it can be considered a benign neoplasm as a rule of thumb.
- However, it should be kept in mind that papillomas may be seen with high-grade urothelial cancers.

8.3.4 Treatment Algorithm

No muscle invasion: Ta, Tis, T1 [32–34]
TUR alone (relapse risk 30%), or
TUR + 6-week intravesical BCG
Postoperative adjuvant treatment indications:

- Subtotal resection
- Residue (+) even after reoperations
- Urine cytology (+)
- Multifocality
- Grade II–III
- Tis, T1

(Following 6 months of BCG treatment, disease (+) → BCG every 6 months + mitomycin/doxorubicin every 3 weeks for 2 years)
Multiple recurrences or disease (+) following 1-year BCG → radical cystectomy/RT
(Radiation tolerance may be worsened due to recurrent intravesical treatments.)
Muscle invasive (+) [34]
Treatment options:

- Radical cystectomy
- Partial cystectomy
- Bladder conserving surgery + chemoradiotherapy

Tumors with no CIS in the dome of the bladder may be treated with partial cystectomy.
Bladder-conserving surgery indications → unifocal T2–3a, <5 cm, hydronephrosis (−), normal bladder functions, complete TUR

Multifocal T2–3a, T3b–4, hydroureter/hydronephrosis, subtotal resection → radical cystectomy

T3b–4 tumors: neoadjuvant chemotherapy + cystectomy + LN dissection + adjuvant chemotherapy
Local relapse

Local relapse after cystectomy → cisplatin + RT (45 Gy pelvis, 60–64 Gy to relapse site)

Relapse after chemoradiotherapy → cystectomy

8.3.5 Radiotherapy

Planning is performed in either the supine or prone position with an empty bladder. IV contrast is given to visualize the bladder. An isocentric four-field box method is usually preferred in conventional simulation.

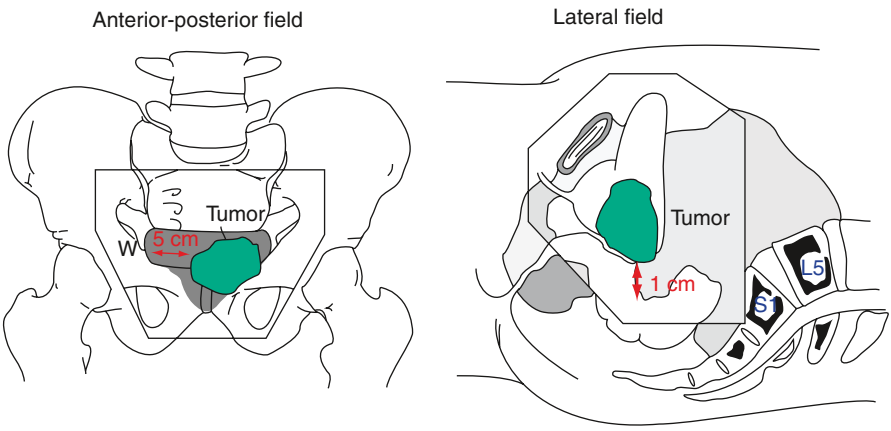

Fig. 8.22 Anterior–posterior and lateral RT fields in bladder cancer (from [35], p 571, Fig. 23.4a, b, reproduced with the permission from Springer Science and Business Media)

Pelvic RT Fields in Bladder Cancer (Fig. 8.22)

Anterior–posterior field

- Superior: between S1 and S2 (midsacrum)
- Inferior: below the obturator foramen (if bladder neck and/or prostatic urethra: 1.5 cm below obturator foramen)
- Lateral: bony pelvis + 1.5–2 cm

Lateral fields

- Superior and inferior: same as anterior–posterior fields
- Anterior: anterior to pubic symphysis + 1 cm
- Posterior: at least 1–3 cm posterior to tumor

Anterior–posterior field: femur heads are shielded; *lateral fields*: two-thirds of posterior rectum and small intestines are shielded.

Boost field:

Bladder + 1.5–2 cm margin

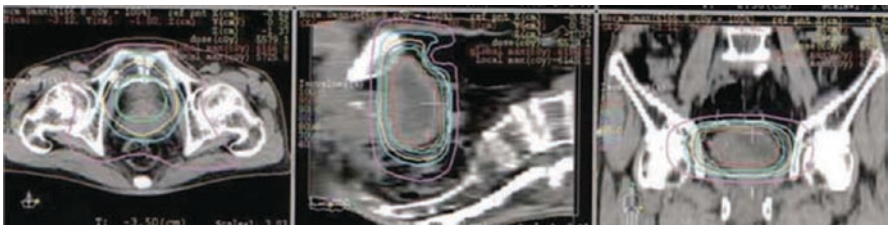

Fig. 8.23 Conformal RT fields in bladder cancer

Conformal RT Volumes (Fig. 8.23) [35]

CTV1: GTV + 0.5 cm
CTV2: pelvic ± common iliac LNs
PTV: CTV + 2 cm

8.3.6 Selected Publications

Danish National Bladder Cancer Group, DAVECA protocol 8201, 1991 → 183 patients with T2–T4a entered a randomized study. Preoperative irradiation (40 Gy) followed by cystectomy vs. radical irradiation (60 Gy) followed by salvage cystectomy in cases of residual tumor.

- A trend for a higher survival rate following combined treatment with preoperative irradiation and cystectomy compared to radical irradiation followed by salvage cystectomy was observed
- There was no difference in surgical complications between planned and salvage cystectomy, and there were no postoperative deaths among the cystectomized patients.
- All male patients experienced erective impotence after cystectomy.
- T-stage, response to radiotherapy and frequency of LN metastases were found to be of prognostic importance.

Sell A et al (1991) Treatment of advanced bladder cancer category T2 T3 and T4a. A randomized multicenter study of preoperative irradiation and cystectomy versus radical irradiation and early salvage cystectomy for residual tumor. DAVECA protocol 8201. Danish Vesical Cancer Group. Scand J Urol Nephrol Suppl 138:193–201

RTOG 85-12, 1993 (1986–1988) → T2–4, N0-2 or NX, M0 were treated with pelvic radiotherapy 40 Gy in 4 weeks and cisplatin 100 mg/m^2 on days 1 and 22. Complete responders were given an additional 24 Gy bladder boost plus a third dose of cisplatin; patients with residual tumor after 40 Gy were assigned radical cystectomy.

- The complete remission rate following cisplatin and 40 Gy for evaluable cases was 31/47 (66%).
- Acute toxicity was acceptable, with only two patients not completing induction therapy
- Patients with poorly differentiated tumors were more likely to achieve complete remission.
- Actuarial survival was 64% at 3 years.
- The chemoradiotherapy regimen was moderately well tolerated and associated with tumor clearance in 66% of the patients treated.

Tester W et al (1993) Combined modality program with possible organ preservation for invasive bladder carcinoma: results of RTOG protocol 85-12. Int J Radiat Oncol Biol Phys 25(5):783–790

RTOG 88-02, 1996 (1988–1990) → 91 patients with T2M0–T4AM0 suitable for radical cystectomy received two courses of methotrexate, cisplatin, and vinblastine (MCV regimen) followed by radiotherapy with 39.6 Gy and concurrent cisplatin. Operable patients who achieved complete response were selected for bladder preservation and treated with consolidation cisplatin–radiotherapy.

- 68 patients (75%) exhibited complete response.
- 14 patients with residual tumors underwent immediate cystectomy.
- 37 of 91 patients (40%) required cystectomy.
- Four-year cumulative risk of invasive local failure was 43%.
- Four-year actuarial risk of distant metastasis was 22%.
- Four-year actuarial survival rate of the entire group was 62%.
- Four-year actuarial rate of survival with bladder intact was 44%.
- Bladder preservation can be achieved in the majority of patients, and the overall survival was similar to that reported with aggressive surgical approaches.

Tester W et al (1996) Neoadjuvant combined modality program with selective organ preservation for invasive bladder cancer: results of Radiation Therapy Oncology Group phase II trial 8802. J Clin Oncol 14(1):119–126

NCI-Kanada, 1996 → 99 eligible patients with T2–T4b. Patients and their physicians selected either definitive radiotherapy or precystectomy radiotherapy; patients were then randomly allocated to receive IV cisplatin 100 mg/m^2 at 2-week intervals for three cycles concurrent with pelvic radiation, or to receive radiation without chemotherapy. Median follow-up was 6.5 years.

- Distant metastases were the same in both study arms.
- 25 of 48 control patients had a first recurrence in the pelvis, compared with 15 of 51 cisplatin-treated patients ($p = 0.036$).
- The pelvic relapse rates of the two groups were significantly reduced by concurrent cisplatin ($p = 0.038$).

- Concurrent cisplatin was found to improve pelvic control of locally advanced bladder cancer with preoperative or definitive radiation, but was not shown to improve overall survival.
- The use of concurrent cisplatin had no detectable effect on distant metastases.

Coppin CM et al (1996) Improved local control of invasive bladder cancer by concurrent cisplatin and preoperative or definitive radiation. The National Cancer Institute of Canada Clinical Trials Group. J Clin Oncol 14(11):2901–2907

RTOG 89-03, 1998 (1990–1993) → 123 patients with T2–T4aNXM0. Randomized to two cycles of MCV before 39.6 Gy pelvic irradiation with concurrent cisplatin 100 mg/m^2 for two courses 3 weeks apart vs. chemoradiotherapy. The CR patients were treated with a boost dose of 25.2 Gy to a total of 64.8 Gy and one additional dose of cisplatin. Patients with residual disease underwent cystectomy. Median follow-up: 60 months.

- Five-year overall survival rate was 49; 48% in arm 1 and 49% in arm 2.
- Distant metastases at 5 years; 33% in arm 1 and 39% in arm 2.
- Five-year survival rate with a functioning bladder was 38, 36% in arm 1 and 40% in arm 2.
- Two cycles of MCV neoadjuvant chemotherapy had no impact on 5-year overall survival.

Shipley WU et al (1998) Phase III trial of neoadjuvant chemotherapy in patients with invasive bladder cancer treated with selective bladder preservation by combined radiation therapy and chemotherapy: initial results of Radiation Therapy Oncology Group 89-03. J Clin Oncol 16(11):3576–3583

SWOG, 2001 (1993–1998) → 60 patients with T2–T4 with nodal involvement, medically or surgically inoperable, or refused cystectomy. 75 mg/m^2 cisplatin on day 1 and 1 g/m^2 daily, 5-fluorouracil on days 1–4 and definitive radiotherapy. Chemotherapy was repeated every 28 days, twice during and twice after radiation.

- The overall response rate was 51%.
- Overall 5-year survival was 32%.
- Five-year survival of the 25 patients who refused surgery was 45%.
- This combined modality may provide another alternative to cystectomy for patients refusing cystectomy.

Hussain MH et al (2001) Combination cisplatin, 5-fluorouracil and radiation therapy for locally advanced unresectable or medically unfit bladder cancer cases: a Southwest Oncology Group Study. J Urol 165(1):56–60

RTOG 95-06, 2000, (1995–1997) → 34 patients with clinical stage T2–T4a, Nx M0 without hydronephrosis. After performing as complete a transurethral resection as possible, induction chemoradiotherapy (cisplatin and 5-fluorouracil, radiation was given twice a day, 3 Gy per fraction to the pelvis for a total of 24 Gy) was administered. Patients with

a complete response received the same drugs combined with twice-daily radiation therapy to the bladder and a bladder tumor volume of 2.5 Gy per fraction for a total consolidation dose of 20 Gy. Median follow-up was 29 months.

- After induction treatment, 22 (67%) of the 33 patients had no tumor detectable on urine cytology or rebiopsy.
- Of the 11 patients who still had detectable tumors, six underwent radical cystectomy.
- No patient required a cystectomy for radiation toxicity.
- Three-year overall survival was 83%.
- Three-year survival with intact bladder was 66%.
- Both the complete response rate to induction therapy and the 3-year survival with an intact bladder were encouraging.

Kaufman DS et al (2000) The initial results in muscle-invading bladder cancer of RTOG 95-06: phase I/II trial of transurethral surgery plus radiation therapy with concurrent cisplatin and 5-fluorouracil followed by selective bladder preservation or cystectomy depending on the initial response. Oncologist 5(6):471–476

RTOG 97-06, 2003, (1998–2000) → 47 eligible patients with stage T2–T4aN0M0. Median follow-up was 26 months. TURBT within 6 weeks of the initiation of induction therapy [13 days of concomitant boost RT, 1.8 Gy to the pelvis in the morning followed by 1.6 Gy to the tumor 4–6 h later and cisplatin (20 mg/m^2)]. Three to four weeks after induction, the patients were evaluated for residual disease.

- CR rate was 74%.
- Three-year rates of locoregional failure, distant metastasis, overall survival, and bladder-intact survival were 27, 29, 61, and 48%, respectively.
- Adjuvant MCV chemotherapy appears to be poorly tolerated.

Hagan MP et al (2003) RTOG 97-06: Initial report of a phase I–II trial of selective bladder conservation using TURBT, twice-daily accelerated irradiation sensitized with cisplatin, and adjuvant MCV combination chemotherapy. Int J Radiat Oncol Biol Phys 57(3):665–672

RTOG 99-06,2006 → 80 patients with T2–T4a; twice-daily radiotherapy with paclitaxel and cisplatin chemotherapy induction (TCI) was administered. Adjuvant gemcitabine and cisplatin were given to all patients.

- TCI resulted in 26% developing grade 3–4 acute toxicity, mainly gastrointestinal (25%).
- The postinduction complete response rate was 81% (65/80).
- Thirty-six patients died (22 of bladder cancer).
- Five-year overall and disease-specific survival rates were 56 and 71%, respectively.

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Gynecological Cancers

9

Murat Beyzadeoglu, Cuneyt Ebruli, and Gokhan Ozyigit

9.1 Cervical Cancer

Cervical cancer constitutes 6% of all female cancers in the USA. It is responsible for 1.6% of all cancer-related mortality and 15% of all gynecologic cancer mortalities in women [1, 2]. It is the most common gynecological cancer in developing and underdeveloped countries.

The uterus is located in the middle of the true pelvis between the rectum and bladder, and makes a right angle with the vagina. The upper two-thirds of the uterus is called the corpus, and the lower one-third is known as the cervix.

The cervix has a cylindrical shape and extends into the upper vagina (Fig. 9.1). It passes between the vagina and the upper uterine cavity via the endocervical canal.

- The endocervical canal is covered with glandular and columnar cells, and the region around the cervical canal is called the endocervix.
- The region facing towards the vagina is termed the exocervix and is covered with squamous epithelial cells.
- Cervical cancers originating from the endocervix are adeno cancers, while those from the exocervix are squamous cell cancers.

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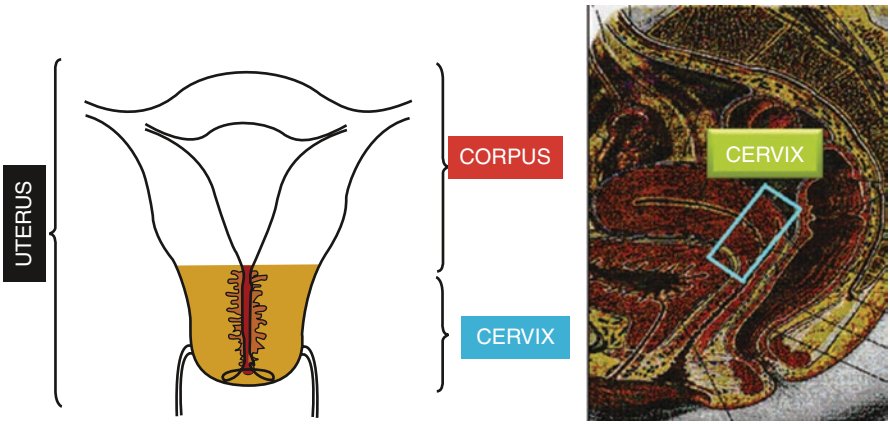

Fig. 9.1 Anatomy of the cervix

9.1.1 Pathology

Cervical cancers are categorized into three major histological subtypes by the World Health Organization (WHO): squamous cell cancers, adenocarcinomas, and others. Approximately 70–80% of all cases are squamous cell cancers [2].

The WHO Cervical Cancer Classification [2, 3]

Squamous cancers → microinvasive squmaous carcinoma, invasive squmaous carcinoma, verrucous carcinoma, condylomatous carcinoma
Adenocarcinoma → mucinous adenocarcinoma, endometrioid-type adenocarcinoma, clear cell carcinoma, serous adenocarcinoma, minimal deviation adenocarcinoma, villoglandular adenocarcinoma, mesonephric carcinoma
Other cancers → adenosquamous cancer, clear cell cancer, small cell cancer, adenoid cystic cancer, mucoepidermoid cancer, adenoid basal cancer, carcinoid cancer, undifferentiated cancer

Squamous cell cancer almost always starts with abnormal metaplastic events in the transformation zone, resulting in sequential lesions from cervical intraepithelial neoplasias (CIN) of grades I, II and III, and microinvasive cancer.

9.1.2 General Presentation

Early period:
(a) Postcoital bleeding
(b) Irregular menstruation
(c) Bloody discharge
(d) Discharge with foul odor

Late period:
(a) Leg and groin pain
(b) Fistulas (cervicovesical, vesicovaginal, cervicorectal, rectovaginal)
(c) Hydronephrosis and renal dysfunction due to ureter obstruction
(d) Edema in lower extremities
(e) Anemia

9.1.3 Staging

The first important step is a bimanual rectovaginal gynecological exam under general anesthesia. The International Federation of Gynecology and Obstetrics (FIGO) revised cervical staging system in 2008 [4]. This staging is performed by the use of clinical exam (inspection, palpation, colposcopy), endoscopic exam (cystoscopy and rectoscopy), direct radiological exams (intravenous pyelography, chest X-ray), and findings from biopsy (tumor depth, size, etc.) [5]. Surgical findings should never be used in staging. The AJCC staging is consistent with FIGO staging.

FIGO Staging (Fig. 9.2) [4]

Stage I. Carcinoma strictly confined to the cervix; extension to the uterine corpus should be disregarded.

IA: Invasive cancer identified only microscopically. All gross lesions, even with superficial invasion, are stage IB cancers. Invasion is limited to measured stromal invasion with a maximum depth of 5 mm* and no wider than 7 mm [*Note: *The depth of invasion should be 5 mm or less taken from the base of the epithelium, either surface or glandular, from which it originates. Vascular space involvement, either venous or lymphatic, should not alter the staging.*].

IA1: Measured invasion of the stroma 3 mm or less in depth and 7 mm or less in diameter.

IA2: Measured invasion of stroma more than 3 mm but 5 mm or less in depth and 7 mm or less in diameter.

IB: Clinical lesions confined to the cervix or preclinical lesions greater than stage IA.

IB1: Clinical visible lesions 4 cm or less in size.

IB2: Clinical visible lesions 4 cm or more in size.

(*continued*)

(continued)

Stage II. Carcinoma that extends beyond the cervix but has not extended onto the pelvic wall. The carcinoma involves the vagina but not extended as far as the lower third section.

IIA: No obvious parametrial involvement. Involvement of as much as the upper two thirds of the vagina (IIA1 less than or equal to 4cm; IIA2 >4cm).

IIB: Obvious parametrial involvement but not onto the pelvic sidewall.

Stage III. Carcinoma that has extended onto the pelvic sidewall and/or involves the lower third of the vagina. On rectal examination, there is no cancer-free space between the tumor and the pelvic sidewall. All cases with a hydronephrosis or nonfunctioning kidney should be included, unless they are known to be due to other causes.

IIIA: No extension onto the pelvic sidewall but involvement of the lower third of the vagina

IIIB: Extension onto the pelvic sidewall or hydronephrosis or nonfunctioning kidney, or regional lymph node metastasis.

Stage IV. Carcinoma that has extended beyond the true pelvis or has clinically involved the mucosa of the bladder and/or rectum.

IVA: Spread of the tumor onto adjacent pelvic organs.

IVB: Spread to distant organs (Including peritoneal spread, involvement of supraclavicular or mediastinal lymph nodes, paraaortic lymph nodes, lung, liver or bone).

Note: FIGO no longer includes Stage0 (Tis)

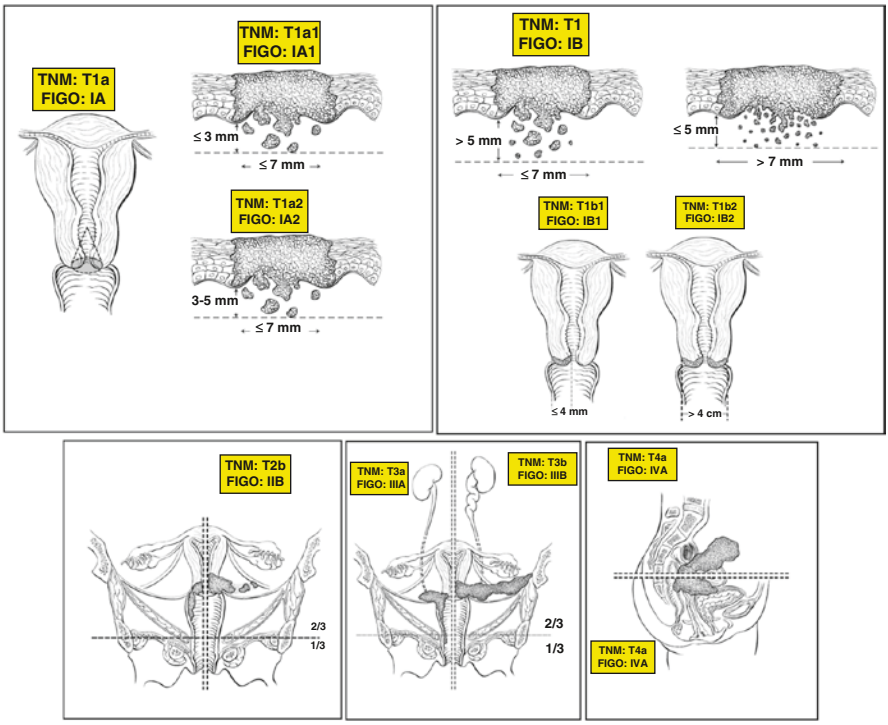

Fig. 9.2 Staging of cervical cancer (from [29], p 251–256, Figs. 28.3–28.10, reproduced with the permission from the American Joint Committee on Cancer)

Lymphatics of Cervix Cancer (Fig. 9.3)

Paracervical
Parametrial
Hypogastric (internal iliac), including obturator
External iliac
Common iliac
Presacral

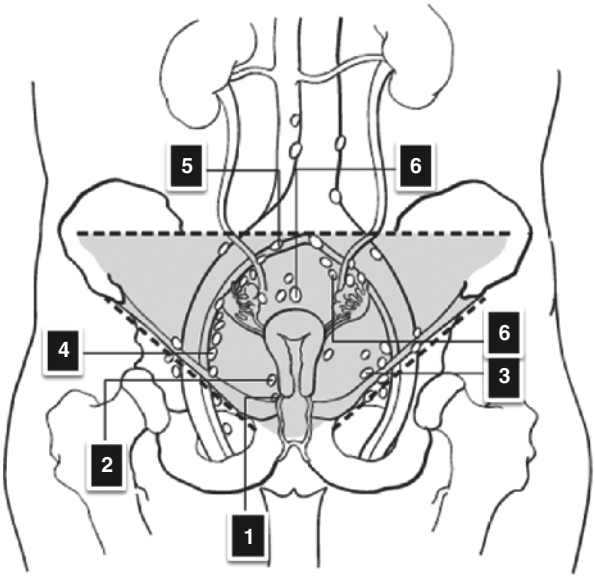

Fig. 9.3 Lymphatics of cervical cancer (from [29], p 250, Figs. 28.2 and 28.3, reproduced with the permission from the American Joint Committee on Cancer)

9.1.4 Treatment Algorithm

The local treatment decision should be made based on tumor size, stage, histology, lymph node (LN) involvement, possible complications of local therapies, requirement for adjuvant therapy and patient choice. However, intraepithelial lesions are treated with superficial ablative modalities (cryosurgery or laser surgery); microinvasive cancers that are less than 3 mm in depth (stage IA1) with conservative surgery; early invasive cancers (stages IA2, IB1 and some small stage IIA tumors) with either radical surgery or radiotherapy; and locally advanced cancers (stages IB2–IVA) with concurrent chemoradiotherapy [6–9].

- *Radical hysterectomy (Type III) and bilateral pelvic LN dissection.* This is the standard surgical approach for stages IB1 and IIA [10]. Here, the uterus, surrounding tissues, and the upper 2–3 cm of the vagina are excised. The cardinal, sacrouterine and vesicouterine ligaments are completely dissected together with the uterus. Pelvic lymphadenectomy is part of radical hysterectomy.
- *Vaginal hysterectomy (Schauta–Amreich operation) and radical trachelectomy* are alternative surgical approaches to spare fertility in patients with a tumor that is less than 2 cm and at stage IB1 [11]. In radical trachelectomy, the uterus is not dissected, and 2–3 cm of the upper vagina together with the cervix and the cardinal–sacrouterine ligaments are excised.

Radiotherapy and surgery are equally effective in patients with stage IB cervical cancer, and survival is nearly 80–90% whether radiotherapy or surgery is used (Table 9.1) [6–9].

Table 9.1 Five-year survival in FIGO stage IB cervical cancer according to surgery or radiotherapy

References	Radiotherapy		Radical hysterectomy	
	n	5-year survival (%)	*n*	5-year survival (%)
Volterrani et al. (1983)	127	91	123	89
Inoue et al. (1984)	59	80	362	91
Lee et al. (1989)	–	–	237	86
Alvarez et al. (1991)	–	–	401	85
Burghardt et al. (1992)	–	–	443	83
Coia et al. (1990)	168	74	–	–
Lowrey et al. (1992)	130	81	–	–
Perez et al. (1992)	394	85	–	–
Eifel et al. (1994)	1494	81	–	–
Landoni et al. (1997)	167	74	170	74

N patient number

Treatment Algorithm for Cervix Cancer [6–9]

Preinvasive

Conization, LEEP (loop electrosurgical excision procedure), laser, cryotherapy, simple hysterectomy.

Stage IA

Total abdominal hysterectomy or cone biopsy.

Alternative → brachytherapy (BT) alone

(LDR → 65–75 Gy)
(HDR → 5–6 × 7 Gy)

Stage IB1
Radical hysterectomy + pelvic LN dissection, or
RT + BT (RT → 45 Gy, whole pelvis) (BT → HDR: 5 × 6 Gy, LDR: 2 × 15–20 Gy)

Stages IB2 and IIA
Concurrent chemoradiotherapy (cisplatin-based)
[RT + BT]
(RT → 45 Gy, whole pelvis)
(BT → HDR: 5 × 6 Gy, LDR: 2 × 15–20 Gy)

Stage IIB
Concurrent chemoradiotherapy (cisplatin-based)
[RT + BT]
(RT → 45–50.4 Gy, whole pelvis)
(BT → HDR: 5 × 6 Gy, LDR: 2 × 15–20 Gy)

Stage IIIA
Concurrent chemoradiotherapy (cisplatin-based)
[RT + BT]
(RT → 45–50.4 Gy, whole pelvis)
(BT → HDR: 5 × 6 Gy, LDR: 2 × 17–20 Gy)

Stages IIIB and IVA
Concurrent chemoradiotherapy (cisplatin-based)
[RT + BT]
(RT → 50–54 Gy, whole pelvis ± paraaortic LN)
(BT → HDR: 5 × 6 Gy, LDR: 2 × 20 Gy)

Stage IVB
Chemotherapy

Postoperative radiotherapy indications [12]:

- Lymphovascular space invasion (LVSI)
- Deep stromal invasion > one-third of stromal depth
- Tumor size > 4 cm
- Adenosquamous, clear cell, small cell, undifferentiated histology

Postoperative chemoradiotherapy indications [12]:

- Surgical margin (+)
- LN (+)
- Parametrial involvement

Prognostic Factors [12]

- Tumor volume (stage)
  Directly related to pelvic and paraaortic
  LN involvement
- Invasion depth
  Related to parametrial extension
- Histology
  RT response is better in squmaous histology
  Adenocarcinomas are more fatal (controversial issue).
- LN involvement/size
  As involvement (+) and/or LN size increases,
  survival decreases
- Lymphovascular space invasion (LVSI)
  Poor prognostic signs, frequent metastases
- Uterine corpus extension, low hemoglobin level

9.1.5 Radiotherapy

9.1.5.1 External Radiotherapy

Anterior–posterior fields (Fig. 9.4)

- Superior: L4–L5 intervertebral space
- Inferior: below the obturator foramens (vagina (−)) or ischial tuberosities (vagina (+))
- Lateral: bony pelvis +1.5–2 cm

Lateral fields (Fig. 9.4)

- Superior and inferior: same as anterior–posterior fields.
- Anterior: posterior to pubis.
- Posterior: between the S2 and S3 vertebrae (midsacrum); maximum care should be given to posterior extension of tumor, and a margin of at least 1–2 cm should be given to the tumor.

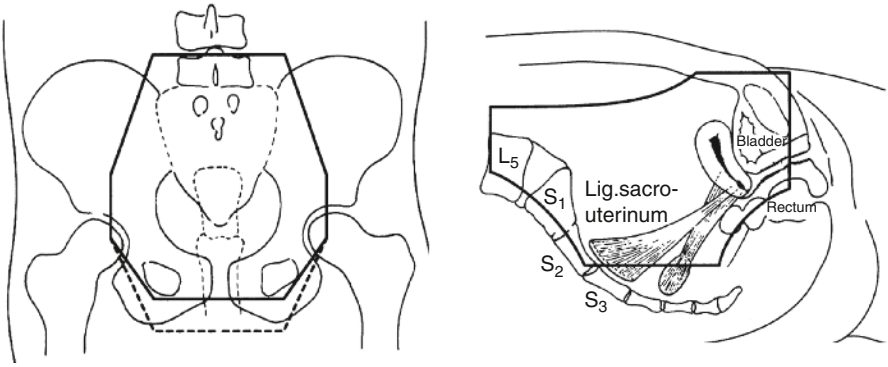

Fig. 9.4 Anterior–posterior and lateral fields in cervical cancer RT [30, p 678, Figs. 29.4–29.5]

Paraaortic LN (+); paraaortic field should be irradiated (Fig. 9.5).

- Prophylactic paraaortic field is not recommended since it has no effect on survival. It also decreases the tolerance of radiotherapy by increasing toxicity [13–16].

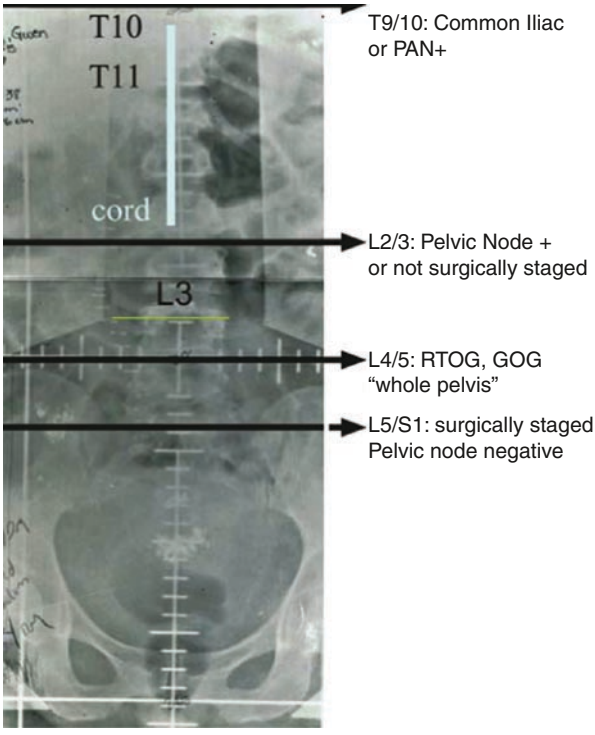

Fig. 9.5 Paraaortic field in cervical cancer RT (from [17], p 583, Fig. 24.1, reproduced with the permission from Springer Science and Business Media)

Pelvic Lymph Node Dissection [13–16]

- Dissected LN number > 20 and no pelvic LN(−), superior border of ant-post: between L5 and S1
- No surgical staging or dissected LN number <20 or pelvic LN(+), superior border of ant-post fields: between the L2 and L3 vertebrae

Lower vaginal involvement (+) → inferior border: includes inguinal LNs.

Energy

High-energy X-rays are used to spare superficial structures. Either the anterior–posterior or the four-field box technique is preferred, and 18 or 25 MV photons are used in the anterior–posterior two-field technique. These techniques can spare the posterior wall of the rectum, abdominal skin, subcutaneous tissues, and superficial small intestinal segments.

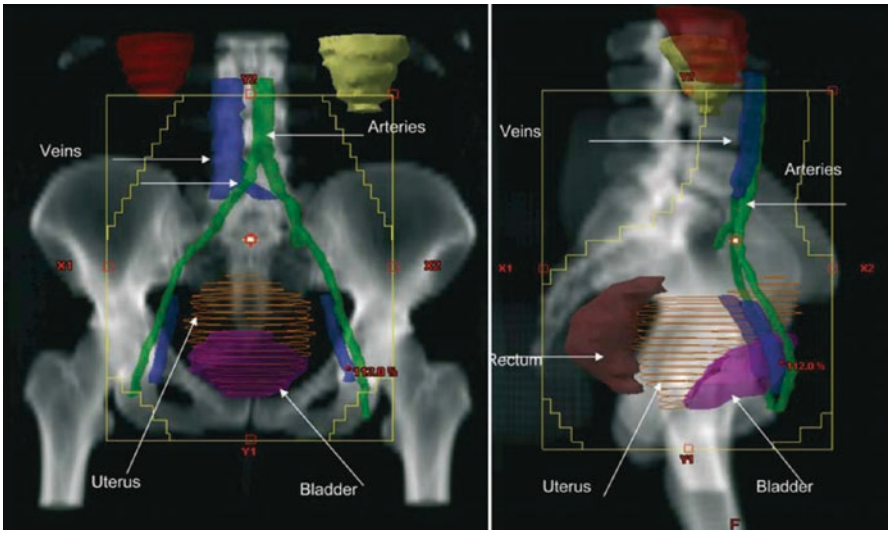

Fig. 9.6 Conformal RT volumes in cervical cancer [31, p 585, Fig. 24.3a, b]

Conformal RT Volumes (Fig. 9.6) [17]

CTV = tumor/tumor bed, entire uterus, upper one-third of vagina, parametrium, iliac LNs. Paraaortic/common iliac LN (+); paraaortic LN.
PTV = CTV + 0.5–1 cm.

9.1.5.2 Brachytherapy

BT plays a very important role in the treatment of gynecological cancers, particularly cervical cancers [18]. Intracavitary and interstitial BT techniques are used in cervical cancers.

Radioactive Sources Used in Brachytherapy

Sources used in BT usually emit gamma rays. Ra^{226} was commonly used until the 1960s in the form of tubes or needles. However, it was replaced with artificial radioactive sources due to protection problems. These new sources are also small and easily bendable for comfortable BT application. Several radioisotopes are currently used in BT (Table 9.2).

Table 9.2 Radionuclides used for brachytherapy applications

Radionuclide	Half-life	Radiation type(s)	Energy
Ra-226	1,600 years	α, β, γ	0.78 MeV
Co-60	5.27 years	β, γ	1.25 MeV
Sr-90	28.7 years	β, γ	0.546 β en
Cs-137	30 years	β, γ	0.662 MeV
Au-198	64.7 h	β, γ	0.42 MeV
Ir-192	73.8 days	γ	0.38 MeV
I-125	60.1 days	α, γ, n	0.028 MeV
Y-90	64 h	α, β, γ	2.27 β en
Am-241	432 years	γ	0.06 MeV
Pd-103	17 days	α, β, γ	0.021 MeV
Sm-145	340 days	γ	0.041 MeV
Yb-169	32 days	γ	0.093 MeV

Source Loading Types in Brachytherapy

Manual afterloading: radioactive sources are applied by long forceps from a certain distance behind a protective barrier. The patient treated with the radioactive sources should be isolated in hospital.
Remote afterloading: the radioactive source is stored within a shielded computer-controlled machine. The machine has a remote controller, and the radioactive source passes through special tubes and applicators placed inside the patient. Thus, such machines are called remote afterloading BT machines.

ICRU 38 [19]

Since techniques, applicators, sources, and dose reference points of intracavitary applications may vary for gynecologic malignancies between institutions, details should be given according to the ICRU-38 report (*Dose and Volume Specifications for Reporting Intracavitary Treatments in Gynecologic Malignancies*) published in 1985. This report standardizes application differences and provides a common language for gynecologic BT applications.

Every application of BT should report five major issues according to this publication: technique, total reference air KERMA (TRAK), reference volume, reference points and doses, and dose rate.

1. Technique

The radioactive source, number and length of sources, and the type of applicator should be mentioned. Applicators are special devices that are placed into the organs to be treated, and the radioactive sources enter these applicators and exit out of them. These come in various shapes and types: metallic (Fletcher–Suit–Delclos); plastic (Delouche); individualized (Chassagne–Pierquin) (Fig. 9.7).

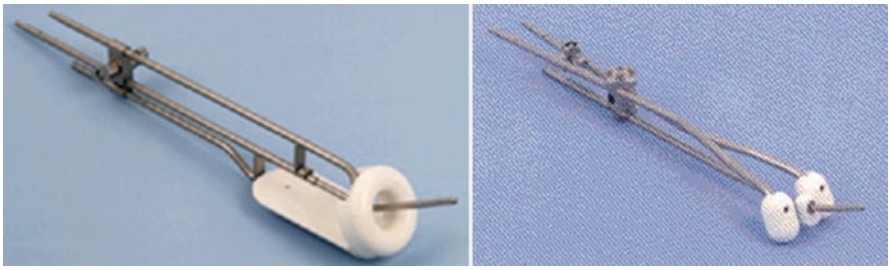

Fig. 9.7 Ring–tandem and ovoid–tandem applicators

2. Reference air KERMA of source

KERMA (kinetic energy released in the medium): this is the combination of the initial kinetic energies of the charged ionizing particles that are liberated by an uncharged ionizing particle per unit mass of material. KERMA is measured in the same units as absorbed dose (Gy). The reference air KERMA is used to define visible activity. It is defined as the dose given at a distance of 1 m of air by a source with an activity of 1 MBq in 1 h. Its units are 1 μ/Gy m^2 = 1 cGy/h cm^2. Its value is 0.0342 for Ir-192.

3. Reference volume (Fig. 9.8)

This is the volume surrounded by the reference isodose, and is independent of technique. It is the combined volume in the 60 Gy isodose curve of external pelvic radiotherapy and intracavitary applications. The reference volume is defined in three planes by combining reference isodoses:

- dh: (height) maximum size parallel to the intrauterine applicator in the oblique frontal plane, including the intrauterine applicator
- dw: (width) maximum size vertical to the intrauterine applicator in the oblique frontal plane, including the intrauterine applicator
- dt: (thickness) maximum size vertical to the intrauterine applicator in the oblique sagittal plane, including the intrauterine applicator

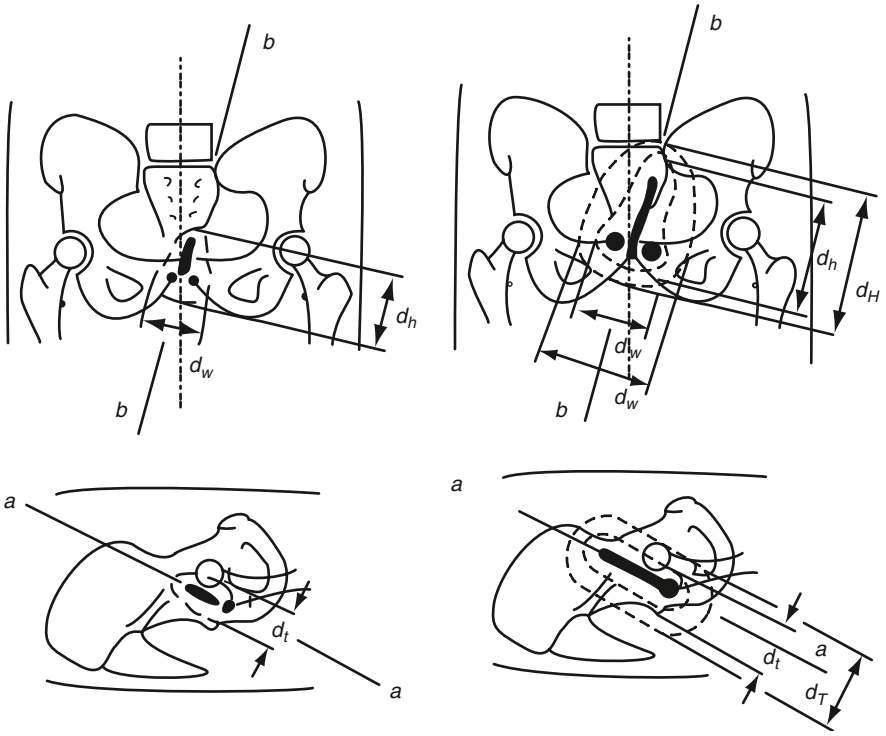

Fig. 9.8 Planes defining reference volumes

4. Reference points (Fig. 9.9)

Bladder reference point. A Foley catheter is placed into the bladder. The Foley balloon is filled with 7 cm^3 of radioopaque material. The catheter is pulled back and stabilized in the bladder neck. A straight line is marked in the anterior–posterior plane from the center of the balloon in a lateral graph. The reference point is the posterior point crossing the back of the balloon on this line. This is the center of the balloon in the anterior–posterior film.

Rectum reference point. An anterior–posterior straight line is marked from the bottom tip of the intrauterine tandem or the middle of the intravaginal ovoids. The point 5 mm back from the vaginal posterior wall is the rectum reference point.

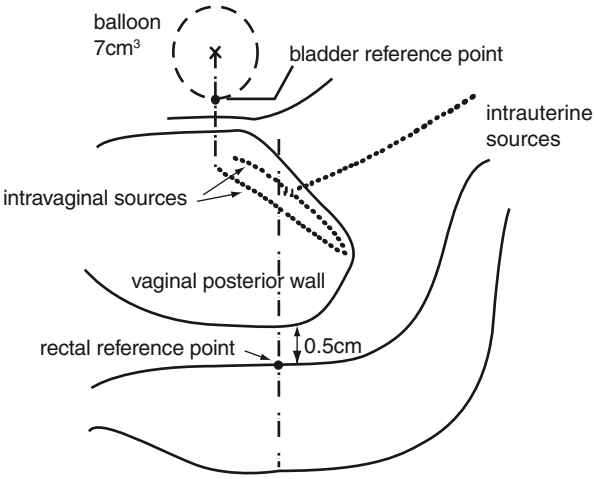

Fig. 9.9 Bladder and rectal reference points according to the ICRU-38 report

Bony reference points; lymphatic trapezoid (Fletcher trapezoid) (Fig. 9.10). A line is marked 2 cm bilaterally from the middle of the L4 vertebra → points 1 and 2 are found. A line vertical from the middle of the S1 to S2 vertebrae to the top of the pubis symphysis is drawn, and two lines bilaterally from the middle of that line are drawn with a length of 6 cm → points 3 and 4 are found. Point 1 is combined with 3, and point 2 with 4. A trapezoid is formed by the combination of these lines; upper points→ lower paraaortic lymphatics; lower points → external iliac lymphatics; middle points → common iliac lymphatics.

Pelvic wall reference points. These are used to calculate the doses for the distal parametrium and obturator lymphatics (Fig. 9.11). Two tangential lines are drawn from the upper

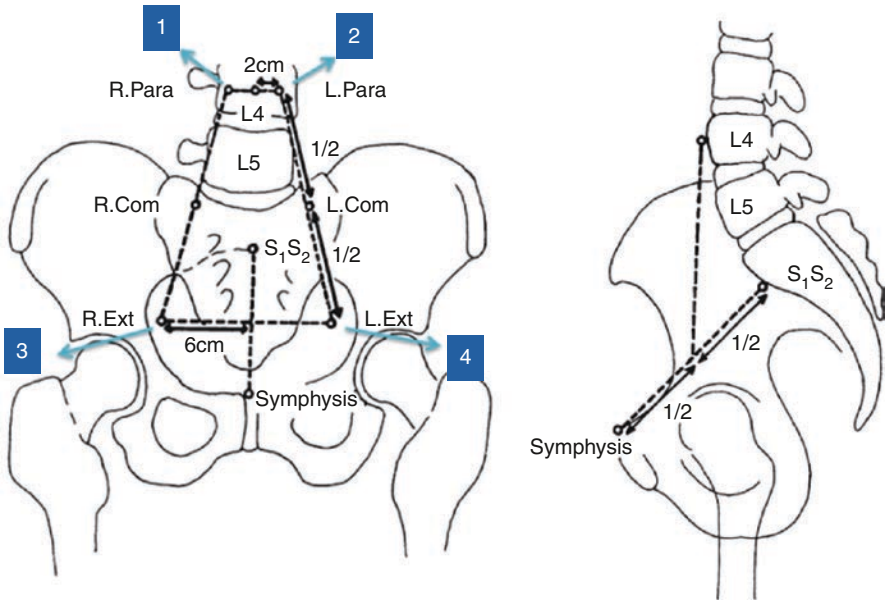

Fig. 9.10 Fletcher trapezoid and bony reference points

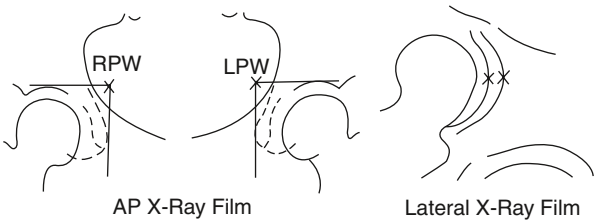

Fig. 9.11 Pelvic wall reference points

and the most medial parts of the acetabulum vertical to each other, and the points where they cross are the pelvic wall reference points (Chassagne point) in the anterior–posterior film. The most upper points of right and left acetabulum are marked, and the lateral projection of the pelvic wall occurs midway between these two points.

5. Dose rate

This is the dose given per unit time. BT applications are categorized into three subgroups according to dose rate (Table 9.3): low dose rate (LDR), 0.4–2 Gy/h; medium dose rate (MDR), 2–12 Gy/h; high dose rate (HDR), >12 Gy/h.

Table 9.3 The advantages and disadvantages of HDR brachytherapy

Advantages	Disadvantages
Better protection from radiation	Potential risks due to its radiobiological features
No requirement for hospitalization	Less experience compared to LDR
Short treatment time	Cost-effectiveness
Patient comfort	Expensive equipment
Low thromboembolism risk	Requires a special room
Less applicator movement	No possibility of correcting position during treatment
Dose optimization	Serious risk in case of machine failure

Dose Prescription Points (Fig. 9.12)

Dose prescription points are used for dose definitions. The most commonly used ones are points A and B.

Point A. This point is defined in the Manchester system as the point 2 cm superior to a horizontal line passing from the top of the lateral fornices at the midline, and 2 cm lateral from the midline. It is the point where radiation necrosis is first seen, and uterine artery crosses ureter. Point A relates to the maximum dose for healthy tissues and the minimum dose for the tumor.

Point B. This point is 3 cm lateral to point A (2 cm superior to the lateral fornices, and from that point 5 cm lateral from the midline), and it shows the dose taken by the obturator LNs.

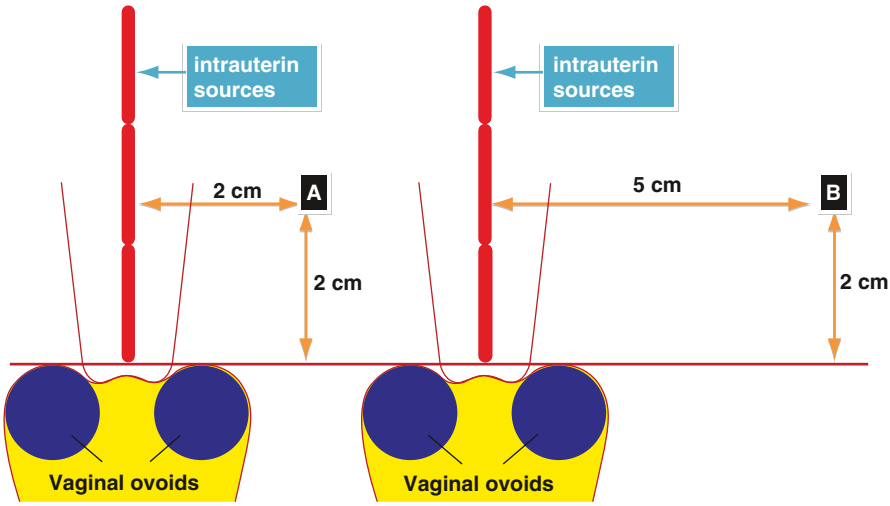

Fig. 9.12 Points A and B

9.1.5.2.1 The Application of Intracavitary Brachytherapy

The patient should be informed about the procedure before BT, and informed consent must be obtained. A detailed gynecological exam should be performed, and the dimensions of the vagina, the size and position of the uterus, and the localization, size and extension of the tumor determined. The application of BT requires cervical dilatation, and thus general anesthesia, spinal anesthesia, paracervical blockage or systemic analgesia with sedation is needed. Treatment is performed on an outpatient basis; the patient should have an open IV line and an empty rectum under sterile surgical conditions.

The patient is positioned in the lithotomy position on a gynecological table. The vulva, perineum, and pelvic region are cleaned and a Foley catheter is placed into the bladder. Its balloon is filled with 7 cc of radioopaque material. A speculum is placed into the vagina, and the cervical os is visualized. The cervical canal is dilated sequentially with bougies of different thicknesses. Two metal markers are placed into the cervical os to verify the position of the intrauterine tandem. The length of the uterine cavity is determined by hysterometry, and the tandem and ovoids are lubricated with 1% viscous lidocaine. The tandem is first placed into the uterine cavity, and then the ovoids or ring are placed into the fornices and they are all stabilized. The angle between the longitidunal axis of the tandem and the diameter of the ring is always 90°. Then, rectal packing with a radioopaque gauze is placed between the rectal wall and the applicators, and the same packing is placed between the bladder and the applicators. A rectal tube is inserted into the rectum to measure the rectal dose in vivo. Dummy catheters are placed into the tandem and ring/or ovoids for dose calculations in orthogonal films. An anterior–posterior and a lateral film are taken at the same position, which shows all of the applicators and the bony points of the Fletcher trapezoid. CT slices can also be used when CT-applicable applicators are used, and 3D BT software is available. The dose is prescribed to point A. The dose distribution should be

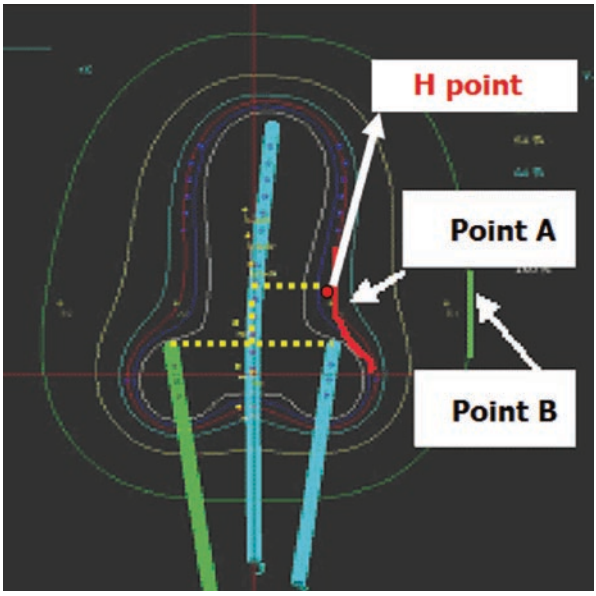

Fig. 9.13 Isodose distribution in cervical brachytherapy

pear-shaped when the tandem is used. Its large side is located in the upper vagina, and its narrow edge is in the uterine fundus (Fig. 9.13).

The source, place and time are optimized in dosimetry; the plan that enables the maximum dose to be delivered to the target and the minimum dose to the bladder and rectum is selected, and the patient is taken to the treatment room. Applicators are connected to the treatment machine with special connecting cables. Health personnel move from the treatment room to the command room and start the BT session. One session takes between 5 and 15 min, depending on the source activity in that session of HDR BT. After the treatment has finished, the applicators are taken out. The same procedure is repeated during each session.

Tolerance doses [18]. Rectum, 75 Gy (mean 68 Gy, <80% of the dose at point A); bladder 80 Gy (mean 70 Gy, 85% of the dose at point A); vagina 120–140 Gy (mean 125 Gy). The vaginal mucosa is a critical organ in cervical cancer RT, and 140% of the dose at point A should not be exceeded. Vaginal mucosa is the target organ in endometrial cancer RT, since recurrence is most common in the vaginal cuff.

Point H [20]. This is recommended as an alternative to point A by the American Brachytherapy Society. The tips of the ovoids are connected with a horizontal line, and 2 cm superior and 2 cm lateral from the midpoint of this line are the H points on the right and left sides. They are practically 2 cm cranial to the top of the ovoids. They are not anatomical points like point A, and they may vary in position according to patient and application.

Point P. This is the most lateral point in the bony pelvis, and it defines the dose taken by external iliac LNs.

9.1.6 Selected Publications

Canada, 2002 → a systematic review of eight randomized trials of cisplatin administered concurrently with external-beam radiotherapy vs. radiotherapy without cisplatin for cervical cancer.

- A statistically significant effect in favor of cisplatin-based chemotherapy plus radiotherapy compared with radiotherapy without cisplatin (relative risk [RR] of death, 0.74).
- The pooled RR of death among the six trials that enrolled only women with locally advanced cervical cancer was 0.78. The pooled RR for the two trials in high-risk early-stage disease also demonstrated a statistically significant benefit of the addition of cisplatin-based chemotherapy to radiotherapy (RR = 0.56).
- Concurrent cisplatin-based chemotherapy plus radiotherapy improves overall survival over various controls in women with locally advanced cervical cancer, large stage IB tumors (prior to surgery), and high-risk early-stage disease (following surgery).

Lukka H et al (2002) Concurrent cisplatin-based chemotherapy plus radiotherapy for cervical cancer: a meta-analysis. Clin Oncol (R Coll Radiol) 14(3):203–212

England, 2001 → 17 published and two unpublished trials of chemoradiation for cervical cancer.

- The absolute benefits in progression-free and overall survival were 16 and 12%, respectively. Significant benefits of chemoradiation on both local (odds ratio 0.61, $p < 0.0001$) and distant recurrence (0.57, $p < 0.0001$) were also recorded.
- Grade 3 or 4 hematological (odds ratio 1.49–8.60) and gastrointestinal (2.22) toxicities were significantly greater in the concomitant chemoradiation group than the control group.
- Concomitant chemotherapy and radiotherapy improves overall and progression-free survival (PFS) and reduces local and distant recurrence in selected patients with cervical cancer, which may give a cytotoxic and sensitization effect.

Green JA et al. (2001) Survival and recurrence after concomitant chemotherapy and radiotherapy for cancer of the uterine cervix: a systematic review and meta-analysis. Lancet 358(9284):781–786

Milan, 1997 → 343 patients with stage IB and IIA cervical carcinoma were randomized to surgery and to radical radiotherapy. Adjuvant radiotherapy was delivered after surgery for women with surgical stage pT2b or greater, less than 3 mm of safe cervical stroma, cut-through, or positive nodes.

- After a median follow-up of 87 (range 57–120) months, 5-year overall and disease-free survivals were identical in the surgery and radiotherapy groups (83 and 74%, respectively, for both groups).

- Significant factors for survival in univariate and multivariate analyses were: cervical diameter, positive lymphangiography, and adenocarcinomatous histotype. 48 (28%) surgery-group patients had severe morbidity compared with 19 (12%) radiotherapy-group patients ($p = 0.0004$).
- The combination of surgery and radiotherapy has the worst morbidity, especially in relation to urological complications. The optimum therapy for each patient should take into account clinical factors such as menopausal status, age, medical illness, histological type, and cervical diameter to yield the best cure with minimum complications.

Landoni F et al. (1997) Randomised study of radical surgery versus radiotherapy for stage Ib–IIa cervical cancer. Lancet 350(9077):535–540

GOG 92, *2006* → 277 patients with stage IB cervical cancer with negative LNs but with two or more of the following features: more than one-third (deep) stromal invasion, capillary lymphatic space involvement, and tumor diameter of 4 cm or more. 137 randomized to pelvic irradiation (RT: 46 Gy in 23 fractions to 50.4 Gy in 28 fractions) and 140 randomized to observation (OBS).

- The RT arm showed a statistically significant (46%) reduction in risk of recurrence (hazard ratio [HR] = 0.54, $p = 0.007$) and a statistically significant reduction in risk of progression or death (HR = 0.58, $p = 0.009$).
- The improvement in overall survival with RT did not reach statistical significance ($p = 0.074$).
- Pelvic RT after radical surgery significantly reduces the risk of recurrence and prolongs PFS in women with stage IB cervical cancer.

Rotman M et al (2006) A phase III randomized trial of postoperative pelvic irradiation in stage IB cervical carcinoma with poor prognostic features: follow-up of a gynecologic oncology group study. Int J Radiat Oncol Biol Phys 65(1):169–176

GOG 109/Intergroup 0107/SWOG 8797/RTOG 9112, *2000* → 268 patients with clinical stage IA2, IB, and IIA carcinoma of the cervix, initially treated with radical hysterectomy and pelvic lymphadenectomy, and who had positive pelvic LNs and/or positive margins and/or microscopic involvement of the parametrium, were randomized to receive RT or RT + CT.

- The addition of concurrent cisplatin-based CT to RT significantly improves progression-free and overall survival for high-risk, early-stage patients who undergo radical hysterectomy and pelvic lymphadenectomy for carcinoma of the cervix.

Peters WA III et al (2005) Concurrent chemotherapy and pelvic radiation therapy compared with pelvic radiation therapy alone as adjuvant therapy after radical surgery in high-risk early-stage cancer of the cervix. J Clin Oncol 18(8):1606–1613

Monk BJ et al (2005) Rethinking the use of radiation and chemotherapy after radical hysterectomy: a clinical-pathologic analysis of a Gynecologic Oncology Group/Southwest Oncology Group/Radiation Therapy Oncology Group trial. Gynecol Oncol 96(3):721–728

GOG 71/RTOG 84-12, 2003 → 256 patients with exophytic or "barrel"-shaped tumors measuring ≥4 cm were randomized to either external RT and intracavitary irradiation or attenuated irradiation followed by extrafascial hysterectomy.

- There was no clinically important benefit of the use of extrafascial hysterectomy. However, there is good evidence to suggest that patients with 4, 5, and 6 cm tumors may have benefited from extrafascial hysterectomy.

Keys HM et al (2003) Radiation therapy with and without extrafascial hysterectomy for bulky stage IB cervical carcinoma: a randomized trial of the Gynecologic Oncology Group. Gynecol Oncol 89(3):343–353

GOG 123, 1999 → women with bulky stage IB cervical cancers (tumor, ≥4 cm in diameter) were randomly assigned to receive radiotherapy alone or in combination with cisplatin (40 mg/m^2 of body-surface area once a week for up to six doses; maximal weekly dose, 70 mg), followed in all patients by adjuvant hysterectomy. The cumulative dose of external pelvic and intracavitary radiation was 75 Gy to point A (cervical parametrium) and 55 Gy to point B (pelvic wall). Cisplatin was given during external radiotherapy, and adjuvant hysterectomy was performed 3–6 weeks later.

- Adding weekly infusions of cisplatin to pelvic radiotherapy followed by hysterectomy significantly reduced the risk of disease recurrence and death in women with bulky stage IB cervical cancers.

Keys HM et al (1999) Cisplatin, radiation, and adjuvant hysterectomy compared with radiation and adjuvant hysterectomy for bulky stage IB cervical carcinoma. N Engl J Med 340(15):1154–1161

GOG 141, 2007 → patients with bulky FIGO stage IB cervical cancer, tumor diameter ≥4 cm. Prospective random allocation was to either NACT (vincristine–cisplatin chemotherapy every 10 days for three cycles) before exploratory laparotomy and planned RHPPL (NACT + RHPPL), or RHPPL only.

- There is no evidence from this trial that NACT offered any additional objective benefit to patients undergoing RHPPL for suboptimal stage IB cervical cancer.

Eddy GL (2007) Treatment of ("bulky") stage IB cervical cancer with or without neoadjuvant vincristine and cisplatin prior to radical hysterectomy and pelvic/para-aortic lymphadenectomy: a phase III trial of the gynecologic oncology group. Gynecol Oncol 106(2):362–369

NCI Canada, 2002 → 259 patients with stage IB to IVA squamous cell cervical cancer with central disease ≥5 cm or histologically confirmed pelvic LN involvement were randomized to receive RT (external-beam RT plus BT) plus weekly CDDP chemotherapy (40 mg/m^2) (arm 1) or the same RT without chemotherapy (arm 2).

- This study did not show a benefit to either pelvic control or survival upon the addition of concurrent weekly CDDP chemotherapy at a dose of 40 mg/m^2 to radical RT.

Pearcey R (2002) Phase III trial comparing radical radiotherapy with and without cisplatin chemotherapy in patients with advanced squamous cell cancer of the cervix. J Clin Oncol 20(4):966–972

RTOG 90-01, 2004 → 403 women with stage IIB to IVA disease, stage IB to IIA disease with a tumor diameter ≥5 cm, or positive pelvic LNs were randomly assigned to receive either EFRT or CTRT.

- The addition of fluorouracil and cisplatin to radiotherapy significantly improved the survival rate of women with locally advanced cervical cancer without increasing the rate of late treatment-related side effects.

Eifel PJ et al (2004) Pelvic irradiation with concurrent chemotherapy versus pelvic and para-aortic irradiation for high-risk cervical cancer: an update of radiation therapy oncology group trial (RTOG) 90-01. J Clin Oncol 22(5):872–880

EORTC, *1998* → 441 patients with stage I and IIB with proximal vaginal and/or parametrial involvement with positive pelvic LNs either on lymphangiogram or at surgery, stage IIB with distal vaginal and/or parametrial involvement, and III regardless of pelvic node status on lymphangiogram were randomized between pelvic irradiation and pelvic and paraaortic irradiation. Patients with clinically or surgically involved paraaortic nodes were not included. The external beam dose to the paraaortic area was 45 Gy.

- Routine paraaortic irradiation for all high-risk patients with cervical carcinoma is of limited value.

Haie C et al (1988) Is prophylactic para-aortic irradiation worthwhile in the treatment of advanced cervical carcinoma? Results of a controlled clinical trial of the EORTC radiotherapy group. Radiother Oncol 11(2):101–112

RTOG 79-20, 1995 → 367 patients with FIGO stage IB or IIA primary cervical cancers measuring 4 cm or greater in lateral diameter or with FIGO stage IIB cervical cancers were randomized to RTOG protocol 79-20 to receive either standard pelvic only irradiation or pelvic plus paraaortic irradiation.

- There was a statistically significant difference in overall survival at 10 years for the pelvic plus paraaortic irradiation arm, without a difference in disease-free survival.

Rotman M et al (1995) Prophylactic extended-field irradiation of para-aortic lymph nodes in stages IIB and bulky IB and IIA cervical carcinomas. Ten-year treatment results of RTOG 79-20. JAMA 274(5):387–393

GOG 191, 2008 → patients with stage IIB–IVA cervical cancer and HGB <14.0 g/dL were randomly assigned to CT/RT±recombinant human erythropoietin (R-HUEPO) (40,000 units s.c. weekly). R-HUEPO was stopped if HGB >14.0 g/dL.

- The impact of maintaining HGB level >12.0 g/dL on PFS, OS and LC remains undetermined.

Thomas G (2008) Phase III trial to evaluate the efficacy of maintaining hemoglobin levels above 12.0 g/dL with erythropoietin vs above 10.0 g/dL without erythropoietin in anemic

patients receiving concurrent radiation and cisplatin for cervical cancer. Gynecol Oncol 108(2):317–325

India, 1994 → randomized trial of HDR vs. LDR BT.

- HDR intracavitary BT was found to be an equally good alternative to conventional LDR BT in the treatment of carcinoma of the uterine cervix.

Patel FD et al (1994) Low dose rate vs. high dose rate brachytherapy in the treatment of carcinoma of the uterine cervix: a clinical trial. Int J Radiat Oncol Biol Phys 28(2): 335–341

Hacettepe, 2007: 141 patients with stage I–II cervical cancer without paraaortic LN metastases and treated by surgery and postoperative radiotherapy (RT). Indications for postoperative external RT were LN metastasis, positive surgical margins, parametrial involvement, pT2 tumor, and presence of any two minor risk factors like lymphovascular space involvement, deep stromal invasion, and tumor diameter between 2 and 4 cm. Median follow-up time was 55 months.

- Five-year OS, DFS, loco-regional recurrence-free, and distant metastases-free survival rates were 70, 68, 77, and 88%, respectively.
- Multivariate analyses revealed that the level and number of metastatic LNs and concomitant CT were unique significant prognostic factors for OS, DFS, and LRFS.
- Endometrial involvement was proven to be significant for DFS and DMFS.
- Patients with less than three LN metastases or those with only obturator LN involvement showed a similar prognosis to their counterparts with no LN metastases.
- Patients with either common iliac LN or more than three LN metastases had a significantly worse outcome.

Atahan IL et al (2007) Radiotherapy in the adjuvant setting of cervical carcinoma: treatment, results, and prognostic factors. Int J Gynecol Cancer 17(4):813–820

9.2 Endometrial Cancer

Endometrial cancer is the fourth most common female cancer following breast, lung and colon cancers. Such cancers have shown a prominent increase in incidence in developed countries, and have become the most common gynecologic cancer. Although its incidence is high, it is only the seventh most common cause of cancer-related mortality, due to early diagnosis and treatment [21].

The corpus is the major part of the uterus, and it extends into the fundus, where uterus combines with the Fallopian tubes. The isthmus is 0.5 cm long and located between the cervix and corpus (Fig. 9.14).

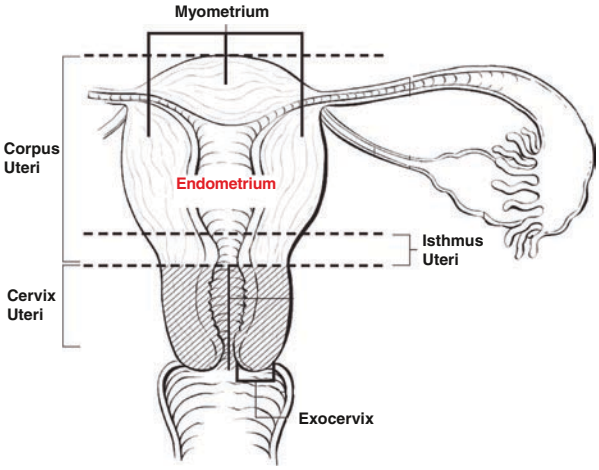

Fig. 9.14 Endometrial anatomy (from [29], p 250, Fig. 28.1, reproduced with the permission from the American Joint Committee on Cancer)

Histologically, the uterine corpus consists of three layers; from innermost to outermost, these are:

1. **Endometrium:** consists of a basal layer and a functional layer that includes endometrial glands.
2. **Myometrium:** consists of smooth muscle and lymph vessels.
3. **Serosa:** the peritoneum that covers the uterine corpus from anterior and posterior, and the cervix only from posterior.

9.2.1 Pathology

Endometrial cancers are generally adenocarcinomas [22]. The basic developmental mechanism is a long period of unbalanced estrogenic excitation with progesterone. This excitation may be exogenous or endogenous. Estrogen-secreting ovarian neoplasms (granulosa cells or functional thecomas) and polycystic ovarian syndrome (Stein–Leventhal syndrome), resulting in the secretion of high levels of estrogen, may cause endometrial hyperplasia and subsequent carcinoma.

Endometrial adenocarcinomas are classified into two groups according to their histomorphological features, pathogenesis and prognosis.

Type 1 endometrial adenocarcinomas. These generally develop from endometrial hyperplasia. There are hyperplasia foci around the carcinoma. Type 1 endometrial carcinomas are well-differentiated and are difficult to distinguish from normal endometrial glands. This type of carcinomas are also called "endometrioid-type" adenocarcinomas.

- They generally do not invade deep myometrium, and they have a good prognosis.
- They constitute 80–95% of all endometrial carcinomas.

Type 2 endometrial adenocarcinomas. These have no associated hyperplasia. Patients are older than those with type I cases. They are less differentiated neoplasias.

- Constitute 10–15% of endometrial cancers, and have a poor prognosis.
- No association with estrogen.
- High grade and high malignant potential.
- Serous and clear cell carcinomas belong in this group of neoplasias.

Cellular Classification [22]

Endometrioid (75–80%)
Ciliary adenocarcinoma
Secretory adenocarcinoma
Papillary or villoglandular
Squamous differentiated adenocarcinoma
Adenoachantoma
Adenosquamous
Uterine papillary serous carcinoma (<10%)
Mucinous (1%)
Clear cell (4%)
Squamous cell (<1%)
Mixed (10%)
Undifferentiated

- Types other than adenocarcinomas have high risks of recurrence and distant metastasis.
- Prognosis is poor in adenosquamous, clear cell and papillary types.

9.2.2 General Presentation

More than 90% of patients with endometrial cancer complain only of vaginal bleeding.

- Most such bleeding is postmenopausal in origin.
- Premenopausal cases have abnormal uterine bleeding.
- Rarely, patients have a feeling of pelvic compression or discomfort, which is a sign of extrauterine disease extension.

Particularly in older women, cervical stenosis causing hematometrium or pyometrium may not result in bleeding. This sign is a poor prognostic factor. More than 50% of cases with pyometrium and associated vaginal discharge have carcinoma in D&C (dilatation and curettage), and most have squamous carcinoma, which is a very rare form of endometrial carcinoma.

Five to seventeen percent of patients are asymptomatic. In asymptomatic cases, the disease is frequently discovered through abnormal PAP smears, incidentally in hysterectomy specimens, or via abnormal radiological findings in the uterus (e.g., thickening of the endometrial wall in pelvic USG).

9.2.3 Staging

Uterine cavity size, endocervical curettage findings, cystoscopy and rectoscopy findings were used in the clinical staging of endometrial cancer until 1988. However, this system could not determine some important prognostic factors such as myometrial invasion depth and lymph node metastasis and had downstage the tumor (22% lower stages than surgical staging).

Prognostic parameters like myometrial invasion depth, peritoneal cytology, lymph node involvement, cervical and adnexal extension were added into 1988 surgical-pathological staging system [23–26]. FIGO recently changed the endometrial cancer staging system in 2009.

FIGO Staging for Endometrial Cancer (Fig. 9.15) [23]

Stage I:	tumor limited to endometrium
Stage IA:	invasion to less than 50% of the myometrium.
Stage IB:	invasion to greater than 50% of the myometrium.
Stage II:	tumor invades stromal connective tissue of the cervix but does not extend beyond uterus.*
Stage IIIA:	tumor invades serosa and/or adnexa (direct extension or metastasis).
Stage IIIB:	Vaginal involvement or metastasis or parametrial involvement.
Stage IIIC1:	metastases in pelvic lymph nodes.
Stage IIIC2:	metastases in para-aortic lymph nodes with or without pelvic lymph node involvement.
Stage IVA:	tumor invasion of bladder and/or bowel mucosa.
Stage IVB:	distant metastases including intra-peritoneal disease and/or inguinal lymph nodes (no pathologic M0; use clinical M0).

*Endocervical glandular involvement only should be considered as stage I and not stage II.

Surgical staging of endometrial cancer should include peritoneal lavage for cytological exam, biopsy of all suspicious lesions by abdominal and pelvic exploration, radical hysterectomy, bilateral salpingo-oopherectomy and bilateral pelvic paraaortic lymph node dissection.

Uterus is thoroughly examined for tumor size, myometrial invasion depth, cervical stromal and glandular extension. All suspicious pelvic and paraaortic lymph nodes should be examined pathologically.

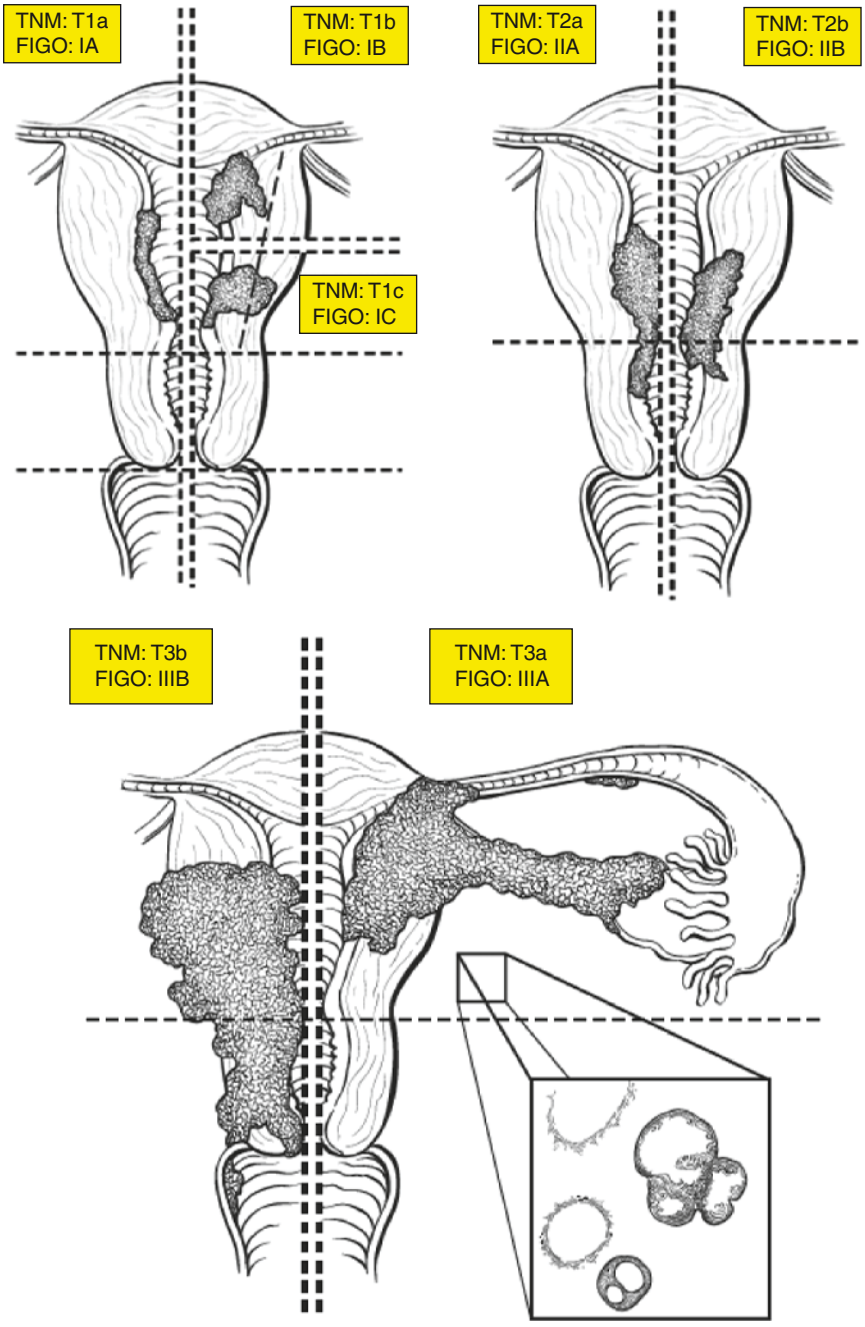

Fig. 9.15 Endometrial cancer staging (from [29], p 261, 262, Figs. 29.1–29.3, reproduced with the permission from the American Joint Committee on Cancer)

Endometrial Cancer Lymphatics (Fig. 9.16)

Parametrial
Obturator
Hypogastric (internal iliac)
External iliac
Common iliac
Presacral
+Paraaortic

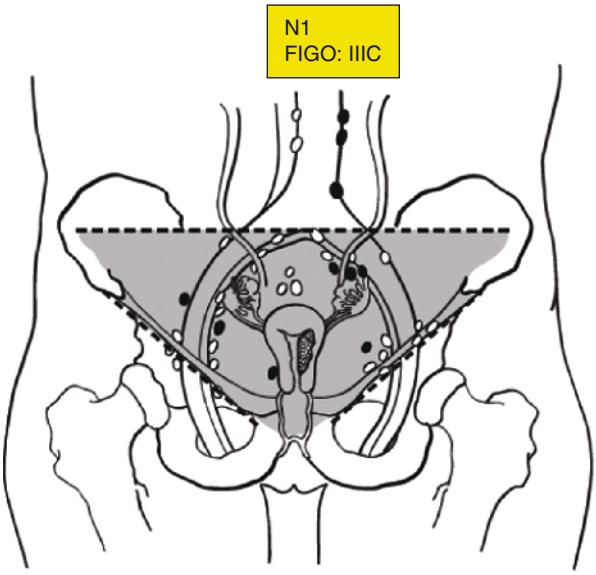

Fig. 9.16 Endometrial lymphatics (from [29], p 263, Fig. 29.5, reproduced with the permission from the American Joint Committee on Cancer)

Prognostic Factors [27]

→Myometrial invasion:

Deep myometrial invasion increases the risk of lymph node metastasis, extrauterine extension and recurrence.

→Pathology:

Other than endometrioid types have increased recurrence and distant metastasis.

→Histological differentiation (grade):

It is almost always associated with increased recurrence risk.

(*continued*)

(continued)

→Lymphovascular space invasion:

It is approximately 15% in early endometrial cancers, but increases with an increased in myometrial invasion depth and tumor grade.

→Lymph node metastasis:

It is the most important prognostic factor in early-stage endometrial cancer.
→Peritoneal cytology:

→Adnexial metastasis:

It is a very high risk for recurrence.

→Tumor size:

Tumors >2 cm; LN metastasis is higher.

→Hormonal receptors:

Progesterone receptor (+) is more determinant for prognosis than estrogen receptor.

→Age:

Young age is a good prognostic factor, since grade and poor histological types are more frequent in older ages.

9.2.4 Treatment Algorithm

Treatment Algorithm for Endometrial Cancer [28]

Stage IA, Grade I–II
TAH + BSO + peritoneal lavage
(if Grade II–III in frozen section: pelvic/paraaortic LN dissection)
Stage IB, Grade I
TAH + BSO + peritoneal lavage
(if Grade II–III in frozen section: pelvic/paraaortic LN dissection)

- LVSI (−) and age <60 years, surveillance after surgery
- LVSI (+) and age >60 years, vaginal cuff BT

Stage IA, Grade III
Stage IB, Grade II–III
TAH + BSO + peritoneal lavage + pelvic/paraaortic LN

- LVSI (−) and age <60 years, surveillance after surgery
- LVSI (+) and age >60 years

Complete surgical staging (+), vaginal cuff BT
Complete surgical staging (−), pelvic RT

Stage IC, Grade I

TAH + BSO + peritoneal lavage + pelvic/paraaortic LN

- LVSI (−) and age <60 years, surveillance after surgery
- LVSI (+) and age >60 years

Complete surgical staging (+), vaginal cuff BT
Complete surgical staging (−), pelvic RT
Stage IC, Grade II
TAH + BSO + peritoneal lavage + pelvic/paraaortic LN
Complete surgical staging (+), vaginal cuff BT
Complete surgical staging (−), pelvic RT
Stage IC, Grade III
TAH + BSO + peritoneal lavage + pelvic/paraaortic LN

- LVSI (−) and age <60, vaginal cuff BT ± pelvic RT (complete surgical staging (+), vaginal cuff BT may be used alone since risk of pelvic relapse is only 3%)
- LVSI (+) and age >60; pelvic RT + vaginal cuff BT

Stage IIA

- Grade I–II + myometrial invasion <½, pelvic RT or vaginal cuff BT
- Grade III + myometrial invasion <½, pelvic RT ± vaginal cuff BT → myometrial invasion >½

Grade I–II → pelvic RT ± vaginal cuff BT
Grade III → pelvic RT + vaginal cuff BT
Stage IIB
Surgery + pelvic RT + vaginal cuff BT
Stage IIIA
Surgery + pelvic RT + vaginal cuff BT
(Paraaortic LN (+), extended field RT)
Stage IIIB
Pelvic RT + vaginal cuff BT
(Paraaortic LN (+), extended field RT)
Stage IIIC
Surgery + RT + vaginal cuff BT

- Lower pelvic LN (+) → pelvic RT
- Upper pelvic LN (+) or paraaortic LN (+) → extended field RT

Stage IVA/B
RT + BT boost or chemotherapy
Special situations
Uterine papillary, serous carcinoma
Stage I–II → pelvic RT + vaginal cuff BT
(High-risk (+), first neoadjuvant CT)
[3–6 cycles carboplatin + paclitaxel]
Stage III–IV → chemotherapy + whole abdomen RT

(*continued*)

(continued)

Medically inoperable

Pelvic RT + BT
[RT → 50.4 Gy (midline block after 20–40 Gy)]
[Brachytherapy → vaginal surface dose 60–80 Gy]
Recurrence
No previous RT → RT + BT boost (total dose 60–70 Gy)
Uterine sarcoma

Surgery (postoperative RT may increase local control in Grade II–III, but no effect on survival)

9.2.5 Radiotherapy

Simulation is performed in the supine position; vaginal and rectal markers are placed into the patient. Oral contrast material may be beneficial for the visualization of intestines.

Anterior–posterior fields (Fig. 9.17)

- Superior: between the L4 and L5 vertebrae (common iliac LN [+] → L3–4)
- Inferior: below obturator foramen if vagina (−), below ischial tuberosities if vagina (+)
- Lateral: bony pelvis + 2 cm

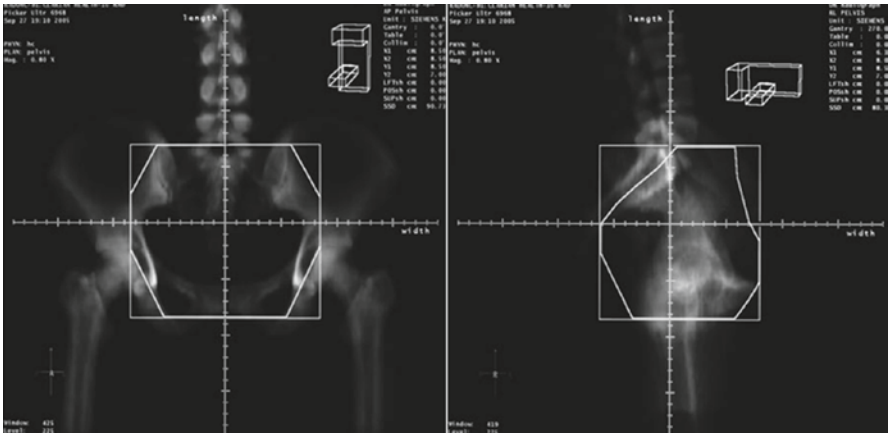

Fig. 9.17 Conventional RT fields in endometrial cancer (from [32], p.614, Fig. 25.6a, reproduced with the permission from Springer Science and Business Media)

Lateral fields

- Superior and inferior: same as anterior–posterior fields
- Anterior: anterior to symphysis pubis
- Posterior: between the S2 and S3 vertebrae (or 2 cm posterior to tumoral extension)

Paraaortic/upper pelvic LN (+) → paraaortic RT (extended field RT)

Dose–Fractionation

- *Postoperative RT:*
  Pelvic RT: 45 Gy/1.8 Gy
  Pelvic extension: total dose 50.4 Gy
  Vaginal cuff BT: 3 × 6–7 Gy (HDR)
  BT alone: 6 × 5.5–6 Gy (HDR)
- *Preoperative RT:*
  Pelvic RT: 45 Gy/1.8 Gy
  Vaginal extension; total dose 50.4 Gy.
  Intracavitary BT: 3 × 6–7 Gy (HDR)
- *Paraaortic LN (+)* (Fig. 9.18):
  Pelvic/paraaortic RT + vaginal cuff BT
- *Whole-abdomen RT* (Fig. 9.19):
  30 Gy/1.5 Gy; then paraaortic and pelvic fields 45 Gy for uterine papillary serous carcinoma (Stage III–IV)

The superior border in whole abdomen is 1 cm above the diaphragm

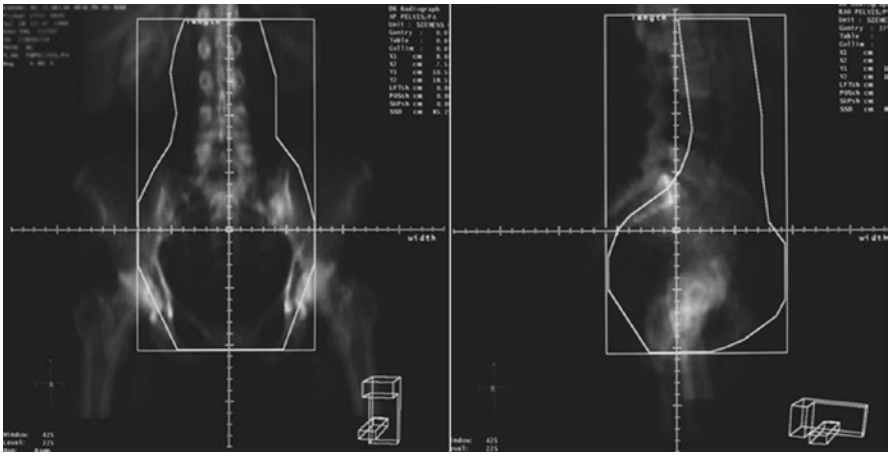

Fig. 9.18 Extended field RT in endometrial cancer (from [32], p 616, Figs. 25.6a2–b2, reproduced with the permission from Springer Science and Business Media)

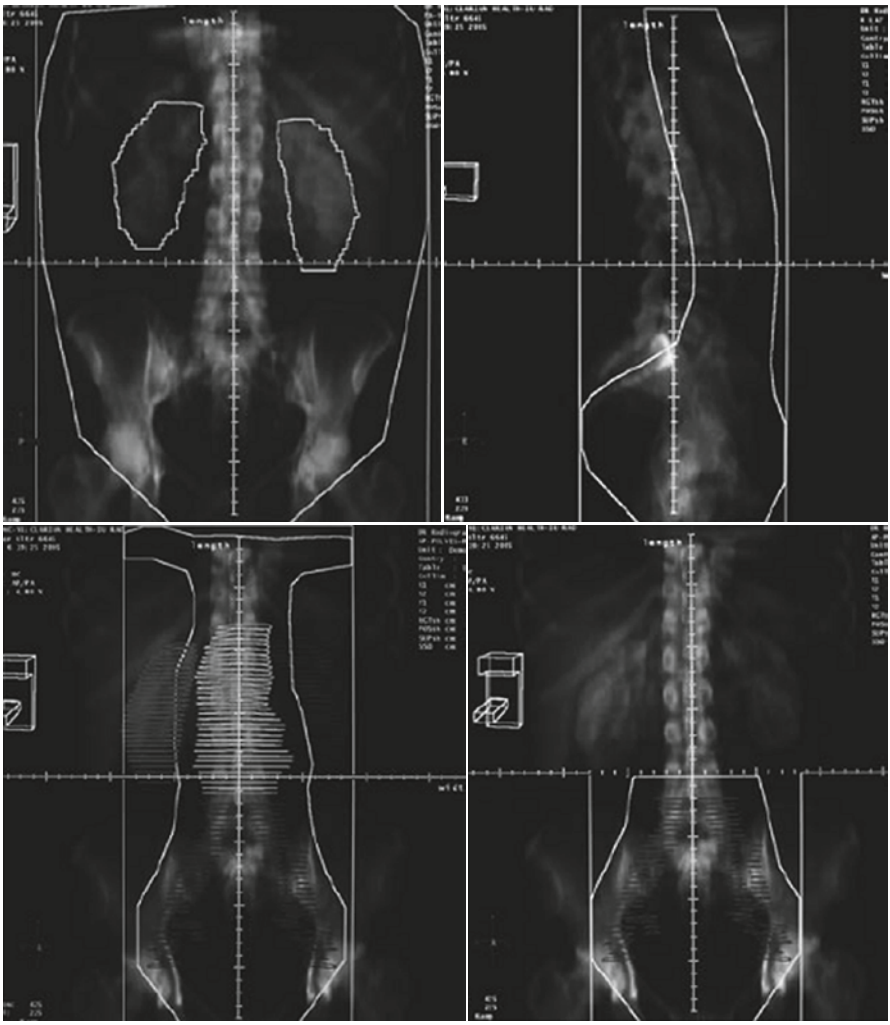

Fig. 9.19 Whole-abdomen RT (from [30], p 618, Fig. 25.8a1, b–e, reproduced with the permission from Springer Science and Business Media)

Brachytherapy [18]

Postoperative vaginal BT. Vaginal cylinders are used in this technique, and target volume is 2/3 of vaginal cuff (Fig. 9.20). It is important to use appropriately sized cylinders that suit the vaginal cuff. Dose is usually prescribed to 0.5 cm from the cylinder surface.

Preoperative intracavitary BT. Y applicators are used in the treatment of intact endometrial cancer (Fig. 9.20). Dose is prescribed to cover entire endometrial serosa. Cervical dilation is performed by Hegar dilators.

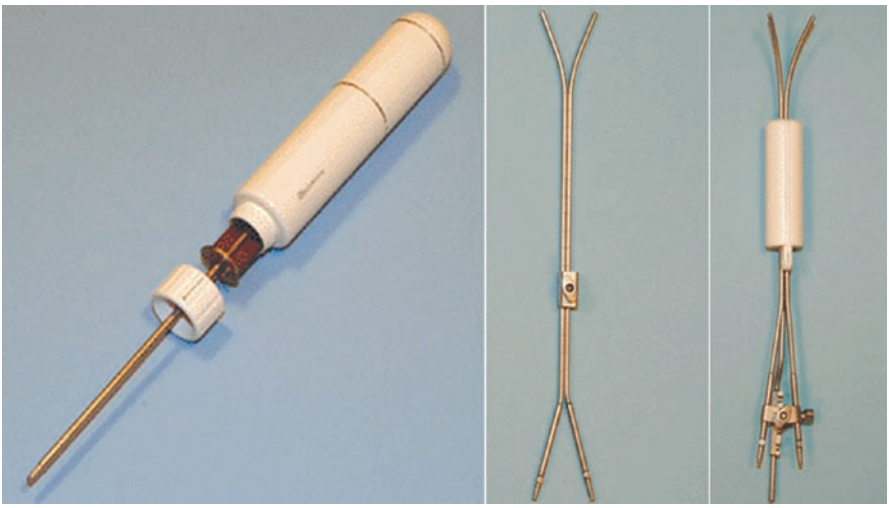

Fig. 9.20 Vaginal cylinders and Y applicator for endometrial brachytherapy applications

9.2.6 Selected Publications

PORTEC, 2005 → 714 stage I endometrial carcinoma patients randomly assigned to post-operative pelvic radiotherapy (RT) or no further treatment, excluding those with stage IC, Grade 3, or stage IB, Grade 1 lesions.

- Ten-year loco-regional relapse rates were 5% (RT) and 14% (controls; $p < 0.0001$), and 10-year overall survivals were 66 and 73%, respectively ($p = 0.09$).
- In view of the significant loco-regional control benefit, radiotherapy remains indicated in stage I endometrial carcinoma patients with high-risk features for loco-regional relapse.

Scholten AN (2005) Postoperative radiotherapy for Stage 1 endometrial carcinoma: long-term outcome of the randomized PORTEC trial with central pathology review. Int J Radiat Oncol Biol Phys 63(3):834–838

GOG 99, 2004 → 448 patients with "intermediate risk" endometrial adenocarcinoma were randomized after surgery to either no additional therapy (NAT) or whole pelvic radiation therapy (PRT). A high intermediate risk (HIR) subgroup of patients was defined as those with (1) moderate to poorly differentiated tumor, presence of lymphovascular invasion, and outer third myometrial invasion; (2) age 50 or greater with any two risk factors listed above; or (3) age of at least 70 with any risk factor listed above. All other eligible participants were considered to be in a low intermediate risk (LIR) subgroup.

- Adjunctive RT in early-stage intermediate risk endometrial carcinoma decreases the risk of recurrence, but should be limited to patients whose risk factors fit the definition of HIR.

Keys HM et al (2004) A phase III trial of surgery with or without adjunctive external pelvic radiation therapy in intermediate risk endometrial adenocarcinoma: a Gynecologic Oncology Group study. Gynecol Oncol 92(3):744–751

JGOG 2033, 2007 → adjuvant PRT vs. cyclophosphamide–doxorubicin–cisplatin (CAP) chemotherapy in women with endometrioid adenocarcinoma with deeper than 50% myometrial invasion.

- No statistically significant differences in PFS and overall survival (OS) were observed.
- Among 120 patients in a high- to intermediate-risk group defined as (1) stage IC in patients over 70 years old or with G3 endometrioid adenocarcinoma or (2) stage II or IIIA (positive cytology), the CAP group had a significantly higher PFS rate (83.8 vs. 66.2%, $p=0.024$) and higher OS rate (89.7 vs. 73.6%, $p=0.006$).
- Adverse effects were not significantly increased in the CAP group vs. the PRT group.
- Adjuvant chemotherapy may be a useful alternative to radiotherapy for intermediate-risk endometrial cancer.

Susumu N (2008) Randomized phase III trial of pelvic radiotherapy versus cisplatin-based combined chemotherapy in patients with intermediate-and high-risk endometrial cancer: A Japanese Gynecologic Oncology Group study. Gynecol Oncol 108(1): 226–233

Sorbe et al. 2005 → 290 low-risk endometrial carcinomas (stages IA–IB and Grades 1–2). The HDR MicroSelectron afterloading equipment (iridium-192) was used. Perspex vaginal applicators with diameters of 20–30 mm were used, and the dose was specified at 5 mm from the surface of the applicator. Six fractions were given, and the overall treatment time was 8 days. The size of the dose per fraction was randomly set to 2.5 Gy (total dose of 15.0 Gy) or 5.0 Gy (total dose of 30.0 Gy).

- The overall loco-regional recurrence rate of the complete series was 1.4% and the rate of vaginal recurrence was 0.7%. There was no difference between the two randomized groups.
- The vaginal shortening (measured by colpometry) was not significant ($p=0.159$) in the 2.5 Gy group (mean, 0.3 cm) but was highly significant ($p<0.000001$) in the 5.0 Gy group (mean 2.1 cm) after 5 years.
- Mucosal atrophy and bleedings were significantly more frequent in the 5.0 Gy group. Symptoms noted in the 2.5 Gy group were no different from those that could be expected in a normal group of postmenopausal women.
- The fractionation schedule recommended for postoperative vaginal irradiation in low-risk endometrial carcinoma is six fractions of 2.5 Gy when the HDR technique is used.

Sorbe B (2005) Intravaginal high-dose-rate brachytherapy for stage I endometrial cancer: a randomized study of two dose-per-fraction levels. Int J Radiat Oncol Biol Phys 62(5):1385–1389

GOG 122, 2006 → 422 patients with stage III or IV endometrial carcinoma having a maximum of 2 cm of postoperative residual disease were randomized to whole-abdominal irradiation (WAI) and doxorubicin–cisplatin (AP) chemotherapy. RT dose was 30 Gy in 20

fractions, with a 15 Gy boost. Chemotherapy consisted of doxorubicin 60 mg/m^2 and cisplatin 50 mg/m^2 every 3 weeks for seven cycles, followed by one cycle of cisplatin.

- Chemotherapy with AP significantly improved progression-free and overall survival compared with WAI.

Randall ME et al (2006) Randomized phase III trial of whole-abdominal irradiation versus doxorubicin and cisplatin chemotherapy in advanced endometrial carcinoma: a Gynecologic Oncology Group study. J Clin Oncol 24(1):36–44

Hacettepe, 2008 → 128 patients with intermediate- to high-risk stage I endometrial adenocarcinoma (any stage I with Grade 3 histology or stage IB Grade 2 or any stage IC disease) were treated with HDR BT alone after complete surgical staging. A total dose of 27.5 Gy with HDR BT, prescribed at 0.5 cm, was delivered in five fractions on 5 consecutive days. Median follow-up was 48 months.

- Six (4.7%) patients developed either local recurrence ($n=2$) or distant metastases ($n=4$).
- Five-year OS and DFS rates were 96 and 93%, respectively.
- Only age was found to be a significant prognostic factor for DFS. Patients younger than 60 years had significantly higher DFS ($p=0.006$).
- None of the patients experienced Grade 3/4 complications due to the vaginal HDR BT.
- Vaginal cuff BT alone is an adequate treatment modality in stage I endometrial adenocarcinoma patients with intermediate- to high-risk features after complete surgical staging with low complication rates.

Atahan IL, Ozyar E, Yildiz F, Ozyigit G et al (2008) Vaginal high dose rate brachytherapy alone in patients with intermediate- to high-risk stage I endometrial carcinoma after radical surgery. Int J Gynecol Cancer 18(6):1294–1299

9.3 Vaginal Cancer

Vaginal cancer is rarely seen, and comprises 1–2% of all gynecological cancers [30]. They are classified into primary and secondary vaginal cancers. Primary vaginal cancer originates from the vagina, while secondary vaginal cancer usually originates from the metastases of cervical and vulvar cancers.

The vagina is a 7–9 cm long cylindrical organ extending from the vestibule to the uterine cervix (Fig. 9.21). Its wall consists of glandular mucous membrane, a muscular layer rich in vascular structures, and adventitial connective tissues. Vaginal mucosa contains mucosal-type stratified nonkeratinized squamous cells that are sensitive to hormones and show cyclic changes. They also have multiple mucosal ridges called rugae.

Lower third of vagina develops from urogenital sinus, and upper two thirds of vagina develops from Mullerian canal similar to inner genital organs such as uterus, Fallopian tubes and ovaries during embryogenesis.

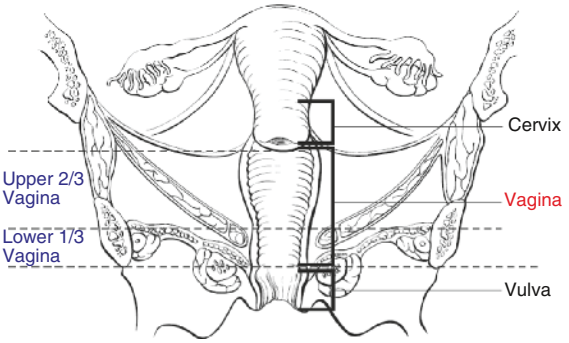

Fig. 9.21 Anatomy of the vagina (from [29], p 244, Fig. 27.1, reproduced with the permission from the American Joint Committee on Cancer)

Primary vaginal cancers are mostly seen in patients over 60 years of age [30].

9.3.1 Pathology

Mostly embryonal sarcomas and endodermal sinus tumors in are observed in childhood, adenocarcinomas related to diethylstilbestrol (DES) in adolescence, and squamous cell cancer in adults. Although vaginal cancers are generally seen in older patients, their frequency among young females has increased in recent years due to HPV infections.

Nearly 80–90% of all pathological cases are squamous cell cancers, and most of these are Grade II–III lesions [30].

Primary vaginal cancers have several subtypes: pure epithelial, mesenchymal, mixed epithelial and mesenchymal, and germ cell tumors.

Invasive squamous cell cancer. This is observed mostly in the posterior wall as an exophytic mass. Lesions may be 3–5 cm long and ulcerated. Advanced lesions are those that easily bleed. Endophytic tumors are less commonly seen. Most of them are microscopically moderately differentiated and show destructive infiltrative growth patterns in vaginal and paravaginal soft tissues.
Verrucous carcinoma. This is the least common variant of squamous cell cancer. They present with postmenopausal bleeding or vaginal discharge, and 0.8–10 cm in diameter, 2–3 cm long verrucous lesions. These tumors grow slowly and rarely metastasize.
Malignant melanoma. These constitute 3% of all vaginal epithelial tumors. They originate from melanocytes found in various places in the vagina. Cases usually occur in the late reproductive or perimenopausal period. It behaves very aggressively and extends early.

Adenocarcinoma. This is observed in 10–15% of cases. It originates from the Bartholin and Skene glands.

- Clear cell carcinoma develops due to DES exposure in utero.

Mesenchymal cancers. Pure primary tumors are very rare, and follow an aggressive and lethal course. Sarcoma botryoides and leiomyosarcomas are the most frequent. In addition, lymphomas, malignant fibrous histiocytomas and postradiotherapy angiosarcomas may be seen.
Germ cell tumors. These are rarely seen in the vagina. Malignant ones are embryonic cell cancers and endodermal sinus tumors. They are observed in newborns.

9.3.2 General Presentation

Most patients present with abnormal vaginal bleeding and discharge. Pelvic pain and other symptoms change according to tumoral extension into surrounding tissues and organs. Anterior tumors produce bladder and urinary symptoms, while posterior ones yield tenesmus and defecation problems.

- Dyspareunia is observed in sexually active females.
- The disease is rarely diagnosed through abnormal PAP smear findings.
- The tumor is grossly exophytic in general, but it may be endophytic. Superficial ulcerations usually occur in advanced stages.
- Most of them localize in the upper one-third of the posterior vaginal wall.
- Chronic pelvic pain is observed in 5% of cases at diagnosis.

9.3.3 Staging

FIGO Staging (Fig. 9.22) [31]

I: Tumor confined to vagina
II: Tumor invades paravaginal tissues but not pelvic wall*
III: Tumor extends to pelvic wall*
IVA: Tumor invades mucosa of the bladder or rectum and/or extends beyond the true pelvis (Bullous edema is not sufficient evidence to classify a tumor as T4)
*[Note: Pelvic wall is defined as muscle, facia, neurovascular structures, or skeletal portions of the bony pelvis].
IVB: Pelvic or inguinal lymph node metastasis

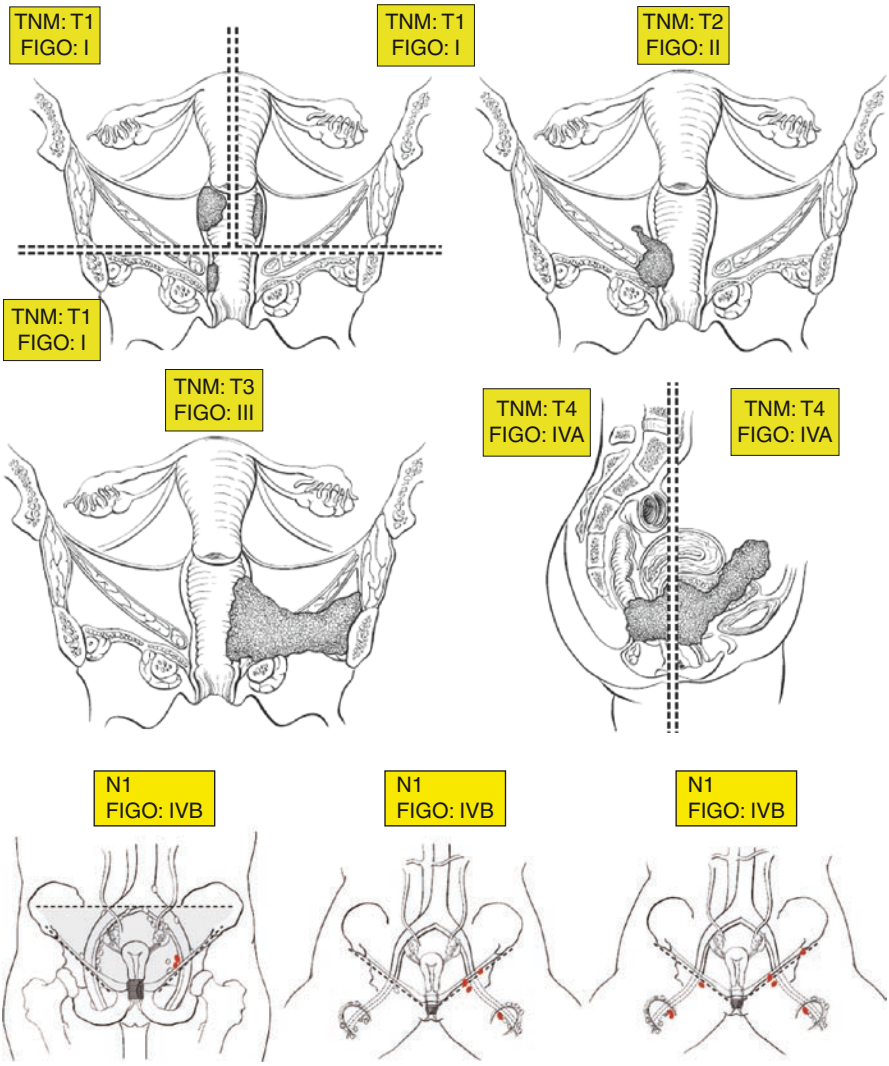

Fig. 9.22 Vaginal cancer staging (from [29], p 245, Figs. 27.4 and 27.5, reproduced with the permission from the American Joint Committee on Cancer)

Lymphatics of Vagina (Fig. 9 23)

Upper 2/3 of vagina: Obturator, internal iliac (hypogastric), external iliac, pelvic lymph nodes

Lower 1/3 of vagina: Inguinal and femoral lymph nodes

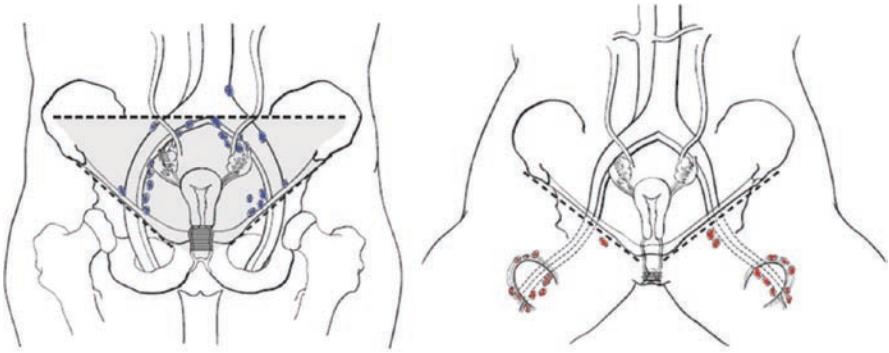

Fig. 9.23 Vaginal lymphatics (from [29], p 243, Figs. 27.2 and 27.3, reproduced with the permission of the American Joint Committee on Cancer)

9.3.4 Treatment Algorithm

Treatment Algorithm for Vaginal Cancer [32]

Stage 0 (CIS)
Cryotherapy, laser, topical 5-FU or wide local excision
(Resistance to treatment; 60–70 Gy BT may be offered for vaginal mucosa)
Stage I (depth <0.5 cm, length <2 cm and Grade I)
Surgery → wide local excision or total vaginectomy + vaginal reconstruction

- Surgical margin (+) or close; postoperative RT.

  Alternative → BT (60–70 Gy)
  Stage I (depth >0.5 cm, length >2 cm or Grade II–III)
  Surgery → wide local excision + LN dissection
  (Upper two-thirds of vagina → pelvic LND)
  (Lower one-third of vagina → inguinal LND)

- Surgical margin (+) or close; postoperative RT.

  Alternative → pelvic RT + vaginal BT
  (After 20; 45–50 Gy with midline block)
  (Lower one-third of vagina (+), inguinal LN is included)
  Stage II
  Pelvic RT + vaginal BT
  (After 20; 45–50 Gy with midline block)
  (Lower one-third of vagina (+), inguinal LN is included)

(*continued*)

(continued)

Stage III/IV
Pelvic RT + vaginal BT
(After 40 Gy: 50 Gy with midline block)
(Lower one-third of vagina (+), inguinal LN is included)
(LN (+), 10–15 Gy to involved LNs)
(Concurrent cisplatin-based chemotherapy may be added to radiotherapy)
Special situations
Clear cell adenocarcinoma

Surgery (radical hysterectomy, vaginectomy, pelvic + paraaortic LND)
Definitive RT in selected cases like stage II–IV
Metastatic disease

Palliative RT ± CT
Recurrence

Pelvic exenteration

9.3.5 Radiotherapy

Conventional RT Fields (Fig. 9.24)

Anterior–posterior:

- Superior: between the L5 and S1 vertebrae
- Inferior: vaginal entrance + tumor + 3 cm
- Lateral: bony pelvis + 2 cm

Lateral:

- Superior and inferior: same as anterior field
- Anterior: 1 cm anterior to pubis
- Posterior: S2–3, or include tumor + 2 cm

Inguinal/femoral LN (+) or lower vaginal tumor; RT field should be extended to include inguinal/femoral lymphatics (Fig. 9.25).

- Therefore, simulation is performed in the frog-leg position.

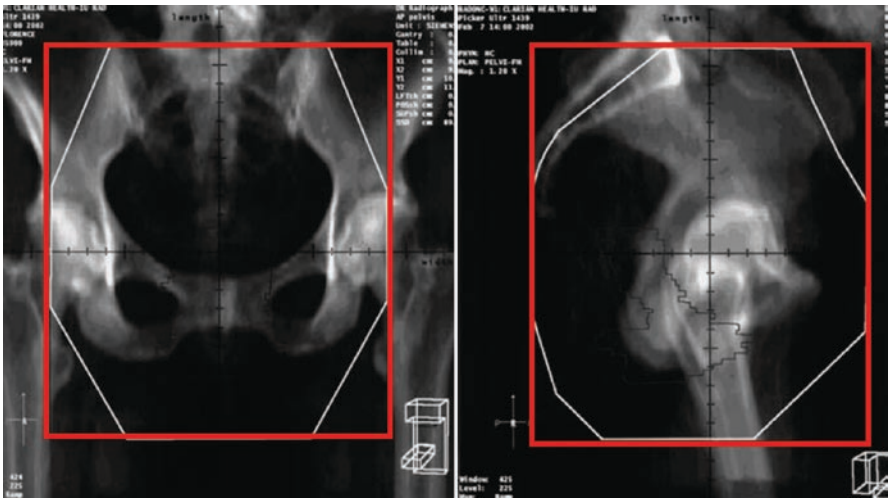

Fig. 9.24 Conventional RT fields in vaginal cancer (from [33], p 663, Fig. 27.1a, b, reproduced with the permission from Springer Science and Business Media)

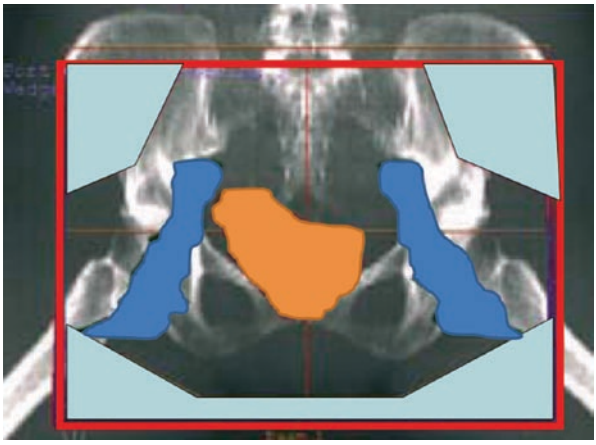

Fig. 9.25 Conventional RT field in lower one-third or inguinal LN (+) vaginal cancer (from [33], p 664, Fig. 27.2a, reproduced with the permission from Springer Science and Business Media)

- Vaginal entrance and rectum should be marked by vaginal marker and rectal tube.
- Total dose: 45–50 Gy in 1.8–2 Gy/day with high-energy photons; then BT if indicated.
- Boost is given by electrons to involved inguinal LNs (10–15 Gy).
- After 20–40 Gy, a midline block is used to protect the rectum according to stage.

LN (−/+); posterior field should include only pelvis (not inguinal regions) to protect femur heads, since inguinal LNs are located superficially.

9.3.6 Selected Publications

M.D. Anderson, 2005 → 193 patients were treated with definitive radiation therapy for squamous cell carcinoma of the vagina.

- Five-year DSS rates were 85% for the 50 patients with stage I, 78% for the 97 patients with stage II, and 58% for the 46 patients with stage III–IVA disease ($p = 0.0013$).
- Five-year DSS rates were 82 and 60% for patients with tumors ≤4 cm or >4 cm, respectively ($p = 0.0001$).
- Five-year pelvic disease control rates were 86% for stage I, 84% for stage II, and 71% for stage III–IVA ($p = 0.027$).
- Excellent outcomes can be achieved with definitive radiation therapy for invasive squamous cell carcinoma of the vagina.
- Treatment must be individualized according to the site and size of the tumor at presentation and the response to initial external-beam radiation therapy.

Frank SJ (2005) Definitive radiation therapy for squamous cell carcinoma of the vagina. Int J Radiat Oncol Biol Phys 62(1):138–147

MSKCC, 1992 → 36 patients were treated with combined external RT and BT, 11 patients were treated with external RT alone, and two patients were treated with BT alone.

- Five-year survival was 44% for stage I, 48% for stage II, 40% for stage III, and 0% for stages IVa and IVb.
- There was a significant increase in the 5-year actuarial survival for those patients who had BT as part of their treatment compared to those patients treated with external RT alone (50 vs. 9%) ($p < 0.001$). For stages II and III, there was a trend toward improved actuarial and crude disease-free survival with the use of a temporary Ir-192 interstitial implant as part of the treatment compared to the use of intracavitary BT as part of the treatment (80 vs. 45%) ($p = 0.25$) and (75 vs. 44%) ($p = 0.08$), respectively.
- BT plays an important role in the management of primary vaginal cancer. A temporary interstitial implant should be used over an intracavitary form of therapy for more invasive disease.

Stock RG (1992) The importance of brachytherapy technique in the management of primary carcinoma of the vagina. Int J Radiat Oncol Biol Phys 24(4):747–753

Washington University, 1988 → 165 patients with vaginal cancer.

- Ten-year disease-free survivals were: stage 0, 94%; stage I, 75%; stage IIA, 55%; stage IIB, 43%; stage III, 32%; stage IV, 0%.
- RT dose delivered to the primary tumor or the parametrial extension was critical in achieving successful results.
- Conclusion: high incidence of distant metastases underscored the need for earlier diagnosis and effective systemic cytotoxic agents if survival is to be significantly improved in these patients.

Perez CA (1988) Definitive irradiation in carcinoma of the vagina: long-term evaluation of results. Int J Radiat Oncol Biol Phys 15(6):1283–1290

Ontario, 2007 → 12 patients were treated with concurrent weekly chemoradiotherapy. Median follow-up was 50 months. All patients received pelvic external RT (EBRT) concurrently with weekly intravenous cis-platinum chemotherapy (40 mg/m^2) followed by BT (BT). The median dose of EBRT was 4,500 cGy given in 25 fractions over 5 weeks.

- Five-year overall survival, PFS, and loco-regional PFS rates were 66, 75, and 92%, respectively.
- It was found to be feasible to deliver concurrent weekly cis-platinum chemotherapy with high-dose radiation, leading to excellent local control and an acceptable toxicity profile.

Samant R (2007) Primary vaginal cancer treated with concurrent chemoradiation using cis-platinum. Int J Radiat Oncol Biol Phys 69(3):746–750

UC Davis, 2004 → 14 patients were treated with primary therapy consisting of concurrent radiation and chemotherapy.

- Chemoradiotherapy was found to be an effective treatment for squamous carcinoma of the vagina.

Dalrymple JL (2004) Chemoradiation for primary invasive squamous carcinoma of the vagina. Int J Gynecol Cancer 14(1):110–117

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Gastrointestinal System Cancers

10

Murat Beyzadeoglu, Cuneyt Ebruli, and Gokhan Ozyigit

10.1 Esophageal Cancer

Esophageal cancer is the fourth most common gastrointestinal cancer, and it constitutes 5% of all cancers. It is common in patients older than 60 years and in black populations [1].

The esophagus is a muscular tube that starts at the C6 vertebra after the hypopharynx and extends into the stomach at the T11 level (Fig. 10.1). The length of the esophagus changes according to age and gender (22–28 cm in adults; 23–30 cm in males; 20–26 cm in females). The distance from the teeth to the cricopharyngeal region is approximately 15 cm in males and 14 cm in females (that from the teeth to the esophagogastric junction is 38–42 cm in males and 2 cm less in females).

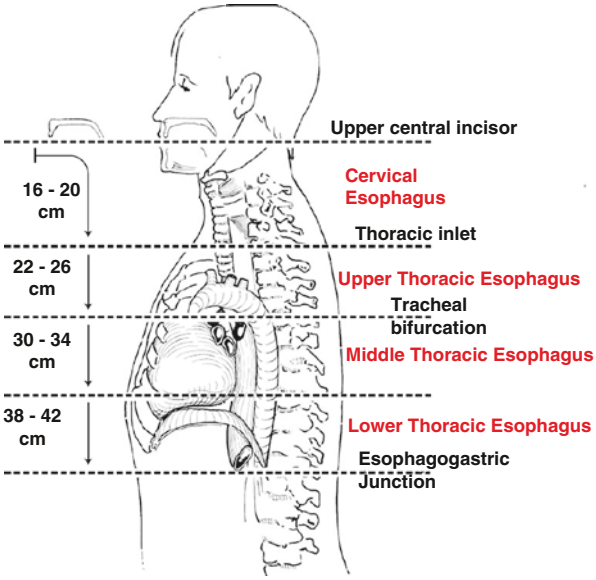

Fig. 10.1 Anatomy of the esophagus (from [35], p 78, Fig. 9.1, reproduced with the permission from the American Joint Committee on Cancer)

M. Beyzadeoglu et al. *Basic Radiation Oncology*,
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The esophagus is anatomically divided into three segments: cervical, thoracic and abdominal:

- *Cervical esophagus*: between the cricopharyngeal region and the T1 vertebra
- *Thoracic esophagus*: between the T1 vertebra and the esophageal hiatus
- *Abdominal esophagus*: between the hiatus and the esophagogastric junction

The surrounding organs, vessels and muscles naturally compress the esophagus and cause three important narrowings that can be seen during endoscopy or fluoroscopy:

1. *Upper narrowing*: the narrowest place at the cricopharyngeal level; caused by the cricopharyngeus muscle.
2. *Middle narrowing*: here, the aortic arch and the left main bronchus cross the esophagus anteriorly and left laterally.
3. *Lower narrowing*: this occurs at the level of the gastroesophageal sphincter and the diaphragmatic hiatus.

The esophagus has no serosal layer.

10.1.1 Pathology

The most common type of esophageal cancer is squamous cell carcinoma [2].

Squamous cell cancers [2]. These constitute nearly 95% of all malignant esophageal tumors. The major symptom is dysphagia. Symptoms start after the tumor fills two-thirds of the lumen, and diagnosis is usually late. Therefore, symptomatic patients commonly show a direct or lymphatic spread. The most common distant metastatic sites are lung, liver, pleura, bone and kidneys. Histologically, most squamous cell cancers are poorly differentiated and show less keratinization. These tumors have no specific laboratory findings. Five-year survival is 5–30%.
Adenocarcinomas [2]. These are mostly localized in the lower parts and close to the esophagogastric junction, and compromise 3–5% of all malignant esophageal tumors. Adenocarcinoma generally develops in the stomach, and extends directly into the esophagus. Primary esophageal adenocarcinoma is rare (2% in the upper half, 8–10% in the lower half). Primary adenocarcinoma originates from submucosal glands. However, adenocarcinoma has a better prognosis than squamous cell cancer.

Adenocarcinoma may develop in cases of Barrett's esophagitis.

Other tumors. Small cell cancer, melanoma, adenoid cystic cancer (cylindroma), carcinosarcoma, pseudosarcoma, lymphoma and metastatic tumors.

- Small cell cancer shows neuroendocrine features and may secrete ADH, ACTH, and calcitonine. Prognosis is poor.
- Mucoepidermoid cancer is rarely seen. It is common in old age and mostly localized in the middle–lower parts of the esophagus.

10.1.2 General Presentation

This disease is asymptomatic in its early stages. However some signs (that can seem insignificant to patients) may be very important.

- The esophagus has a very rich lymphatic and nerve supply. Therefore, any tumor may cause segmental paralysis at that site and result in minimal swallowing difficulties. Retrosternal filling is then felt by the patient, who tries to tolerate this by drinking water. These findings form part of the daily routine and are insignificant to most patients.
- In case organic obstruction occurs, patients tend to chewing the food more than before and will eat fluidy foods unaware of the obstruction. That is why most patients present with advanced metastatic stage.

Dysphagia is the most important finding. It is the first sign in 98% of cases. Dysphagia should not be mixed with odynophagia.
Retrosternal pain spreading to the neck, back and epigastric region, especially with swallowing, shows the infiltration of the tumor into surrounding organs.
Weight loss, anorexia, vomiting and pyrosis are common signs. Lower-region tumors may be mixed with signs of gastric ulcer. Tumor invasions or metastases cause respiratory system complications. Aspiration pneumonia and tracheoesophageal fistulas are dramatic clinical situations.
Hoarseness may be seen due to recurrent laryngeal nerve involvement. In addition, minor GIS bleeding may be observed. Symptoms related to metastases are common in advanced stages.

10.1.3 Staging

Primary Tumor (T)* (Fig. 10.2) [3]

TX: Primary tumor cannot be assessed
T0: No evidence of primary tumor
Tis: High-grade dysplasia**
T1: Tumor invades lamina propria or submucosa
T1a: Invasion of lamina propria or muscularis mucosa
T1b: Invasion of submucosa
T2: Tumor invades muscularis propria
T3: Tumor invades adventitia
T4: Tumor invades adjacent structures
T4a: Resectable tumor invading pleura, pericardium, or diaphragm
T4b:Unresectable tumor invading other adjacent structures such as aorta, vertebral body, trachea etc.
*At least maximal dimension of tumor must be recorded; multiple tumors require the T(m) suffix.
**High-grade dysplasia includes all noninvasive neoplastic epithelia that was formerly called carcinoma in situ, a diagnosis that is no longer used for columnar mucosa anywhere in the gastrointestinal tract.

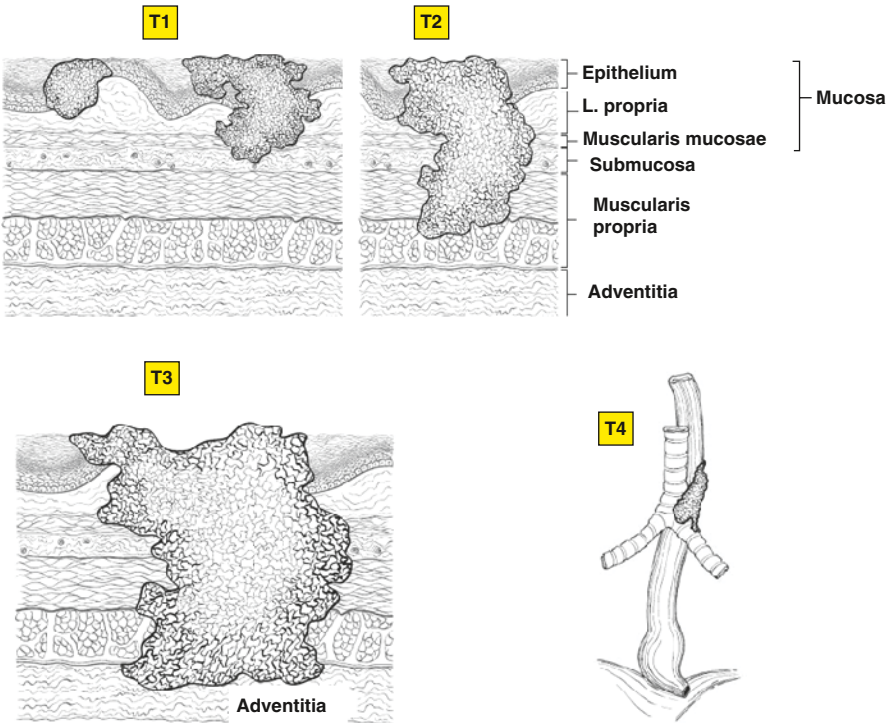

Fig. 10.2 T staging in esophageal cancer (from [35], pp 82, 83, Figs. 9.3–9.5, reproduced with the permission from the American Joint Committee on Cancer)

Esophageus Lymphatics (Fig. 10.3) [3]

Cervical esophagus: Scalen, internal jugular, upper and lower cervical, periesophagial, supraclavicular lymph nodes.
Upper thoracic esophagus: Upper periesophagiogastric LN at the level of azygos vein
Middle thoracic esophagus: Subcarinal LN
Lower thoracic esophagus: Lower periesophagiogastric LN below the level of azygos vein
Esophagogastric region: Lower periesophagiogastric LN below the level of azygos vein, diaphragmatic, pericardiac, left perigastric, celiac

Regional Lymph Nodes (N) (Fig. 10.4)

NX: Regional lymph nodes cannot be assessed
N0: No regional lymph node metastasis
N1: Metastasis in 1-2 regional lymph nodes
N2: Metastasis in 3-6 regional lymph nodes
N3: Metastasis in seven or more regional lymph nodes
*Number must be recorded for total number of regional nodes sampled and total number of reported nodes with metastasis

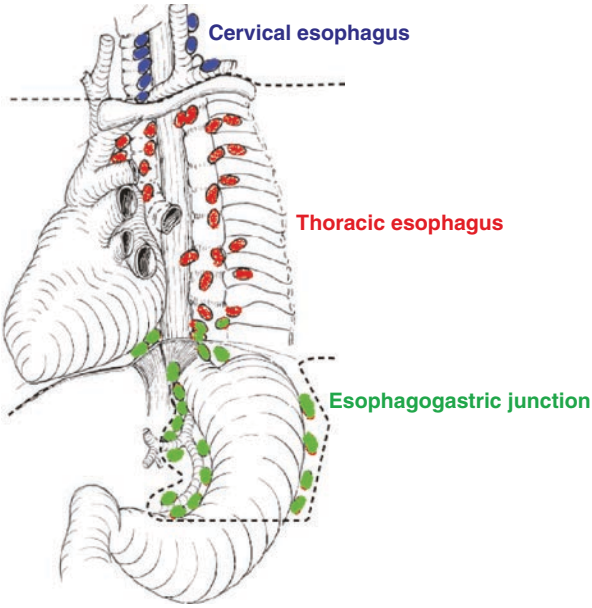

Fig. 10.3 Esophageal lymphatics (from [35], p 80, Fig. 9.2, reproduced with the permission from the American Joint Committee on Cancer)

Distant metastasis (M)
MX: distant metastasis cannot be assessed
M0: no distant metastasis
M1: distant metastasis

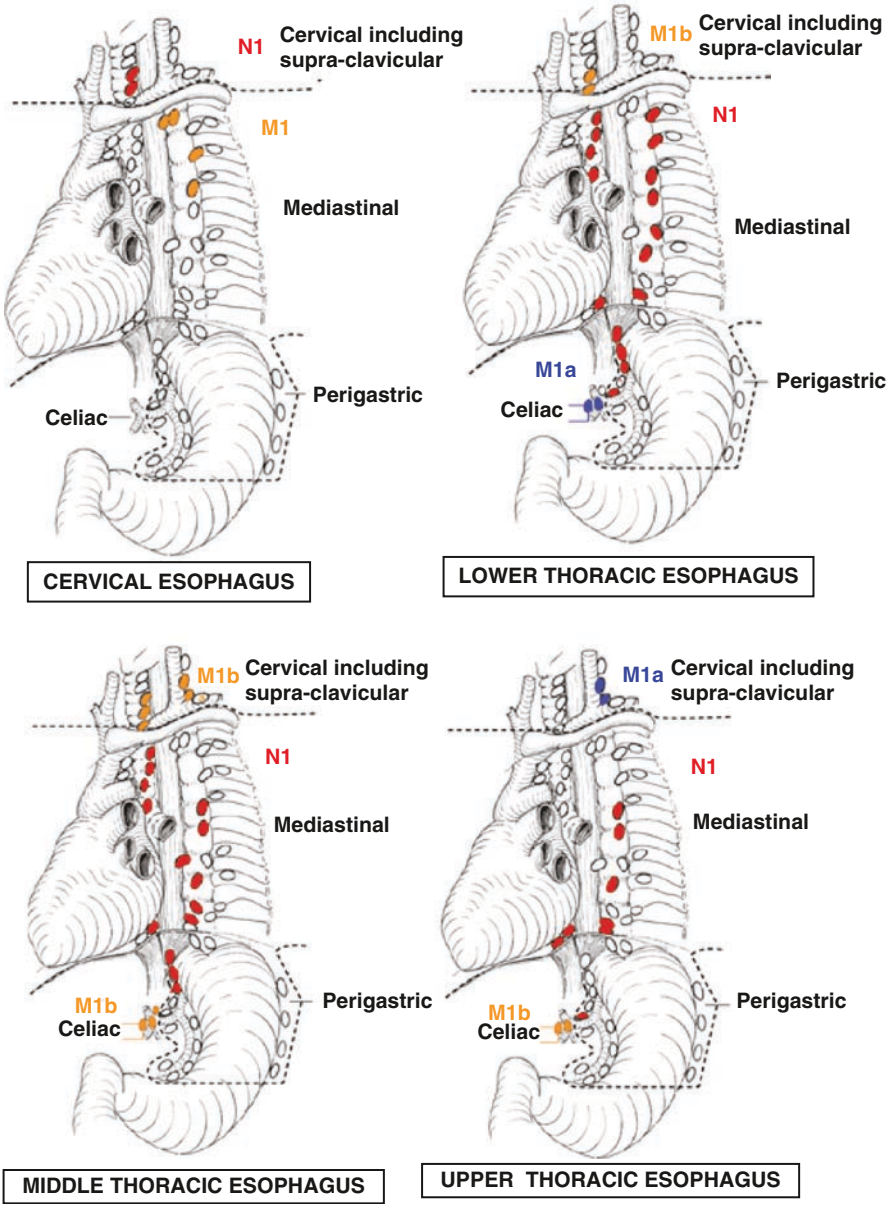

Fig. 10.4 N staging in esophageal cancer (from [35], pp 84–87, Figs. 9.6–9.9, reproduced with the permission from the American Joint Committee on Cancer)

Location of Primary:

Cervical esophagus: between hypopharynx and thoracic inlet (sternal notch)
Upper thoracic esophagus: between thoracic inlet and lower border of azygos vein.
Middle thoracic esophagus: between azygos vein and inferior pulmonary veins.
Lower thoracic esophagus/esophagogastric junction: between inferior pulmonary veins and inferiorly by the stomach.

AJCC Stage Groups

Squamous cell cancer*

Stage	T	N	M	Grade	Tumor Location**
Stage 0	Tis	0	0	1, X	Any
Stage IA	1	0	0	1, X	Any
Stage IB	1	0	0	2, 3	Any
	2-3	0	0	1, X	Lower, X
Stage IIA	2-3	0	0	1, X	Upper, middle
	2-3	0	0	2-3	Lower, X
Stage IIB	2-3	0	0	2-3	Upper, middle
	1-2	1	0	Any	Any
Stage IIIA	1-2	2	0	Any	Any
	3	1	0	Any	Any
	4a	0	0	Any	Any
Stage IIIB	3	2	0	Any	Any
Stage IIIC	4a	1-2	0	Any	Any
	4b	Any	0	Any	Any
	Any	3	0	Any	Any
Stage IV	Any	Any	1	Any	Any

*Or mixed histology including a squamous component.

**Location of the primary cancer site is defined by the position of the upper (proximal) edge of the tumor in the esophagus

AJCC Stage Groups

Adenocarcinoma

	T	N	M	Grade
Stage 0	Tis	0	0	1, X
Stage IA	1	0	0	1-2, X
Stage IB	1	0	0	3
	2	0	0	1-2, X

(*continued*)

(*continued*)

	T	N	M	Grade
Stage IIA	2	0	0	3
Stage IIB	3	0	0	Any
	1-2	1	0	Any
Stage IIIA	1-2	2	0	Any
	3	1	0	Any
	4a	0	0	Any
Stage IIIB	3	2	0	Any
Stage IIIC	4a	1-2	0	Any
	4b	Any	0	Any
	Any	N3	0	Any
Stage IV	Any	Any	1	Any

10.1.4 Treatment Algorithm

Stage I–III, resectable, surgery ± RT [5]
(RT: surgical margin (+) or close)
Alternative → neoadjuvant chemoradiotherapy + surgery
(Chemoradiotherapy, 5-FU + cisplatin, 50 Gy)
(T2N0M0 cases, PNI (+), LVI (+) or age <40, neoadjuvant chemoradiotherapy may be added)
Alternative → definitive chemoradiotherapy
(Chemoradiotherapy, 5-FU + cisplatin, 50 Gy)
(particularly for cervical esophageal cancers)

Stage I–II–III, inoperable [5]
Definitive chemoradiotherapy (chemoradiotherapy, 5-FU + cisplatin, 50 Gy)

Stage IV
Definitive chemoradiotherapy, or
RT alone, or
Chemotherapy, or
Best supportive care

10.1.5 Radiotherapy

The patient is simulated in the supine position. Oral barium contrast solution is used to visualize the esophagus and the site of the tumor (the narrowed part of the esophagus due to the tumor).

Conventional RT Fields (Fig. 10.5)

Cervical esophagus RT
Superior: 5 cm proximal to tumor + supraclavicular LN + upper mediastinal LN
Inferior: 5 cm distal to tumor
Lateral: tumor + 2.5–3 cm + mediastinal LN + 2/3 of clavicle for SCF LN.
Middle esophagus RT
Superior: 5 cm proximal to tumor + upper mediastinal LN
Inferior: 5 cm distal to tumor + mediastinal LN
Lateral: tumor + 2.5–3 cm + mediastinal LN

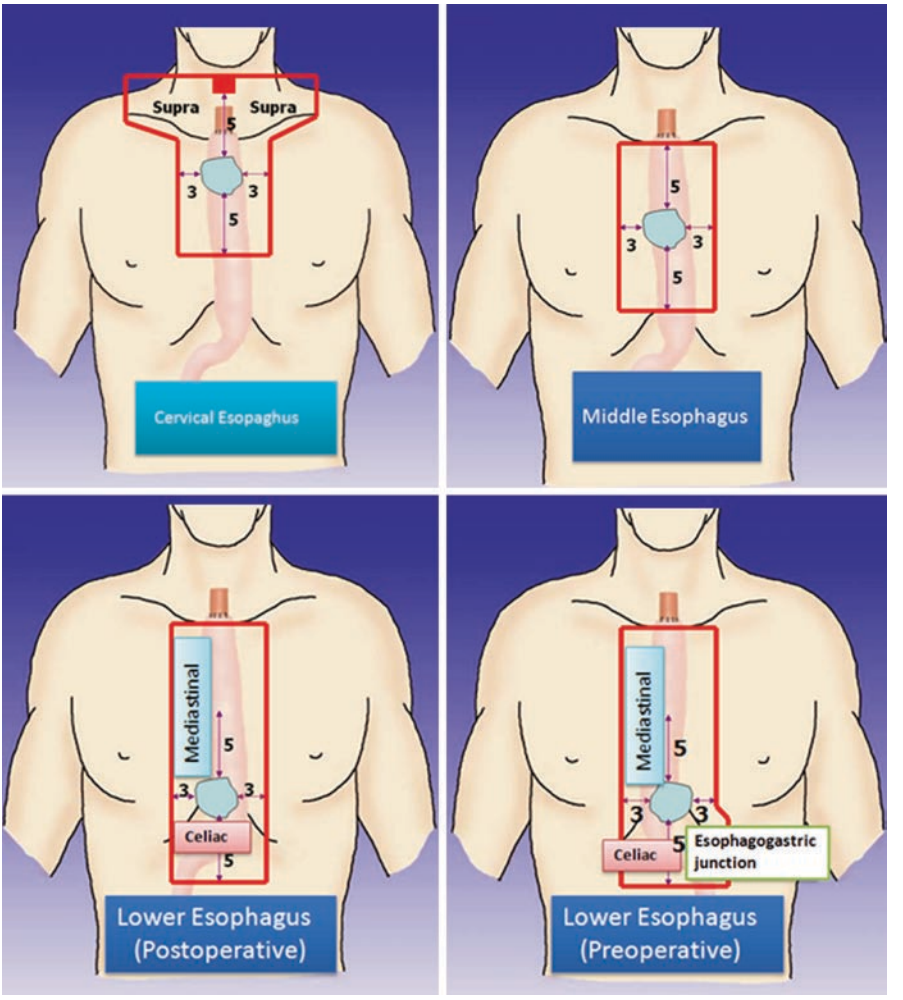

Fig. 10.5 RT fields in esophageal tumors

Lower esophagus RT
Superior: 5 cm proximal to tumor + mediastinal LN
Inferior: 5 cm distal to tumor + mediastinal LN + celiac LN (until L1–2 vertebrae)
Lateral: tumor + 2.5–3 cm + mediastinal LN

- Anterior–posterior field is used until 45 Gy, then 50.4 Gy by oblique or three fields (one anterior, two posterior-oblique fields) by sparing the spinal cord

Conformal RT volumes (Fig. 10.6) [6]

GTV: tumor + involved lymph nodes (nodal GTV may be separately delineated)
CTV: GTV + 1 cm (lateral) + 3 cm (superior/inferior)
PTV: CTV + 1 cm

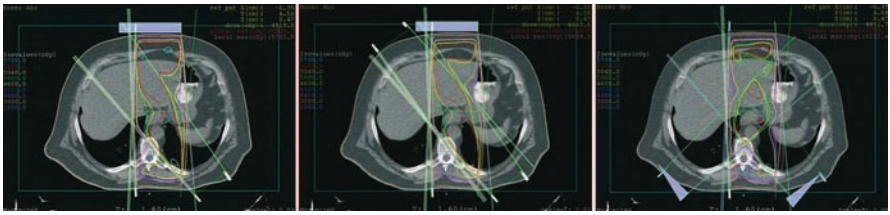

Fig. 10.6 Conformal RT volumes in esophageal cancer [36, p 520, Fig. 20.5a–c]

10.1.6 Selected Publications

Hong Kong, 1993 → 60 patients with curative resection; 30 each were randomized into the radiotherapy group (CR + R) and the control group (CR). Seventy patients with palliative resection; 35 each were randomized into the radiotherapy group (PR + R) and the control group (PR).

- Patients receiving postoperative radiotherapy had lower survival due to irradiation-related death and the early appearance of metastatic diseases.

Fok M (1993) Postoperative radiotherapy for carcinoma of the esophagus: a prospective, randomized controlled study. Surgery 113(2):138–147

Scandinavian trial, 1992 → 186 patients were randomized to four treatment groups: group 1, surgery alone; group 2, preoperative chemotherapy (cisplatin and bleomycin) and surgery; group 3, preoperative irradiation (35 Gy) and surgery; group 4, preoperative chemotherapy, radiotherapy, and surgery.

- Preoperative irradiation had a beneficial effect on intermediate-term survival, whereas the chemotherapy did not influence survival.

Nygaard K (1992) Pre-operative radiotherapy prolongs survival in operable esophageal carcinoma: a randomized, multicenter study of pre-operative radiotherapy and chemotherapy. The second Scandinavian trial in esophageal cancer. World J Surg 16(6):1104–1109; discussion 1110

Scotch, 1992 → 176 patients were randomly assigned to preoperative radiotherapy or surgery alone. Patients assigned to the radiotherapy arm received 20 Gy in ten fractions using parallel opposed 4 MV beams.

- Low-dose preoperative radiotherapy offered no advantage over surgery alone.

Arnott SJ (1992) Low dose preoperative radiotherapy for carcinoma of the oesophagus: results of a randomized clinical trial. Radiother Oncol 24(2):108–113

Metaanalysis, 2005 → 1,147 patients from five randomized trials were used to assess whether preoperative radiotherapy improves overall survival. Median follow-up was 9 years.

- The hazard ratio (HR) of 0.89 (95% CI 0.78–1.01) suggests an overall reduction in the risk of death of 11% and an absolute survival benefit of 3% at 2 years and 4% at 5 years. This result is not conventionally statistically significant ($p = 0.062$).
- There was no clear evidence that preoperative radiotherapy improves the survival of patients with potentially resectable esophageal cancer.

Arnott SJ (2005) Preoperative radiotherapy for esophageal carcinoma. Cochrane Database Syst Rev (4):CD001799

CALGB 9781/RTOG 97-16, 2008 → patients were randomized to treatment with either surgery alone or cisplatin (100 mg/m^2) and 5FU (1,000 mg/m^2/day × 4 days) on weeks 1 and 5 concurrent with radiation therapy (50.4 Gy to 1.8 Gy/fraction over 5.6 weeks) followed by esophagectomy with lymph node dissection.

- This trial demonstrated a survival advantage with the use of chemoradiation therapy followed by surgery in the treatment of esophageal cancer. The observed survival difference was statistically significant and suggested that trimodality therapy is an appropriate standard of care for patients with this disease.

Tepper J et al (2008) Phase III trial of trimodality therapy with cisplatin, fluorouracil, radiotherapy, and surgery compared with surgery alone for esophageal cancer: CALGB 9781. J Clin Oncol 26(7):1086–1092

TROG/AGITG, 2005 → 128 patients were randomly assigned to surgery alone and 128 patients to surgery after 80 mg/m^2 cisplatin on day 1, 800 mg/m^2 fluorouracil on days 1–4, with concurrent radiotherapy of 35 Gy given in 15 fractions.

- Preoperative chemoradiotherapy with cisplatin and fluorouracil did not improve progression-free or overall survival for patients with resectable esophageal cancer compared with surgery alone.

Burmeister BH et al (2005) Surgery alone versus chemoradiotherapy followed by surgery for resectable cancer of the oesophagus: a randomised controlled phase III trial. Lancet Oncol 6(9):659–668

Ireland, 1996 → patients assigned to multimodal therapy received two courses of chemotherapy (fluorouracil and cisplatin) and radiotherapy (40 Gy, administered in 15 fractions beginning concurrently with the first course of chemotherapy), followed by surgery.

- Multimodal treatment was found to be superior to surgery alone for patients with resectable adenocarcinoma of the esophagus.

Walsh TN (1996) A comparison of multimodal therapy and surgery for esophageal adenocarcinoma. N Engl J Med 335(7):462–467

EORTC, 1997 → the preoperative combined therapy consisted of radiotherapy, in a dose of 18.5 Gy delivered in five fractions of 3.7 Gy for 2 weeks, and cisplatin administered before the first day of radiotherapy. The surgical plan included one-stage en bloc esophagectomy and proximal gastrectomy by the abdominal and right thoracic routes, to be performed immediately after randomization in the group assigned to surgery alone and 2–4 weeks after the completion of preoperative chemoradiotherapy in the group assigned to combined therapy.

- Preoperative chemoradiotherapy did not improve overall survival, but it prolonged disease-free survival and survival free of local disease.

Bosset JF et al (1997) Chemoradiotherapy followed by surgery compared with surgery alone in squamous-cell cancer of the esophagus. N Engl J Med 337(3):161–167

FFCD 9102, 2007 → 259 patients with operable T3N0-1M0 thoracic esophageal cancer. Patients received two cycles of fluorouracil (FU) and cisplatin and either conventional (46 Gy in 4.5 weeks) or split-course (15 Gy, days 1–5 and 22–26) concomitant radiotherapy. Patients with response were randomly assigned to surgery (arm A) or continuation of chemoradiation (arm B; three cycles of FU/cisplatin and either conventional [20 Gy] or split-course [15 Gy] radiotherapy).

- There was no benefit from the addition of surgery after chemoradiation compared with the continuation of additional chemoradiation in patients who responded to chemoradiation.

Bedenne L (2007) Chemoradiation followed by surgery compared with chemoradiation alone in squamous cancer of the esophagus: FFCD 9102. J Clin Oncol 25(10):1160–1168

Germany, 2005 → 172 patients with locally advanced squamous cell carcinoma of the esophagus were randomly allocated to either induction chemotherapy followed by chemoradiotherapy (40 Gy) followed by surgery, or the same induction chemotherapy followed by chemoradiotherapy (at least 65 Gy) without surgery.

- Adding surgery to chemoradiotherapy improved local tumor control but did not increase survival of patients with locally advanced esophageal SCC.

Stahl M et al (2005) Chemoradiation with and without surgery in patients with locally advanced squamous cell carcinoma of the esophagus. J Clin Oncol 23(10):2310–2317

Shandong randomized trial, 2006 → 269 patients with resectable esophageal cancer in the chest were randomized into two groups: 135 in the surgery group and 134 in the radiotherapy group.

- The results with late course accelerated hyperfractionated conformal radiotherapy alone were found to be comparable to those achieved by radical surgery for patients with resectable esophageal cancer in the chest.

Sun XD (2006) Randomized clinical study of surgery versus radiotherapy alone in the treatment of resectable esophageal cancer in the chest. Zhonghua Zhong Liu Za Zhi 28(10):784–787

RTOG 85-01, 1992 → patients with squamous cell or adenocarcinoma of the esophagus, T1–3 N0–1 M0. Combined modality therapy ($n=134$): 50 Gy in 25 fractions over 5 weeks, plus cisplatin and fluorouracil. In the randomized study, combined therapy was compared with RT only ($n=62$): 64 Gy in 32 fractions over 6.4 weeks.

- Combined therapy increased the survival of patients who had squamous cell or adenocarcinoma of the esophagus, T1–3 N0–1 M0, compared with RT alone.

Cooper JS et al (1999) Chemoradiotherapy of locally advanced esophageal cancer: long-term follow-up of a prospective randomized trial (RTOG 85-01). Radiation Therapy Oncology Group. JAMA 281(17):1623–1627

ECOG EST-1282, 1998 → randomization: combined use of 5-FU, mitomycin C, and radiation therapy vs. radiation therapy alone.

- Two- and five-year survivals were 12 and 7% in the radiation alone arm and 27 and 9% in the chemoradiation arm.
- Patients treated with chemoradiation had a longer median survival (14.8 months) compared to patients receiving radiation therapy alone (9.2 months). This difference was statistically significant.

Smith TJ et al (1998) Combined chemoradiotherapy vs. radiotherapy alone for early stage squamous cell carcinoma of the esophagus: a study of the Eastern Cooperative Oncology Group. Int J Radiat Oncol Biol Phys 42(2):269–276

10.2 Gastric Cancer

Gastric cancer is the third most common cancer in the world and the second highest cause of cancer-related mortality [7]. Its incidence is high in Japan, China and Russia, and it is less commonly seen in the USA and Canada. Low socio-economic status, cigarette smoking, and high alcohol consumption are correlated with gastric cancer.

The stomach is an intraperitoneal organ that starts at the T11 vertebra and ends in the duodenum on the right side of the midline.

- It is divided into five anatomic regions (Fig. 10.7):
  The *cardia* surrounds the gastroesophageal junction, and is 1–3 cm long.
  The *fundus* is the proximal part of the stomach.
  The *corpus* is next to the fundus.
  The *antrum* is the angled part of the distal stomach.
  The *pylorus* separates the antrum and duodenum.
- The superomedial border is the lesser curvature and inferolateral border is the greater curvature of the stomach.

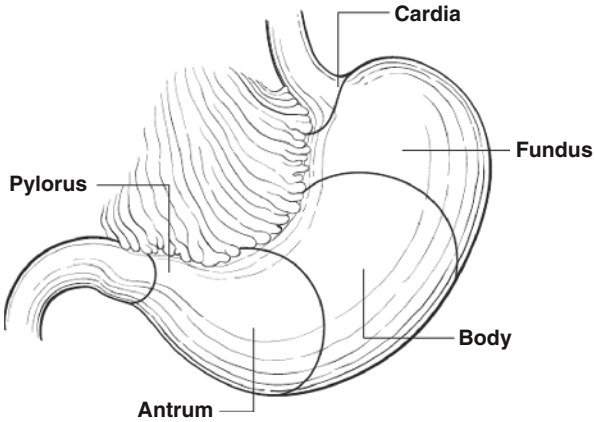

Fig. 10.7 Anatomy of the stomach (from [35], p 90, Fig.10.1, reproduced with the permission from the American Joint Committee on Cancer)

The stomach is histologically composed of five layers from the innermost to the outermost: mucosal, submucosal, muscularis propria, subserosal and serosal.

- The gastric mucosa has three microscopic subtypes: cardiac, fundic, and antral mucosa.
- Submucosa is a loose connective tissue containing elastic leaves, arteries, veins, lymphatic veins and Meissner's neural networks.
- The external muscular layer consists of three layers: outer longitudinal, inner circular, and oblique. The inner circular layer forms a pyloric sphincter at the gastroduodenal junction. Auerbach's (myenteric) plexus is located between the longitudinal and circular layers.

10.2.1 Pathology

There are various classification systems for gastric cancers [8].

1926 Bormann
Type I (polypoid)
Type II (fungating)
Type III (ulcerated)
Type IV (infiltrative)
1953 Stout
Fungating
Penetrating
Superficial
Linitis plastica
Nonspecific
1965 Lauren
Intestinal
Diffuse
1977 Ming
Expansive
Infiltrative
1981 Japanese Society for Gastric Cancer
Papillary
Tubular
Less differentiated
Mucinous
Signet-ring cell
2000 WHO classification
Adenocarcinoma
  Intestinal type
  Diffuse type
Papillary adenocarcinoma
Tubular adenocarcinoma
Mucinous adenocarcinoma
Signet-ring cell carcinoma
Adenosquamous carcinoma
Squamous cell carcinoma
Small cell carcinoma
Undifferentiated carcinoma
Others

Gastric cancers are commonly localized in the antrum/distal stomach (40%), the proximal stomach and the gastroesophageal junction (35%) ,and the corpus (25%).

10.2.2 General Presentation

Early gastric cancers usually have no symptoms or signs. Epigastric fullness, pain, nausea and vomiting may be seen, but none of them are specific for gastric cancers. Symptoms

may be observed in the early period according to the localization of tumor. In addition, bleeding, obstructive findings and masses can be found in physical exams.

- Gastric/perigastric discomfort, pain and fullness
- Rapid weight loss
- Nausea and vomiting
- Fullness after meals
- GIS bleeding, or occult bleeding
- Iron deficiency anemia in two-thirds of patients

- Lymph node metastasis ratio is 18% in serosa (−) cases, and 5-year survival in these cases after resection is over 50%.
- Lymph node metastasis ratio is 80% in serosa (+) cases, and prognosis is very poor in these patients.
- Implantation metastases from seeded tumors may develop when the tumor reaches the serosa. These tumors characteristically implant into the ovaries (*Krukenberg tumor*) and the cul-de-sac in the pelvis (*Blumer's shelf*).
- A left supraclavicular lymph node metastasis is called a *Virchow node*.
- A periumbilical lymph node metastasis is called a *Sister Mary Joseph nodule*.
- An axillary lymph node metastasis is known as an *Irish nodule*.

10.2.3 Staging

Primary Tumor (T) (Fig. 10.8) [9]

Tx: Primary tumor cannot be assessed
Tis: Carcinoma in situ: intraepithelial tumor without invasion of the lamina propria
T1: Tumor invades lamina propria or submucosa
  T1a: invasion of lamina propria or muscularis propria
  T1b: invasion of submucosa
T2: Tumor invades the muscularis propria
T3: Tumor penetrates subserosal connective tissue without invasion of visceral peritoneum or adjacent structures
T4: Tumor invades serosa or adjacent structures
  T4a: Tumor invades serosa (visceral peritoneum)
  T4b: Tumor invades adjacent structures

Regional lymph nodes (N)
N0: no regional lymph node metastasis
N1: metastasis in 1–2 regional lymph nodes
N2: metastasis in 3–6 regional lymph nodes
N3: metastasis in more than 7 regional lymph nodes
  N3a: Metastases in 7–15 regional lymph nodes
  N3b: Metastases in 16 or more regional lymph nodes

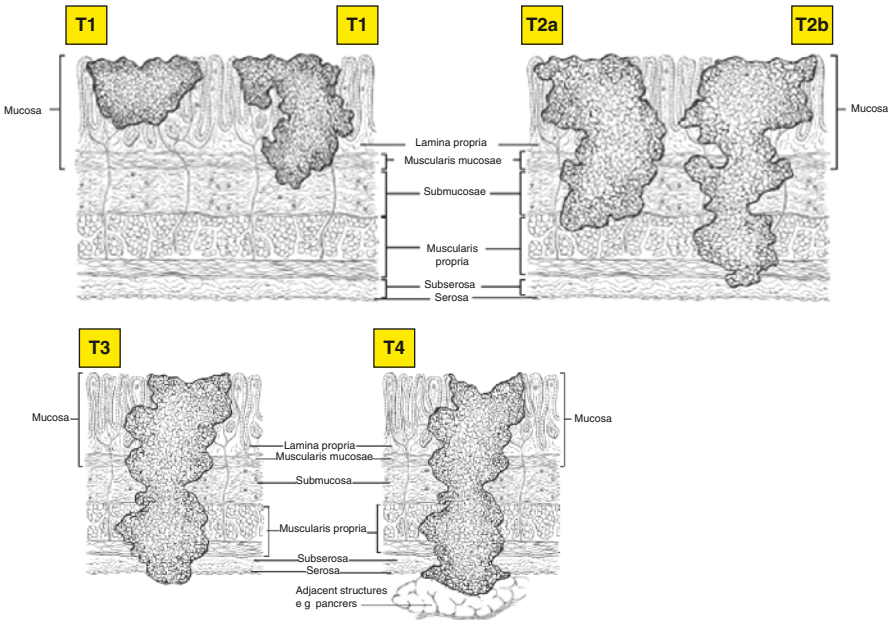

Fig. 10.8 T staging in gastric cancer (from [35], pp 93, 94, Figs. 10.3 and 10.4, reproduced with the permission from the American Joint Committee on Cancer)

AJCC Stage Groups

Stage 0: TisN0M0
Stage IA: T1N0M0
Stage IB: T1N1M0; T2N0M0
Stage IIA: T1N2M0; T2N1M0; T3N0M0
Stage IIB: T4aN0M0; T3N1M0; T2N2M0; T1N3M0
Stage IIIA: T4aN1M0; T3N2M0; T2N3M0
Stage IIIB: T4bN0M0; T4bN1M0; T4aN2M0; T3N3M0
Stage IIIB: T4bN2M0; T4bN3M0; T4aN3M0
Stage IV: Any T, Any N, M1

Japanese staging system for gastric cancer [10]
N1 (1. compartment): involvement of 1, 2, 3, 4, 5, 6 lymph nodes
N2 (2. compartment): involvement of 7, 8, 9, 10, 11 lymph nodes
N3 (3. compartment): involvement of 12, 13, 14, 15, 16 lymph nodes
P parameter
P0: peritoneal involvement (−).
P1: peritoneal involvement (+).
PX: peritoneal involvement is unknown.

Gastric Lymphatics (Fig. 10.9)

1, 2 Perigastric
3, 4 Lesser and greater curvature
5 Suprapyloric (right gastric)
6 Infrapyloric
7 Left gastric
8 Common hepatic
9 Celiac
10 Splenic hilum
11 Splenic
12 Hepaticoduodenal
Lymph nodes accepted as distant metastases: posterior pancreatic (13), sup. mesenteric [14], middle colic (15), paraaortic (16), portal, retroperitoneal

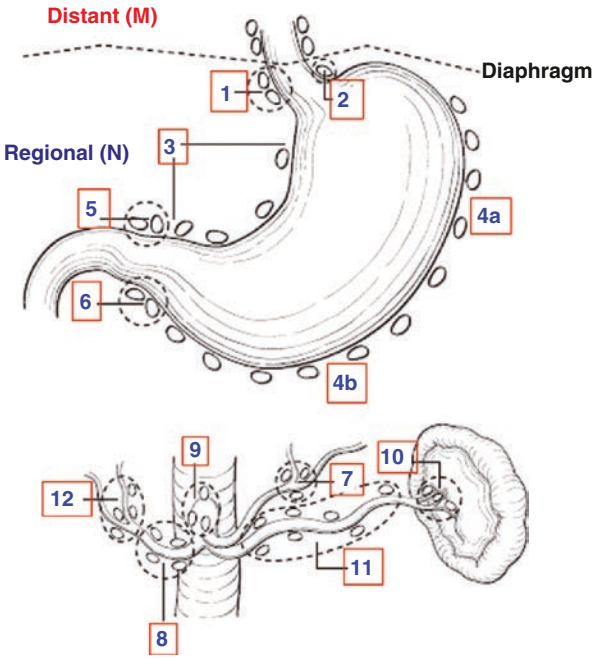

Fig. 10.9 Gastric lymphatics (from [35], p 91, Fig. 10.2a, b, reproduced with the permission from the American Joint Committee on Cancer)

H parameter
H0: hepatic metastasis (−).
H1: hepatic metastasis (+).
HX: hepatic metastasis is unknown.
N parameter
N0: lymphatic involvement (−)
N1: 1. compartment involvement

N2: 2. compartment involvement
N3: 3. compartment involvement
CY (peritoneal cytology) parameter
CY0: peritoneal cytology is benign or indeterminate.
CY1: peritoneal cytology (+).
CYX: peritoneal cytology is not performed.
M parameter
M0: distant metastasis (−) [peritoneum, liver, cytologic metastases]
M1: distant metastasis (+) [other than peritoneum, liver, cytologic metastases]

D0 dissection → inadequate dissection of N1 lymphatics
D1 dissection → complete dissection of N1 lymphatics (LN next to stomach)
D2 dissection → complete dissection of N1+N2 lymphatics (N1 + celiac axis LN)
D3 dissection → complete dissection of N1+N2+N3 lymphatics

Japanese Staging System Groupings:
Stage Ia: T1N0
Stage Ib: T1N1, T2N0
Stage II: T1N2, T2N1, T3N0
Stage IIIa: T4N0, T3N1, T2N2
Stage IIIb: T4N1, T3N2
Stage IV: H1, P1, CY1, M1, N3

Will Rogers phenomenon. The stage determined by the AJCC staging system may differ from the Japanese nodal–anatomic staging system due to extensive lymph node dissection in the latter. This may cause upstaging, and is known as the Will Rogers phenomenon.

10.2.4 Treatment Algorithm

Treatment Algorithm for Gastric Cancer [11,12]

Stage IA, Stage IB (no invasion beyond muscularis propria (−) T2N0)
Surgery alone
Stage IB (T1N1 or invasion beyond muscularis propria (+) T2N0)
Stage II–IV, M0
Surgery + one cycle CT + concurrent chemoradiotherapy with second cycle of CT
(RT → 45 Gy) (CT → 5-FU + leucovorin)
Stage I–IV, M0 (unresectable or inoperable)
Concurrent chemoradiotherapy
(RT → 45 Gy) (CT → 5-FU + leucovorin)
Alternative → CT alone (if RT is not given)

Low KPS → best supportive care
RT alone for palliative purposes, but no effect on survival
M1
Palliative CT ± RT or palliative surgery

Prognostic factors

- Patient age: poor prognosis in the young.
- Tumor stage: invasion depth and lymph node metastasis.
- Localization: prognosis is better in lower gastric tumors.
- Microscopic type and grade: intestinal type is better than diffuse type according to the Lauren classification.
- Inflammatory reaction: extensive inflammation around the tumor is a good prognostic sign.
- Perineural invasion.
- Lymphovascular space invasion.
- Surgical margin, lymph node involvement.
- Surgery: radical LN dissection was reported to be better than standard lymph node dissection (controversial).

- Total gastrectomy or subtotal gastrectomy is used for lower gastric cancers. D2 lymph node dissection may be added.
- Total gastrectomy + D2 lymph node dissection is performed for middle gastric tumors.
- Total gastrectomy + D2 lymph node dissection is standard procedure for upper gastric tumors.
- Paraaortic lymph node dissection is performed for tumors of the fundus or cardia due to extraperitoneal lymph node drainage.

10.2.5 Radiotherapy

Anterior–posterior (Fig. 10.10):

- Superior: above the left diaphragm including the site of anastomosis with at least a 2 cm margin (nearly at the level of the T10–11 vertebrae (left hemidiaphragm)
- Inferior: L3–4
- Lateral: include porta hepatis and gastric bed

RT fields in gastric cancer:

Celiac lymph nodes are at the level of the T12–L1 vertebrae.

Porta hepatis lymphatics are included by extending the field 2 cm right lateral to the paraaortic field at the level of the T11–L1 vertebrae.

Paraaortic lymphatics are included by extending the field below the L3 vertebra.

The superior border may be extended to include the site of anastomosis and the paraesophageal region in proximal tumors located in the cardia.

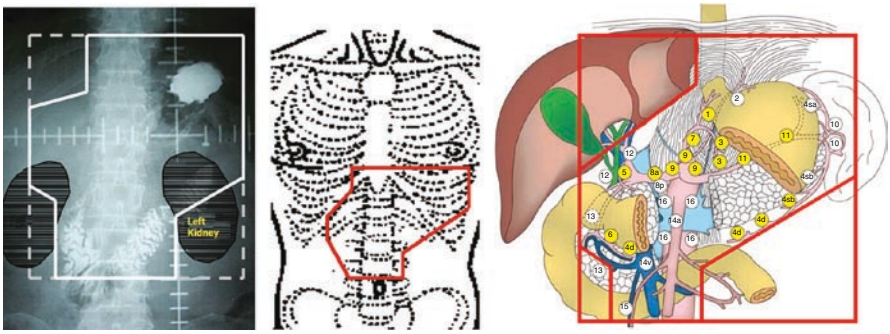

Fig. 10.10 Schematic illustration of radiotherapy fields for gastric cancer (from Fig. 334b [37], p 526, Fig. 21.2, reproduced with the permission from Springer Science and Business Media)

- Simulation is performed in the supine position. Hands should be at the sides if the anterior–posterior fields are used, or above the head if multiple fields are used, such as conformal therapies.
- Oral barium contrast is used to visualize the site of anastomosis, the esophagus and the gastric remnant, as well as the small intestine.
- Kidneys should be visualized by IV contrast material.

Total RT dose: 45 Gy in 1.8 Gy/day.

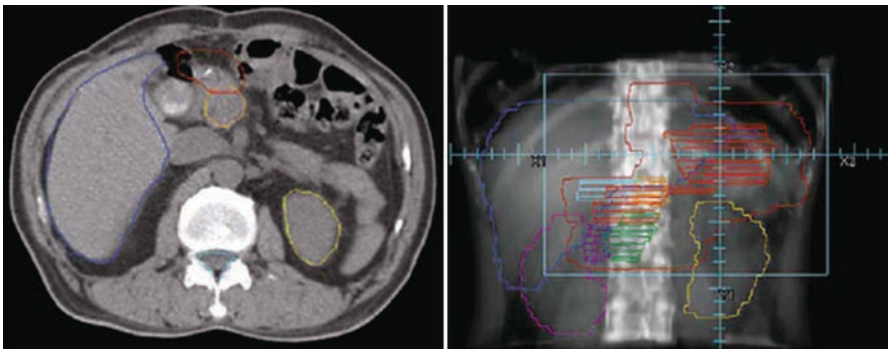

Fig. 10.11 Conformal RT volumes in gastric cancer

Conformal RT Volumes (Fig. 10.11) [13]

CTV1: tumor, or tumor bed
CTV2: greater and lesser curvature lymphatics, celiac axis lymphatics (pancreaticoduodenal, splenic, suprapancreatic, porta hepatis), paraaortic lymph nodes (until the levels of the L3–4 vertebrae) ± paraesophageal region
PTV: CTV + 1 cm
Critical organs: liver, kidneys, small intestines, spinal cord

10.2.6 Selected Publications

Intergroup: INT 0116, 2001 → 556 patients with resected adenocarcinoma of the stomach or gastroesophageal junction were randomly assigned to surgery plus postoperative chemoradiotherapy or surgery alone. The adjuvant treatment was 425 mg/m^2 of fluorouracil plus 20 mg/m^2 of leucovorin (LV) for 5 days, followed by 45 Gy of radiation at 1.8 Gy/day, given 5 days/week for 5 weeks, with modified doses of fluorouracil and LV on the first four and the last three days of radiotherapy. One month after the completion of radiotherapy, two 5-day cycles of fluorouracil (425 mg/m^2) plus LV (20 mg/m^2) were given 1 month apart.

- The median overall survival in the surgery-only group was 27 months, as compared with 36 months in the chemoradiotherapy group; the hazard ratio for death was 1.35 ($p = 0.005$).
- The hazard ratio for relapse was 1.52 ($p < 0.001$).
- Three patients (1%) died from toxic effects of the chemoradiotherapy; grade 3 toxic effects occurred in 41 percent of the patients in the chemoradiotherapy group, and grade 4 toxic effects occurred in 32%.
- Postoperative chemoradiotherapy is standard therapy for all patients at high risk for recurrence of adenocarcinoma of the stomach or gastroesophageal junction who have undergone curative resection.

MacDonald JS et al (2001) Chemoradiotherapy after surgery compared with surgery alone for adenocarcinoma of the stomach or gastroesophageal junction. N Engl J Med 345(10):725–730

Consensus report, 2002 → this consensus report reviewed the following issues:

- Data supporting RT.
- Important clinical and anatomic issues related to RT.
- Details of the practical application of RT to commonly occurring clinical presentations.
- Supportive therapy during and after radiochemotherapy was also discussed in detail.

Smalley SR et al (2002) Gastric surgical adjuvant radiotherapy consensus report: rationale and treatment implementation. Int J Radiat Oncol Biol Phys 52(2):283–293

10.3 Pancreatic Cancer

Pancreatic cancer is the second most common GIS cancer in the USA and has a very poor prognosis [14]. The chances of early diagnosis are very low.

- The pancreas is localized in the posterior abdominal wall, and it is relatively fixed at the second lumbar vertebra.
- It extends transversely from the second part of the duodenal concavity to the splenic hilum.
- It is surrounded by the duodenum, the stomach, the spleen anterosuperiorly, and the duodenum, jejunum, transverse colon and spleen anteroinferiorly.
- Posterior: right renal vessels, inferior vena cava, portal vein, crura of diaphragm, aorta, celiac plexus, thoracic ductus, superior mesenteric vessels, splenic vessels, left renal vessels and left kidney.
- It is 15–20 cm in length, 3.1 cm in width, and 1–1.5 cm thick.
- The pancreas is anatomically divided into five sections: the head, uncinate process, neck, corpus and tail (Fig. 10.12).

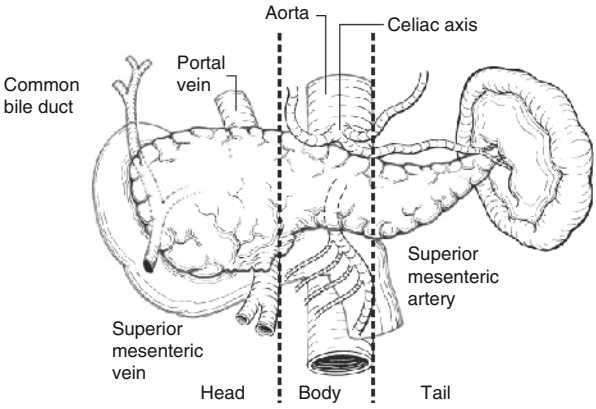

Fig. 10.12 Anatomy of the pancreas (from [35], p 156, Fig. 18.1, reproduced with the permission from the American Joint Committee on Cancer)

Pancreatic head. This is just on the right of the L2 vertebra. A virtual line passing from the portal vein superiorly and the superior mesenteric vein inferiorly forms the border for the head and neck.
Uncinate process. This is the part of the head that extends inferiorly. This section is sometimes never present; if it is, it surrounds the superior mesenteric artery and vein completely.
Pancreatic neck. This covers the portal vein and the superior mesenteric vein; 1.5–2.5 cm in length.
Corpus. This crosses the L1 vertebra.

The major pancreatic duct (Wirsung's canal) starts at the tail and passes through the entire gland, producing many branches. It enters the major duodenal papilla from the second part of the duodenum together with the choledoc duct. The pancreatic duct may also separately enter the duodenum.

The accessory pancreatic duct (Santorini's canal), if present, drains the upper part of the pancreas and then enters the duodenum from the minor duodenal papilla (superior to the main pancreatic duct).

10.3.1 Pathology

Ductal epithelial cells constitute only 5% of the entire pancreatic tissue. However, more than 90% of all exocrine pancreatic cancers are adenocarcinomas originating from these ductal epithelial cells [15].

Macroscopically, the tumor is an irregularly bordered, firm, pale mass. Bleeding and necrosis are not usually present. Ductal cancers are classified according to glandular shape, mucin production and epithelial anaplasia into well, moderate and less differentiated.

- Only 1% of exocrine pancreatic cancers are of the acinic cell type.

Pancreatic cancer is localized in the pancreatic head (60–70%), pancreatic corpus (15–20%), or pancreatic tail (5–10%). Pancreatic cancer is multifocal in 16–30% of cases [15].

10.3.2 General Presentation

The most common symptoms are weight loss, jaundice, pain, anorexia, itching and occult bleeding.

- Most common triad: jaundice, pain, weight loss (weight loss and upper abdominal pain, 75% of cases; jaundice depending on the proximity of the lesion to the choledoc canal, 50–90% of cases)

10.3.3 Staging

Primary Tumor (T) (Fig. 10.13) [16]

TX: Primary tumor cannot be assessed
T0: No evidence of primary tumor
Tis: Carcinoma in situ
T1: Tumor is limited to the pancreas and is 2 cm or less in greatest dimension
T2: Tumor is limited to the pancreas and is more than 2 cm in greatest dimension
T3: Tumor extends beyond the pancreas but without involvement of the celiac axis or the superior mesenteric artery
T4: Tumor involves the celiac axis or the superior mesenteric artery (unresectable primary tumor)

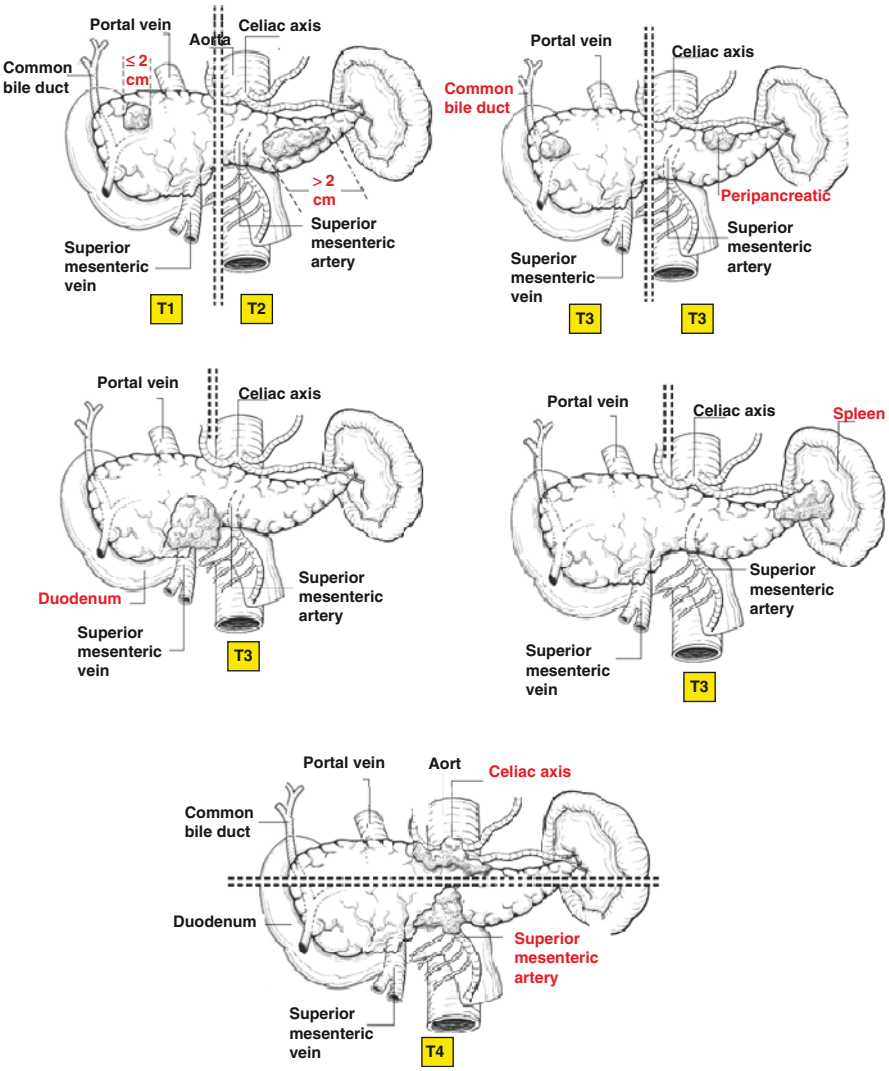

Fig. 10.13 T staging in pancreatic cancer (from [35], pp 158–161, Figs.18.5, 18.6a–c, 18.7, reproduced with the permission from the American Joint Committee on Cancer)

Regional Lymph Nodes (N)

NX: Regional lymph nodes cannot be assessed
N0: No regional lymph node metastasis
N1: Regional lymph node metastasis

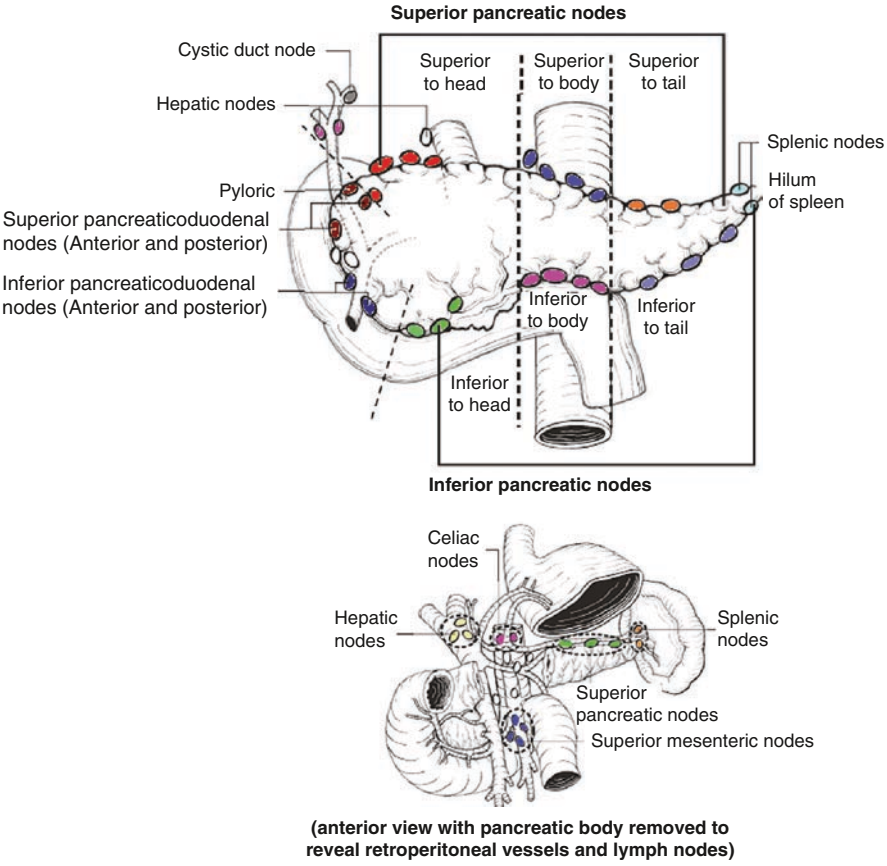

Fig. 10.14 Pancreatic lymphatics

Pancreas head cancers metastasize frequently to the superior pancreatic and posterior pancreaticoduodenal lymph nodes, and they can also involve inferior pancreatic and anterior pancreaticoduodenal lymph nodes (Fig. 10.14).

AJCC Stage Groups

Stage 0: TisN0M0
Stage IA: T1N0M0
Stage IB: T2N0M0
Stage IIA: T3N0M0
Stage IIB: T1N1M0; T2N1M0; T3N1M0
Stage III: T4, any N, M0
Stage IV: Any T, any N, M1

- The peritoneum and liver are the most frequent metastatic sites. Extraabdominal metastasis is frequently to lungs.

10.3.4 Treatment Algorithm

Stage I–II (resectable) [17]
Pancreaticoduodenectomy (Whipple) + chemotherapy ± chemoradiotherapy or RT alone
(RT → 45–50.4 Gy)
(CT → 5-FU/gemcitabine)
Stage III (unresectable) [17]
Chemoradiotherapy or RT alone + CT
Metastatic
Chemotherapy, palliative RT, best supportive care

Whipple operation [18]: this was defined by Allen Whipple in 1935. This operation is the most common surgical approach for periampullary cancers. Pancreatic head, uncinate process, duodenum, distal stomach, proximal jejunum and regional lymph nodes are dissected. Truncal vagotomy is generally not performed. Reconstruction is done by pancreatojejunostomy, hepaticojejunostomy and gastrojejunostomy, respectively. Gastrojejunostomy is done by Roux-en-Y to prevent alkaline reflux.

10.3.5 Radiotherapy

Simulation is done in the supine position with arms upon head. Stomach and duodenum is visualized with oral contrast; kidneys with IV contrast. Liver within field should be shielded as much as possible.

Anterior–Posterior Fields (Fig. 10.15):

- Superior: above T11 vertebra
- Inferior: below L3 vertebra
- Left lateral:
  Pancreatic head tumor → vertebral corpus + 2 cm
  Pancreatic corpus tumor → vertebral corpus + 5 cm
  Pancreatic tail tumor → vertebral corpus + 8 cm (left lateral border should be modified according to the tumor/tumor bed + 3 cm if required)
- Right lateral:
  Pancreatic head → include duodenum (generally costovertebral joint)
  Pancreatic corpus tumor → vertebral corpus + 2 cm
  Pancreatic tail tumor → vertebral corpus + 2 cm

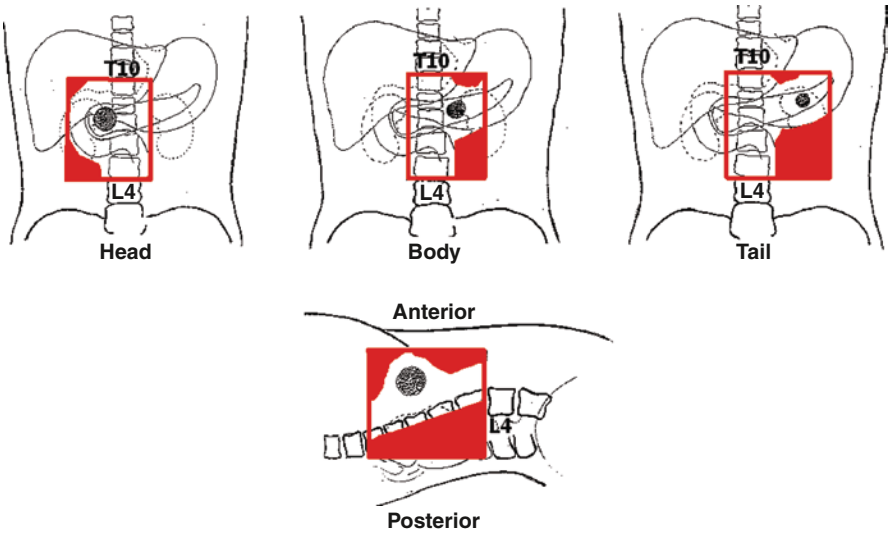

Fig. 10.15 Conventional anterior–posterior fields for different localizations of pancreatic cancer

Lateral Fields

- Anterior: tumor + 2 cm (includes duodenum)
- Posterior: half of vertebral corpus by sparing the spinal cord
- Superior–inferior: same as anterior–posterior fields

The pancreas is between the L1 and L2 vertebrae. Celiac axis is at the level of the T12 vertebra. Superior mesenteric artery is at the level of the L1 vertebra.

Total dose: 45 Gy/1.8 Gy with high-energy photons. Boost dose can be given by adding lateral or oblique fields (50.4–54 Gy).

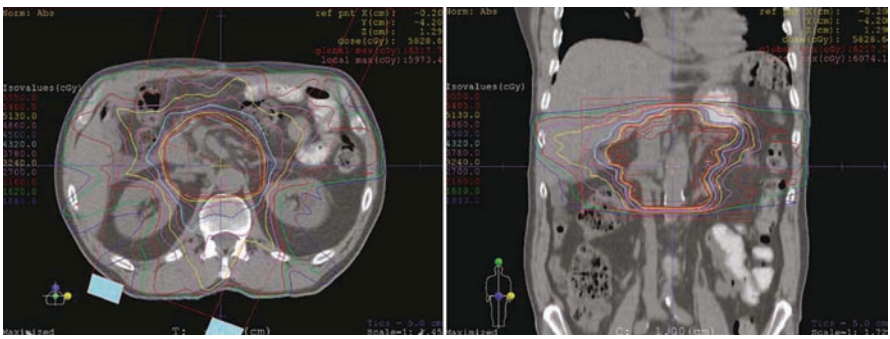

Fig. 10.16 Conformal RT fields in pancreatic cancer

Conformal RT Volumes (Fig. 10.16) [19]

CTV: [tumor/tumor bed + 1–2 cm] + regional lymphatics

- Lymphatics:corpus: upper and lower pancreaticoduodenal, superior and inferior pancreatic, celiac
- Head: corpus lymphatics + porta hepatis lymphatics
- Tail: corpus lymphatics (except pancreaticoduodenal LN) + splenic hilum LN

PTV: CTV + 1–1.5 cm
Critical organs: liver, kidneys, small intestines, spinal cord

10.3.6 Selected Publications

ESPAC-1, 2001 → after resection, 541 patients were randomly assigned to adjuvant chemoradiotherapy (20 Gy in ten daily fractions over 2 weeks with 500 mg/m^2 fluorouracil intravenously on days 1–3, repeated after 2 weeks) or chemotherapy (intravenous fluorouracil 425 mg/m^2 and folinic acid 20 mg/m^2 daily for 5 days, monthly for 6 months). Clinicians randomized the patients into a two-by-two factorial design (observation, chemoradiotherapy alone, chemotherapy alone, or both) or into one of the main treatment comparisons (chemoradiotherapy vs. no chemoradiotherapy or chemotherapy vs. no chemotherapy).

- This study showed no survival benefit for adjuvant chemoradiotherapy but revealed a potential benefit for adjuvant chemotherapy.

Neoptolemos JP et al (2001) Adjuvant chemoradiotherapy and chemotherapy in resectable pancreatic cancer: a randomised controlled trial. Lancet 358(9293):1576–1585

→ *2004 Update*: Adjuvant chemotherapy had a significant survival benefit in patients with resected pancreatic cancer, whereas adjuvant chemoradiotherapy had a deleterious effect on survival.

Neoptolemos JP et al (2004) A randomized trial of chemoradiotherapy and chemotherapy after resection of pancreatic cancer. N Engl J Med 350(12):1200–1210

(*Editors' note*. This trial was seriously criticized due its design and several issues related with RT. Therefore, the results of this trial did not affect practice in North American series.)

EORTC, 1999 → 218 patients were randomized to an observation group vs. a treatment group (RT + chemotherapy).

- Adjuvant RT in combination with 5-FU was found to be safe and well tolerated. However, the benefit in this study was small; routine use of adjuvant chemoradiotherapy was not warranted as standard treatment in cancer of the head of the pancreas or periampullary region.

Klinkenbijl JH et al (1999) Adjuvant radiotherapy and 5-fluorouracil after curative resection of cancer of the pancreas and periampullary region: phase III trial of the EORTC Gastrointestinal Tract Cancer Cooperative Group. Ann Surg 230(6):776–782

GITSG, 1985 → 22 patients randomized to no adjuvant treatment and 21 to combined therapy were analyzed. Median survival for the treatment group (20 months) was significantly longer than that observed for the control group (11 months).

Kalser MH et al (1985) Pancreatic cancer. Adjuvant combined radiation and chemotherapy following curative resection. Arch Surg 120(8):899–903

RTOG 97-04/Intergroup, 2006 → 442 patients. Pre- and post-chemoradiotherapy 5-FU vs. pre- and post-chemoradiotherapy gemcitabine. ChemoRT = 50.4 Gy 1.8 Gy/fraction/day with CI 5-FU, 250 mg/m^2/day during RT for all pts.

- The addition of gemcitabine to postoperative adjuvant 5-FU CRT significantly improved survival.

Regine WF et al (2006) RTOG 9704 a phase III study of adjuvant pre and post chemoradiation (CRT) 5-FU vs. gemcitabine (G) for resected pancreatic adenocarcinoma. J Clin Oncol (2006 ASCO Annual Meeting Proceedings Part I) 24(18S (June 20 Suppl)):4007

GITSG 9273, 1981 →194 patients with locally unresectable adenocarcinoma of the pancreas were randomly assigned to therapy with high-dose (60 Gy) radiation therapy alone, to moderate-dose (40 Gy) radiation + 5-FU, and to high-dose radiation plus 5-FU.

- Median survival with radiation alone was only 5.5 months from the date of diagnosis. Both 5-FU-containing treatment regimens produced a highly significant survival improvement when compared with radiation alone.
- Survival differences between 4,000 rads plus 5-FU and 6,000 rads plus 5-FU were not significant, with an overall median survival of 10 months.

Moertel CG et al (1981) Therapy of locally unresectable pancreatic carcinoma: a randomized comparison of high dose (6000 rads) radiation alone, moderate dose radiation (4000 rads + 5-fluorouracil), and high dose radiation + 5-fluorouracil: The Gastrointestinal Tumor Study Group. Cancer 48(8):1705–1710

GITSG 9283,1988 → this trial compared multidrug chemotherapy [streptozocin, mitomycin, and 5-FU (SMF)] vs. radiation combined with 5-FU followed by the same three-drug SMF combination.

- An improved median survival for the combined-modality therapy (42 weeks) compared with chemotherapy alone (32 weeks) was demonstrated. Overall survival following this combined-modality treatment program (41% at 1 year) was significantly superior to that following SMF chemotherapy alone (19% at 1 year) ($p < 0.02$).
- Combined-modality therapy was found to be superior to either optimal radiotherapy or chemotherapy alone.

Gastrointestinal Tumor Study Group (1988) Treatment of locally unresectable carcinoma of the pancreas: comparison of combined-modality therapy (chemotherapy plus radiotherapy) to chemotherapy alone. J Natl Cancer Inst 80(10):751–755

FFCD-SFRO, 2006 → randomization: chemo-RT (60 Gy in 6 weeks, 2 Gy/fraction, concomitant with 5-FU and cisplatin) or gemcitabine (G) (1,000 mg/m^2 weekly 7q8w) as induction treatment.

- Study was stopped before the planned inclusion due to lower survival with initial chemo-RT when compared to G alone.

Chauffert B (2006) Phase III trial comparing initial chemoradiotherapy (intermittent cisplatin and infusional 5-FU) followed by gemcitabine vs. gemcitabine alone in patients with locally advanced non metastatic pancreatic cancer. J Clin Oncol (2006 ASCO Annual Meeting Proceedings Part I) 24(18S):4008

South Florida, 2008 → intratumoral (32)P was associated with more serious adverse events and did not improve survival for locally advanced unresectable pancreatic cancer.

Rosemurgy A (2008) (32)P as an adjunct to standard therapy for locally advanced unresectable pancreatic cancer: a randomized trial. J Gastrointest Surg 12(4):682–688

10.4 Rectal Cancer

Colon and rectal cancers are the most common gastrointestinal malignant neoplasms. They are the fourth most common of all cancers, and the second most common cause of cancer-related mortality [20].

Colorectal cancer is the most frequent type of cancer after breast and ovary cancer in females, and lung cancer in males.

The rectum is a part of the large intestine; it starts at the promontorium and exits at the anus inferiorly (Fig. 10.17). The rectum extends antero-inferiorly, following the sacral concavity for 13–15 cm, and reaching 2–3 cm below the coccyx. At this level, it turns back along the canal and passes within the levator muscles before ending at the anus, forming an anal canal that is nearly 3–4 cm in length. The length and diameter of the rectum change depending on its fullness.

The rectum is classically divided into three parts: the upper third, the middle third, and the lower third. Each part is practically assumed to be 5 cm in length.

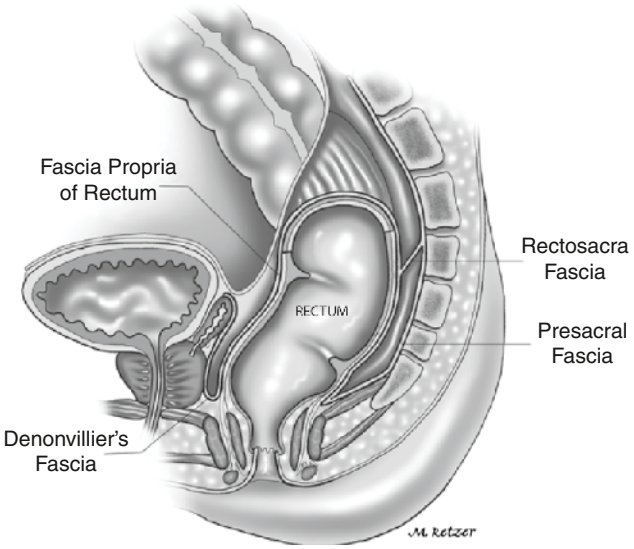

Fig. 10.17 Anatomy of the rectum [Wexner et al. [38], p 3, Fig. 1a]

Rectum–peritoneum relationship:

- The upper third of the rectum is covered with peritoneum on the anterior and lateral surfaces. Only a small part of the thin mesorectum has no peritoneum on the posterior part.
- The middle third of the rectum is covered with peritoneum on its anterior surface; its lateral and posterior surfaces have no peritoneum.
- The peritoneum skips the rectovesical pouch and covers the seminal vesicles and the bladder in males. It forms the rectouterine pouch and passes over the vagina and the uterus in females.
- The lower third of the rectum has no peritoneum.

The peritoneal reflection (Douglas' pouch) that turns anteriorly in front of the rectum is 8–9 cm from the anal verge in males and 5–8 cm in females.

10.4.1 Pathology

Most rectal cancers (95%) are adenocarcinomas [21].

Colorectal Cancers According to the WHO Classification

Adenocarcinoma
Mucinous adenocarcinoma
Signet-ring cell carcinoma

Adenosquamous carcinoma
Squamous cell carcinoma
Undifferentiated carcinoma

10.4.2 General Presentation

Frequent defecation, tenesmus, decrease in stool diameter and volume, fresh blood and mucous discharge in stool may be seen in rectal cancers. Perineal and sacral pain is seen in advanced stages due to surrounding organ invasion.

There are several staging systems in rectal cancer other than the TNM (AJCC) (2002) staging system: Duke's staging (1930) and Astler-Coller staging (modified Duke's) (1954) (Fig. 10.20).

Change in defecation habits. This is the most common sign associated with colorectal cancers. Constipation, diarrhea or constipation–diarrhea may be observed.

- *Bleeding*. The second most common symptom is bleeding, which may be prominent or occult.
- *Rectal mucous discharge*. This may be rectal discharge or it may be mixed with stool or blood. When tumor is close to distal, mucous discharge begins.
- *Morning diarrhea*. Here, mucous and blood collecting in the rectal cancer are discharged as a mixed bloody–mucous material with a foul smell in the morning, termed morning diarrhea. There is no stool in this material.
- *Pain*. Pain is seen in the advanced stages of rectal cancer. The involvement of the sacral plexus causes sacral and sciatic pain.
- A digital rectal exam may reveal a mass in the rectum.
- The carcinoembryonic antigen level may be high, but this should not be used as a diagnostic or screening tool.

10.4.3 Staging

Primary Tumor (T) (Fig. 10.18) [22]

TX: Primary tumor cannot be assessed
T0: No evidence of primary tumor
Tis: Carcinoma in situ; intraepithelial or invasion of the lamina propria*
T1: Tumor invades submucosa
T2: Tumor invades muscularis propria

T3: Tumor invades through the muscularis propria pericolorectal tissues
T4a: Tumor penetrates to the surface of the visceral peritoneum
T4b: Tumor directly invades or adherent to other organs or structures (Fig. 10.19)

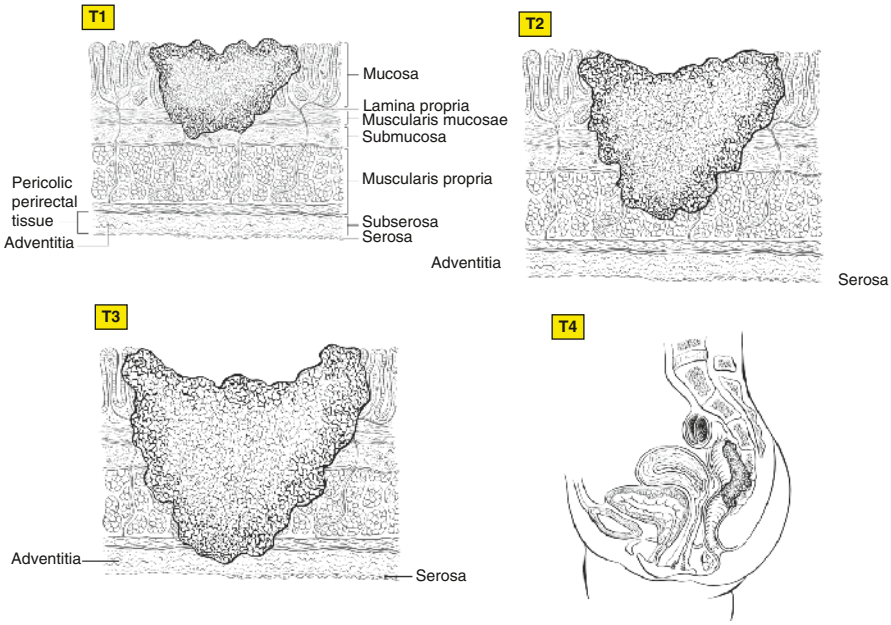

Fig. 10.18 T staging in rectal cancer (from [35], pp 111–113, Figs. 12.4–12.7, reproduced with the permission from the American Joint Committee on Cancer)

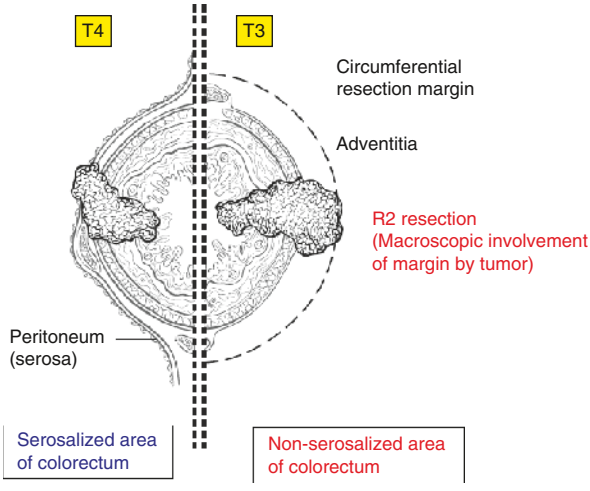

Fig. 10.19 T3–4 staging according to peritoneal status in rectal cancer (from [35], p 116, Fig. 12.11, reproduced with the permission from the American Joint Committee on Cancer)

Regional Lymph Nodes (N)

NX: Regional lymph nodes cannot be assessed
N0: No regional lymph node metastasis
N1: Metastasis in one to three regional lymph nodes
N1a: Metastasis in one regional lymph node
N1b: Metastases in 2-3 regional lymph nodes
N1c: Tumor deposits in the subserosa, mesentry, or nonperitonealized pericolic or perirectal tissues without regional nodal metastases
N2: Metastasis in four or more regional lymph nodes
N2a: Metastasis in 4-6 regional lymph nodes
N2b: Metastasis in seven or more regional lymph nodes

Distant Metastasis (M)

M0: No distant metastasis
M1a: Metastasis confined to one organ or site (e.g. liver, lung, ovary, nonregional node)
M1b: Metastases in more than one organ/site or the peritoneum

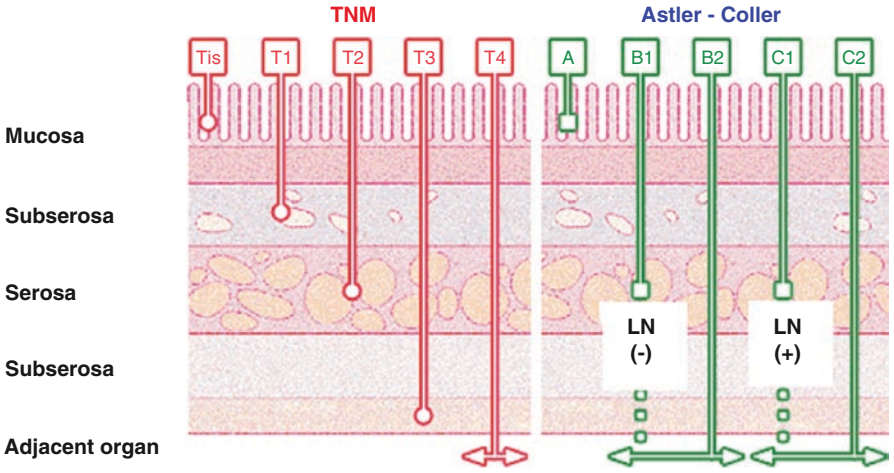

Fig. 10.20 Comparison of the TNM and Astler-Coller rectal cancer staging systems [22–24]

AJCC Stage Groups

Stage 0: TisN0M0
Stage I: T1N0M0; T2N0M0
Stage IIA: T3N0M0
Stage IIB: T4aN0M0

Stage IIC: T4bN0M0
Stage IIIA: T1-2N1-1cM0; T1N2aM0
Stage IIIB: T3-4aN1-1cM0; T2-3N2aM0; T1-2N2bM0
Stage IIIC: T4aN2aM0; T3-4aN2bM0; T4bN1-2M0
Stage IVA: Any T, any N, M1a
Stage IVA: Any T, any N, M1b

10.4.4 Treatment Algorithm

Stage I [25]
Lower one-third rectal cancers → APR
Upper/middle one-third rectal cancers → low anterior resection (LAR)
Highly-selected T1 tumors with good prognostic factors: local excision alone

- Good prognostic factors: tumor size <3 cm, circumferential resection line <1/3, maximum distance from anal verge <8 cm, well-differentiated, surgical margin >3 mm, LVSI (−), PNI (−)
- T1 tumors with good prognostic factors (+), surveillance after surgery

Stage II–III (resectable) [25]
Preoperative 5-FU/RT + transabdominal surgery + adjuvant CT
Stage III (unresectable and T4) [25]
5-FU/RT (then surgery if possible) + CT
Stage IV
CT or surgery or RT or combinations of them

Abdominoperineal resection (APR) (Miles' operation) [26]: tumoral tissue + entire rectum are dissected and a permanent colostomy is opened.

Lower anterior resection (LAR) [26]: tumoral tissue + the upper parts of the rectum are dissected and a permanent colostomy is not opened.

Postoperative RT [27]
Advantages:

- There is no overtreatment with radiation due to pathological confirmation of exact stage.
- RT field is accurately designed since tumoral extension is known.

Disadvantages:

- RT efficacy may decrease due to hypoxic medium after surgery.
- Postoperative adhesions may increase intestinal side effects of RT.
- Field size increases after APR due to the inclusion of the perineal scar in the RT portal.

Preoperative RT [28]
Advantages:
- Large and advanced tumors may be downsized during radiation and the chances of resection may also increase.
- Tumor cells that may be implanted into the surgical region are eradicated.
- Tumor cells that may enter circulation are eradicated and distant metastatic risk decreases.
- Tumor cells are more oxic before surgery and sensitive to radiation.

Disadvantages:
- Overtreatment of early or metastatic tumors
- Delayed surgery and risk of stage advancement
- Postoperative perineal complications may increase

10.4.5 Radiotherapy

Simulation is performed in either the supine or the prone position. The prone position with a full bladder may decrease the small intestinal dose.

- Rectal and vaginal markers are useful during simulation. The perineal scar should be wired after APR.
- Oral contrast may be used to visualize the small intestine, and the bladder is preferably full.

Anterior–posterior fields (Fig. 10.21):

- Superior: between levels L5 and S1
- Inferior: preoperative, tumor + 3 cm; LAR, below obturator foramen or tumor + 3 cm; APR, includes perineal scar
- Lateral: bony pelvis+2 cm

Lateral fields (Fig. 10.22):

- Superior–inferior: same as anterior–posterior fields
- Anterior: ≤T3 tumors, posterior to pubic symphysis; T4 tumors, anterior to pubic symphysis
- Posterior: includes sacrum

Boost field → tumor/tumor bed + 2–3 cm. Sacral concavity should be included in lateral fields.

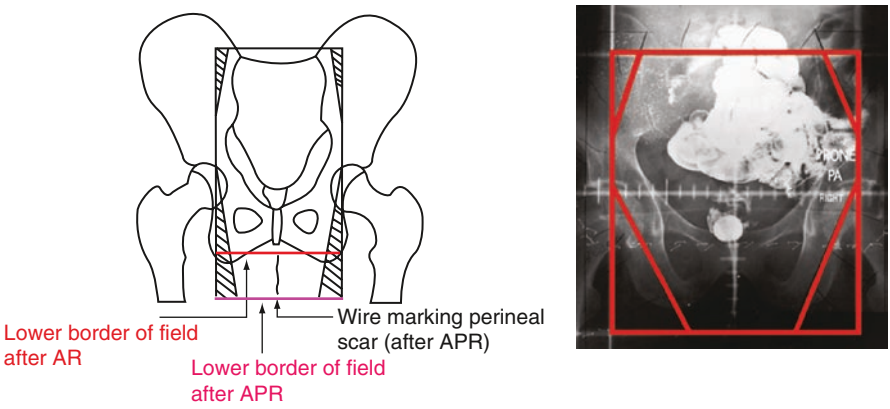

Fig. 10.21 Conventional anterior–posterior RT fields in rectal cancer [37, p 563, Fig. 24.4]

Dose

1.8 Gy/day, total dose: 45 Gy four field-box technique, 5.4 Gy boost may be given.

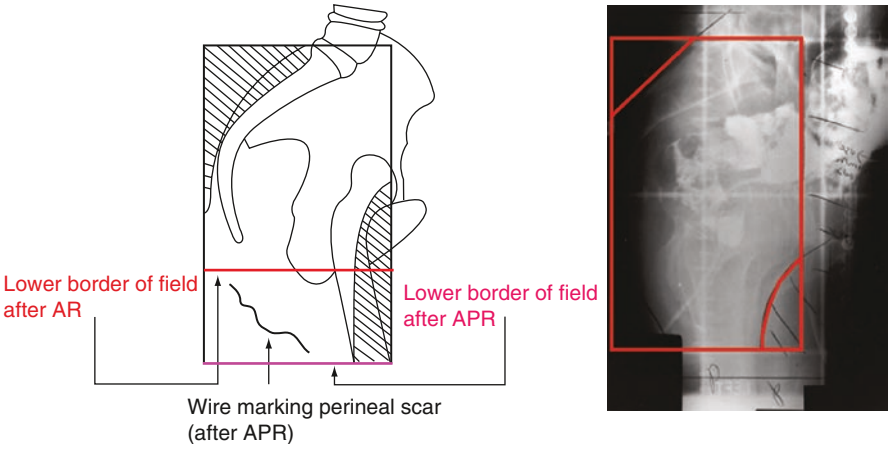

Fig. 10.22 Conventional lateral RT field in rectal cancer [37, p 563, Fig. 24.5]

Conformal RT Volumes [29]

- CTV: tumor/tumor bed + perirectal tissue, presacral region and internal iliac LNs
  A craniocaudal 2 cm margin is added to the tumor.
  One to two centimeters of the bladder and prostate/vagina are included (particularly in T4 cases).
  Anterior wall of the promontorium and sacrum is within the CTV.
- PTV: CTV + 1–1.5 cm

10.4.6 Selected Publications

NSABP R-01, 1988 → the patients were randomized to receive no further treatment (184 patients), postoperative adjuvant chemotherapy with 5-FU, semustine, and vincristine (MOF) (187 patients), or postoperative RT (184 patients).

- Postoperative radiation therapy reduced the incidence of locoregional recurrence, but it failed to affect overall disease-free survival and survival.

Fisher B et al (1988) Postoperative adjuvant chemotherapy or radiation therapy for rectal cancer: results from NSABP protocol R-01. J Natl Cancer Inst 80(1):21–29

NSABP R-02, 2000 → patients were randomized to postoperative adjuvant chemotherapy alone ($n=348$) or chemotherapy with postoperative radiotherapy ($n=346$).

- The addition of postoperative RT to chemotherapy in Dukes' B and C rectal cancer did not alter the subsequent incidence of distant disease, although there was a reduction in locoregional relapse when compared with chemotherapy alone.

Wolmark N et al (2000) Randomized trial of postoperative adjuvant chemotherapy with or without radiotherapy for carcinoma of the rectum: National Surgical Adjuvant Breast and Bowel Project Protocol R-02. J Natl Cancer Inst 92(5):388–396

MRC 3, 1996 → surgery alone ($n=235$) vs. surgery followed 4–6 weeks later by radiotherapy ($n=234$), of 40 Gy in 20 fractions.

- Postoperative radiotherapy delayed and prevented the local recurrence of rectal cancer.

Medical Research Council Rectal Cancer Working Party (1996) Randomised trial of surgery alone versus surgery followed by radiotherapy for mobile cancer of the rectum. Lancet 348(9042):1610–1614

Intergroup INT-0114, *1997* → 1,695 patients were treated with two cycles of chemotherapy followed by chemo-RT and two additional cycles of chemotherapy. Chemotherapy regimens were bolus fluorouracil (5-FU), 5-FU and LV, 5-FU and levamisole, and 5-FU, LV, and levamisole. Pelvic irradiation was given to a dose of 45 Gy to the whole pelvis and a boost to 50.4–54 Gy.

- There was no advantage to LV- or levamisole-containing regimens over bolus 5-FU alone in the adjuvant treatment of rectal cancer when combined with irradiation.

Tepper JE et al (2002) Adjuvant therapy in rectal cancer: analysis of stage, sex, and local control—final report of intergroup 0114. J Clin Oncol 20(7):1744–1750

Intergroup INT-0144, 2006 → after surgery of T3–4, N0, M0 or T1–4, N1, 2M0 rectal adenocarcinoma, 1,917 patients were randomized to bolus FU in two 5-day cycles every 28 days before and after RT plus FU via protracted venous infusion (PVI) during RT; arm 2 (PVI-only arm), PVI 42 days before and 56 days after RT + PVI; or bolus-only arm, with bolus FU + LV in two 5-day cycles before and after XRT, plus bolus FU + LV (levamisole was administered in each cycle before and after RT).

- All arms provided similar relapse-free survivals and OS, along with different toxicity profiles and central catheter requirements.

Smalley SR (2006) Phase III trial of fluorouracil-based chemotherapy regimens plus radiotherapy in postoperative adjuvant rectal cancer: GI INT 0144. J Clin Oncol 24(22):3542–3547

German Rectal Cancer Study, 2004 → preoperative chemoradiotherapy, as compared with postoperative chemoradiotherapy, improved local control and was associated with reduced toxicity but with no improvement in overall survival.

Sauer R et al (2004) Preoperative versus postoperative chemoradiotherapy for rectal cancer. N Engl J Med 351(17):1731–1740

Netherlands, 2007 → 1,861 patients with resectable rectal cancer were randomized between total mesorectal excision (TME) preceded by 5 × 5 Gy or TME alone. No chemotherapy was allowed. Preoperative short-term radiotherapy improved local control in patients with clinically resectable rectal cancer. However, there was no effect on overall survival.

Peeters KC (2007) The TME Trial after a median follow-up of 6 years: increased local control but no survival benefit in irradiated patients with resectable rectal carcinoma. Ann Surg 246(5):693–701

MRC,1996 → preoperative RT reduced the rate of local recurrence of rectal cancer in patients with locally advanced disease.

Medical Research Council Rectal Cancer Working Party (1996) Randomised trial of surgery alone versus radiotherapy followed by surgery for potentially operable locally advanced rectal cancer. Lancet 348(9042):1605–1610

Swedish Rectal Cancer Trial, *2005* → preoperative RT with 25 Gy in 1 week before curative surgery for rectal cancer was found to be beneficial to overall and cancer-specific survival and local recurrence rates after long-term follow-up.

Folkesson J et al (2005) Swedish Rectal Cancer Trial: long lasting benefits from radiotherapy on survival and local recurrence rate. J Clin Oncol 23(24):5644–5650

UK, 1994 → 468 patients randomized to RT (3 × 5 Gy over 5 days within 2 days of operation) followed by surgery, or to surgery alone. Long-term survival was unaffected, but long-term local recurrence was reduced by the addition of low-dose RT to surgery. Perioperative mortality was increased.

Goldberg PA (1994) Long-term results of a randomised trial of short-course low-dose adjuvant pre-operative radiotherapy for rectal cancer: reduction in local treatment failure. Eur J Cancer 30A(11):1602–1606

10.5 Anal Cancer

Anal canal cancers constitute 1% of all colorectal cancers and 10% of all rectal cancers. They are usually observed in those aged 60–65 years. Incidence is 1/100,000 in females and 0.5–0.8/100,000 in males [30].

The rectum forms the anal canal, which is 3–4 cm in length and ends at the anus. The anal canal is defined as either the surgical or the anatomical canal (Fig. 10.23).

Anatomical anal canal: between the anal verge and the dentate line).
Surgical anal canal: 3–4 cm section localized between the anal verge and the anorectal ring.
Anorectal ring: this is felt as a muscular ring during a digital exam, and it is the proximal endpoint of the internal sphincter muscle–puborectal muscle complex.

- It forms the border of the rectum–anal canal.

The length of the anal canal shows individual variations (2–8 cm, mean 3.5–4 cm). These variations are important in cancer surgery. For instance, it is theoretically possible to conserve sphincter function when a tumor is palpated at 5 cm in a patient with a 3 cm anal canal. However, the sphincter cannot be conserved in distal rectal tumors that extend into the anal canal and invade the sphincter muscles.

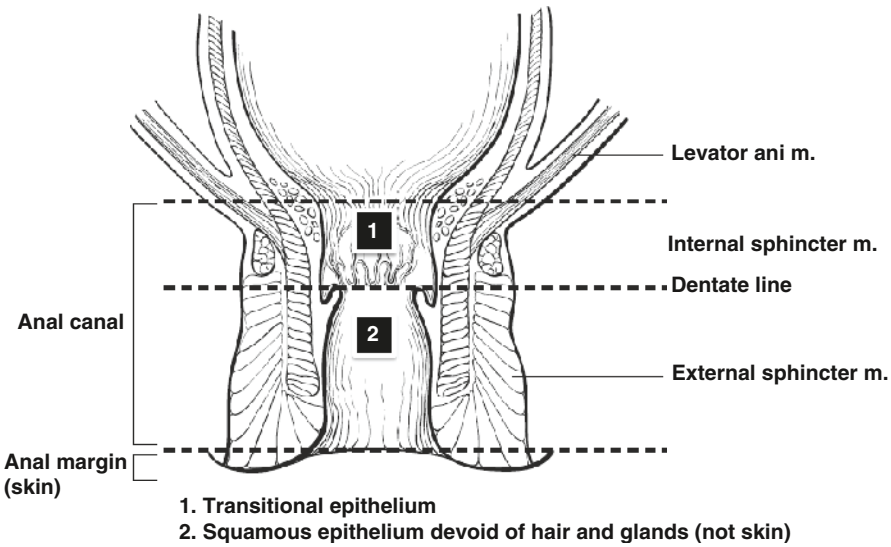

Fig. 10.23 Anatomy of the anal canal

The epithelium proximal to the dentate line is transitional epithelium, while the epithelium distal to it until the anal verge is a special nonkeratinized squamous epithelium with no hair follicles or sweat glands, also termed anoderm.

10.5.1 Pathology

Most anal cancers are squamous cell cancers (~60%), followed by transitional cell cancers (~25%) and adeno cancers (~7%) [31]. Less frequent ones are basaloid cell cancers (cloacogenic cancer) and malignant melanomas. Small cell cancers are very rare but have a high risk of distant metastasis.

Anal cancers occur between the anal verge and 2 cm beyond the dentate line; tumors occurring further from the dentate line are called rectal cancers.

10.5.2 General Presentation

Anal cancers usually give symptoms in their early stages. Bleeding, pain around the anus or feelings of compression in the anal canal, anal itching, anal swelling and changes in bowel habits are the main symptoms.

10.5.3 Staging

Primary Tumor (T) (Fig. 10.24) [32]

TX: Primary tumor cannot be assessed
T0: No evidence of primary tumor
Tis: Carcinoma *in situ* (Bowen's disease, high-grade squamous and anal intraepithelial lesions)
T1: Tumor 2 cm or less in greatest dimension
T2: Tumor more than 2 cm but not more than 5 cm in greatest dimension
T3: Tumor more than 5 cm in greatest dimension
T4: Tumor of any size that invades adjacent organ(s); e.g., vagina, urethra, bladder*
*Direct invasion of the rectal wall, perirectal skin, subcutaneous tissue, or the sphincter muscle(s) is not classified as T4

Anal Canal Lymphatics (Fig. 10.25) [32]

⟶ Perirectal LN
Anorectal
Perirectal
Lateral sacral
⟶ Internal iliac (hypogastric) LN
⟶ Inguinal LN
Superficial inguinal
Deep femoral
⟶ Above dentate line: Internal iliac LN
⟶ Below dentate line: ingunial LN

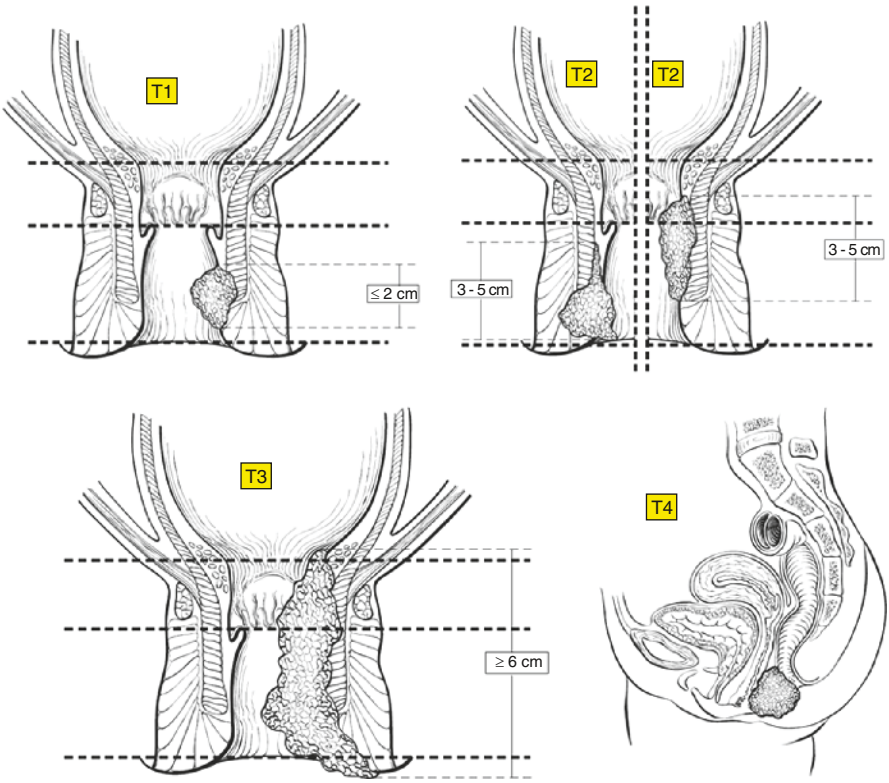

Fig. 10.24 T staging in anal cancer (from [35], p 122, Figs. 13.3 and 13.4, reproduced with the permission from the American Joint Committee on Cancer)

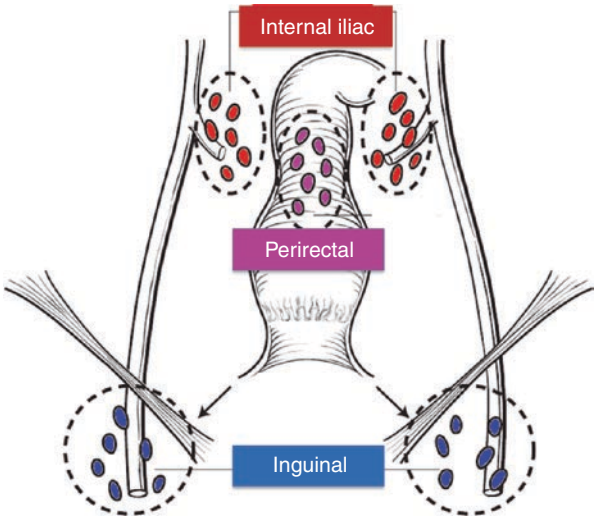

Fig. 10.25 Anal canal lymphatics (from [35], p 121, Fig. 13.2, reproduced with the permission from the American Joint Committee on Cancer)

Regional Lymph Nodes (N) (Fig. 10.26)

NX: regional lymph nodes cannot be assessed
N0: no regional lymph node metastasis
N1: metastasis in perirectal lymph node(s)
N2: metastasis in unilateral internal iliac and/or inguinal lymph node(s)
N3: metastasis in perirectal and inguinal lymph nodes and/or bilateral internal iliac and/or inguinal lymph nodes

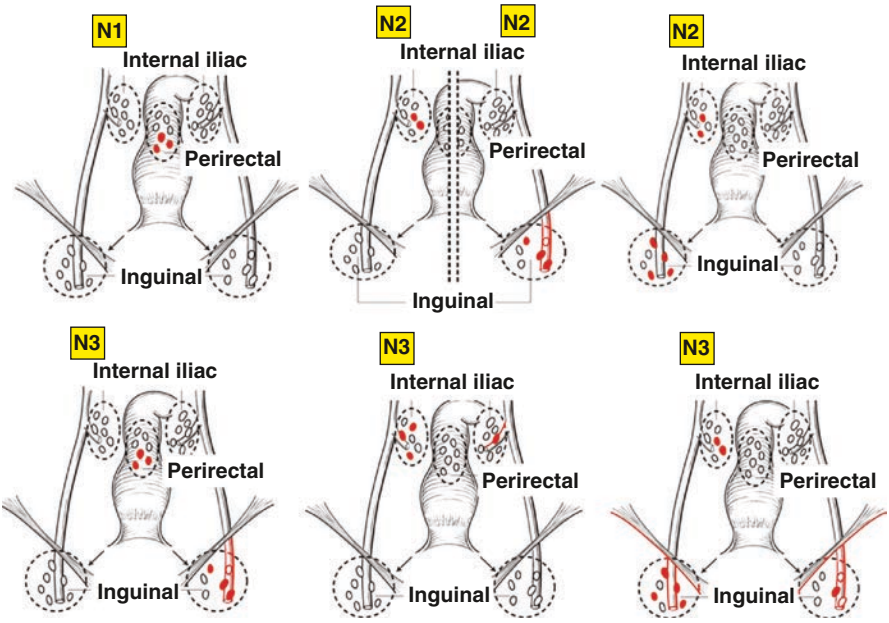

Fig. 10.26 N staging in anal cancer (from [35], pp 123–125, Figs. 13.7, 13.8a, b, 13.9a–c, reproduced with the permission from the American Joint Committee on Cancer)

AJCC Stage Groupings

Stage 0:	TisN0M0
Stage I:	T1N0M0
Stage II:	T2N0M0; T3N0M0
Stage IIIA:	T1N1M0; T2N1M0; T3N1M0; T4N0M0
Stage IIIB:	T4N1M0; Any T, N2M0; Any T, N3M0
Stage IV:	Any T, Any N, M1

10.5.4 Treatment Algorithm

T1 tumor (small and well differentiated) [33]
Local excision

- Tm < 2 cm, well-differentiated, superficially spreading, and negative surgical margin after excision.
- Sphincter invasion in circumferential excision line >40%, chemoradiotherapy should be used due to risk of incontinence after excision.

Stage I–III [33]
Concurrent chemoradiotherapy (CT → mitomycin + 5-FU)
Stage IV
Palliative therapies and their combinations
Recurrence, salvage therapy
APR, or RT if no previous RT history

10.5.5 Radiotherapy

The anal region may be irradiated with various techniques due to the complex anatomy of this region and the inguinal lymphatics. These techniques include wide anterior field–narrow posterior field, the four-field box technique, 3D conformal radiotherapy, and IMRT.

- The aim when using these techniques is to decrease the doses supplied to the genital organs, bladder, small intestine and femur heads, and to increase the doses supplied to deep inguinal lymphatics.
- Femur fractures start at 45 Gy and their incidence increases prominently after 50 Gy.
- Deep inguinal lymph nodes are usually located 5–6 cm from the skin.

Conventional RT Fields in Anal Cancer (Fig. 10.27)

Anterior field until 36 Gy:

- Superior: above sacroiliac joints
- Inferior: below the anal verge or 3 cm below the tumor
- Lateral: medial side of the trochanter major, including inguinal lymph nodes

Anterior field between 36 and 45 Gy

- Superior: below sacroiliac joints.
- Inferior: below the anal verge or 3 cm below the tumor
- Lateral: tips of femur heads

Posterior field until 45 Gy:

- Superior: above sacroiliac joints
- Inferior: below the anal verge or 3 cm below the tumor
- Lateral: tips of femur heads

Anterior–posterior boost field 50.4–54 Gy:

- Tumor/tumor bed + 2.5 cm

Electron boosts are added to inguinal regions (Fig. 10.28).

- LN (−): total dose is completed to 45 Gy.
- LN (+): total dose is completed to 50.4–54 Gy.

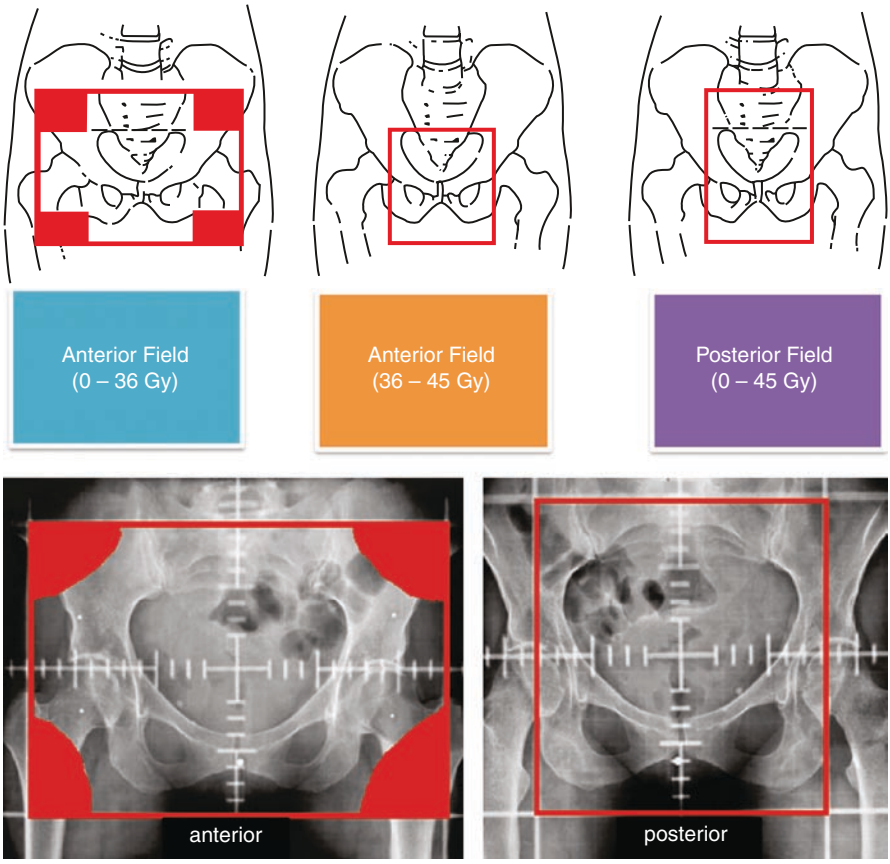

Fig. 10.27 Conventional RT fields in anal cancer (from Fig. 355b–e [39], p 555, Fig. 22.6a–c, reproduced with the permission from the Springer Science and Business Media)

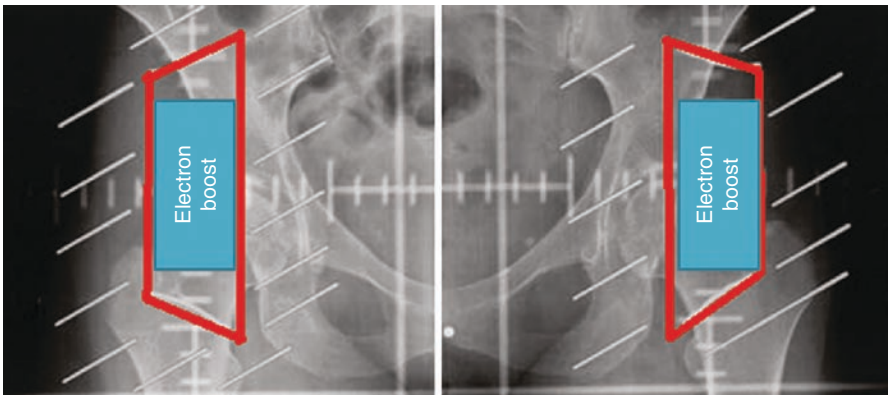

Fig. 10.28 Inguinal boost fields in anal cancer [36, p 555, Fig. 22.6c]

- Simulation is performed in the prone position with arms on chest.
- Anal marker is used to visualize the anal verge.
- Inguinal field may be marked with wires for visualization.
- Palpable inguinal lymph nodes are marked with wires.
- A full bladder is recommended to decrease toxicity to the small intestine.
- The penis is placed cranially to prevent its bolus effect on the scrotum.
- Inguinal electron boost is applied in the supine position.
- High energy X-rays (6–18 MV) are used.
- Inguinal electron boost is applied with suitable electron energies, and bolus may be used if required.

Conformal RT Volumes [34]

CTV: [tumor/tumor bed, pelvic LN, inguinal LN, perianal tissues] + 1–2 cm
PTV: CTV + 1.5 cm

10.5.6 Selected Publications

EORTC, 1997 → 110 patients were randomized between RT alone (45 Gy given in 5 weeks) and a combination of RT and chemotherapy (750 mg/m^2 daily fluorouracil as a continuous infusion and a single dose of mitomycin 15 mg/m^2). After a rest period of 6 weeks, a boost of 20 or 15 Gy was given in cases of partial or complete response, respectively.

- The concomitant use of RT and chemotherapy resulted in a significantly improved locoregional control rate and a reduction in the need for colostomy in patients with locally advanced anal cancer without a significant increase in late side effects.

Bartelink H (1997) Concomitant radiotherapy and chemotherapy is superior to radiotherapy alone in the treatment of locally advanced anal cancer: results of a phase III randomized trial of the European Organization for Research and Treatment of Cancer Radiotherapy and Gastrointestinal Cooperative Groups. J Clin Oncol 15(5):2040–2049

UKCCCR, 1996 → 585 patients were randomized to receive initially either 45 Gy RT over 4–5 weeks or the same regimen of RT combined with 5-FU by continuous infusion during the first and the final weeks of radiotherapy and mitomycin on day 1 of the first course.

- The standard treatment for most patients with epidermoid anal cancer should be a combination of radiotherapy and infused 5-FU and mitomycin, with surgery reserved for those who fail to improve on this regimen.

UK Coordinating Committee on Cancer Research (1996) Epidermoid anal cancer: results from the UKCCCR randomised trial of radiotherapy alone versus radiotherapy, 5-fluorouracil, and mitomycin. UKCCCR Anal Cancer Trial Working Party. Lancet 348(9034):1049–1054

RTOG 87-04, 1996 → 310 patients were randomized to receive either radiotherapy (RT) and fluorouracil (5-FU) or radiotherapy, 5-FU, and mitomycin C.

- Despite greater toxicity, the use of mitomycin C in a definitive chemo-RT regimen for anal cancer was justified, particularly in patients with large primary tumors.

Flam M (1996) Role of mitomycin in combination with fluorouracil and radiotherapy, and of salvage chemoradiation in the definitive nonsurgical treatment of epidermoid carcinoma of the anal canal: results of a phase III randomized intergroup study. J Clin Oncol 14(9):2527–2539

RTOG 83-14, 1989 → 79 patients with any primary tumor stage of anal canal carcinoma were treated by RT combined with mitomycin given by bolus IV injection and 5-FU given by continuous infusion. Radiation was delivered to the perineum and pelvis to a total dose of 40.8 Gy in 4.5–5 weeks. The inguinal nodal areas received 40.8 Gy, calculated at a depth of 3 cm in the center of the nodal area.

- The overall survival rates were 97% at 1 year and 73% at 3 years.
- Combined therapy was effective for patients with anal cancer, and allowed preservation of the sphincter and of sexual function.

Sischy B et al (1989) Definitive irradiation and chemotherapy for radiosensitization in management of anal carcinoma: interim report on Radiation Therapy Oncology Group study no. 8314. J Natl Cancer Inst 81(11):850–856

Salama et al., 2007 → 53 patients were treated with concurrent chemotherapy and IMRT for anal cancer. Preliminary outcomes suggested that concurrent chemotherapy and IMRT for anal canal cancers was effective and favorably tolerated compared with historical standards.

Salama JK (2007) Concurrent chemotherapy and intensity-modulated radiation therapy for anal canal cancer patients: a multicenter experience. J Clin Oncol 25(29):4581–4586

University of Chicago, 2005 → IMRT reduced the mean doses to small bowel, bladder, and genitalia. Treatment was well tolerated, with no serious acute nonhematologic toxicity. There were no treatment breaks attributable to gastrointestinal or skin toxicity. At a median follow-up of 20.3 months, there were no other local failures. Two-year overall survival, disease-free survival and colostomy-free survival were: 91, 65 and 82%, respectively.

Milano MT et al (2005) Intensity-modulated radiation therapy (IMRT) in the treatment of anal cancer: toxicity and clinical outcome. Int J Radiat Oncol Biol Phys 63(2): 354–361

RTOG 92-08, 1996 → increases in RT dose over those used in conventional chemotherapy regimens for anal cancers did not increase local control when given in a split-course fashion.

John M (1996) Dose escalation in chemoradiation for anal cancer: preliminary results of RTOG 92-08. Cancer J Sci Am 2(4):205–211

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Soft Tissue Sarcoma

11

Murat Beyzadeoglu, Cuneyt Ebruli, and Gokhan Ozyigit

Soft tissue sarcomas (STS) are rarely seen among adult solid tumors. Sarcomas constitute 1% of all cancers. They have different biological behaviors as well as several histological subtypes. They can develop at any site in the body. Nearly 50% of patients with soft tissue sarcomas die of the disease due to relapse or distant metastasis within 5 years of diagnosis. Therefore, treatment and follow-up of this disease are very difficult [1].

Sarcomas are malignant tumors originating from mesoderm–mesenchyme.

11.1 Pathology

STSs are classified histologically according to their cellular origin [2]. Electron microscopic, histochemical, flow cytometric, cytogenetic and tissue culture studies may be used to determine histological subtypes. Malignant STSs include:

- Angiosarcoma
- Epithelioid sarcoma
- Synovial sarcoma
- Malignant schwannoma
- Clear cell sarcoma
- Malignant fibrous histiocytoma (MFH)
- Neuroectodermal tumor
- Dermatofibrosarcoma
- Liposarcoma
- Leiomyosarcoma
- Rhabdomyosarcoma (RMS)
- Hemangiopericytoma
- Myxoid chondrosarcoma
- Synovial chondrosarcoma
- Mesenchymal chondrosarcoma

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Localization frequency of STS: lower extremity (45%), trunk (30%), upper extremity (15%), and head–neck (9%) [3].

Extremities → liposarcoma, MFH, synovial sarcoma, fibrosarcoma, myxoid liposarcoma.

Retroperitoneal → liposarcoma, leiomyosarcoma.

Head–neck → MFH.

Incidence rates of histological STS subtypes: MFH (20–30%), liposarcoma (10–20%), leiomyosarcoma, fibrosarcoma, synovial sarcoma, RMS and schwannoma (5–10%) [3].

MFH [4]. Mostly seen in the fifth to seventh decades, although also in children and adolescents. It commonly presents as a painless mass in the lower extremities followed by the upper extremities and the retroperitoneal region. Two-thirds of tumors of this type are localized intramuscularly, and they can be seen together with Hodgkin's lymphoma, non-Hodgkin's lymphoma and multiple myeloma.

- There are five histological subtypes of MFH: (1) storiform/pleomorphic (most common), (2) myxoid, (3) giant cell, (4) inflammatory (generally retroperitoneal), (5) angiomatoid.
- Low-, moderate- and high-grade patients have 10-year survivals of 90, 60 and 20%, respectively.
- Distant metastasis is mostly to lung (90%), bone (8%) and liver (1%).

Liposarcoma [5]. Mostly seen in adults aged between 50 and 65 years. They commonly develop in the thigh and the retroperitoneal region.

- Liposarcoma exhibits three basic forms with different morphologies, natural histories, and karyotypic and genetic features.
  1. *Well-differentiated liposarcomas*. These grow slowly over many years and become very large, deep, painless masses. They usually do not metastasize and are locally aggressive tumors.
  2. *Myxoid/round cell liposarcoma*s. These constitute 40% of all liposarcomas. They usually appear in deep soft tissues of extremities, and 66% occur in the thigh. A round cell component of >5% is a poor prognostic sign, with a 5-year survival rate of nearly 50%. Pure myxoid ones are considered to be low grade, and the 5-year survival rate associated with them is 90%. Retroperitoneal and axillary metastases can occur without pulmonary metastases.
  3. *Pleomorphic liposarcomas*. These are high-grade tumors with high mitotic activity, bleeding and necrosis. They constitute less than 5% of all liposarcomas and are mostly seen in the lower extremities. Lung metastases are seen in 50% of all such patients in the early stages.

Fibrosarcoma [6]. These exhibit adult and infantile types. They are deeply seated painless masses that are most common in patients between 40 and 60 years of age, and they mostly occur in the trunk and thigh. Ninety percent of them are well differentiated. Infantile fibrosarcoma is seen in the first 2 years of life and is commonly congenital; it originates from the extremities and rarely metastasizes.

Leiomyosarcoma [7]. These are seen in all age groups. More than half of them are localized in the retroperitoneal or intraabdominal regions. They can also be seen in the gastrointestinal system or uterus.

- They are generally resistant to chemotherapy and radiotherapy. Five-year survival is nearly 30%.
- Skin leiomyosarcomas are generally seen as extremity nodules. Deep extremity leiomyosarcomas are frequently located in the thigh and the middle and large veins.
- Retroperitoneal tumors are usually larger than 10 cm, and show a tendency for local recurrence and distant metastases to the liver and lung.

Synovial sarcoma [8]. These originate from tenosynovial mesothelial tissue, and are generally seen in young adults. These tumors typically localize in the tendon sheath and the paraarticular regions of joints. More than 50% of cases are seen in the lower extremities (particularly in the knee) and the remaining occur in the arms. They are commonly calcific and have a characteristic appearance.

- Synovial sarcomas are also seen in regions that do not have synovial tissues (head–neck 10%, chest and abdominal wall <10%, or intrathoracic region).
- Synovial sarcomas include characteristic chromosomal translocations: t(X;18)(p11.2;q11.2). These translocations are the gold standard in synovial sarcoma diagnosis → almost all are high grade in the staging system.
- They have high rates of local recurrence and lymph node metastases. Five-year survival is nearly 30%.

RMS [9]. These develop from striated muscles. All are high grade in the staging system.

- They are the most common STS in childhood.
- Localization: head–neck (35%), trunk and extremities (35%), genitourinary system (30%).
- They have a tendency for local recurrence.
- Early metastases in the venous and lymphatic systems are seen.
- They present three subtypes:
  - *Embryonal RMS*. These affect infants and children. Localization: head–neck (70%), genital region (15–20%). Botryoid sarcoma also belongs in this group. Five-year survival is nearly 70%.
  - *Alveolar RMS*. These affect those 13–18 years of age and may develop in any region. They are highly aggressive. Five-year survival is nearly 50%.
  - *Pleomorphic RMS*. These are seen in those over 30 years of age. They are very rare and develop from the extremities. They are commonly anaplastic and may be mixed with MFH. Five-year survival is nearly 25%.

(*continued*)

(continued)

Malignant schwannomas (malignant peripheral nerve sheath tumors [MPNST]) [10]. These are also known as neurofibrosarcomas and neurogenic sarcomas. They affect young and middle-aged adults. Most of them are high grade and are characteristically positive for S-100.

- These tumors originate from nerve sheath rather than nerves. Legs and the retroperitoneum are the most common localizations.
- MPNST may develop in 5% of patients with neurofibromatosis (NF), which usually originates from plexiform neurofibroma. Such patients have a poorer prognosis.
- MPNSTs have larger volumes and higher grades than the other types.

Desmoid tumors (aggressive fibromatosis) [11]. These differentiate from fibrous tissue; they are locally invasive and aggressive, showing fibroblastic proliferation. They have high recurrence rates after local resection. Desmoid tumors are locally invasive and rarely metastasize. The tumor usually does not result in mortality, but rather causes functional morbidity.

- Desmoids show various localizations and presentations. They may develop in the abdominal walls of pregnant women, and form intraabdominal mesenteric masses. They may also cause large extremity masses in older cases. Abdominal desmoids may be a component of familial adenomatous polyposis syndrome.

11.2 General Presentation

The first and only symptom of most STSs is a painless mass. Furthermore, they present with signs of compression or metastatic symptoms according to the localization.

Stewart–Treves syndrome [12] → chronic upper extremity lymphedema in leimyosarcoma

- Sarcomas typically metastasize by a hematogenous route. Lung metastasis is frequent. Extremity sarcomas frequently metastasize to the lungs, whereas retroperitoneal STSs metastasize to the liver.
- The most frequent lymph node metastases are from clear cell sarcoma, RMS, epithelioid sarcoma, synovial sarcoma, and angiosarcoma, respectively.
- The following STSs generally do not metastasize: liposarcoma (myxoid and well-differentiated types), fibrosarcoma (infantile and well-differentiated types), MFH (superficial type), dermatofibrosarcoma protuberans.

11.3 Staging

Tumor Grade (G) [13]

GX: Grade cannot be assessed
G1: Grade 1
G2: Grade 2
G3: Grade 3

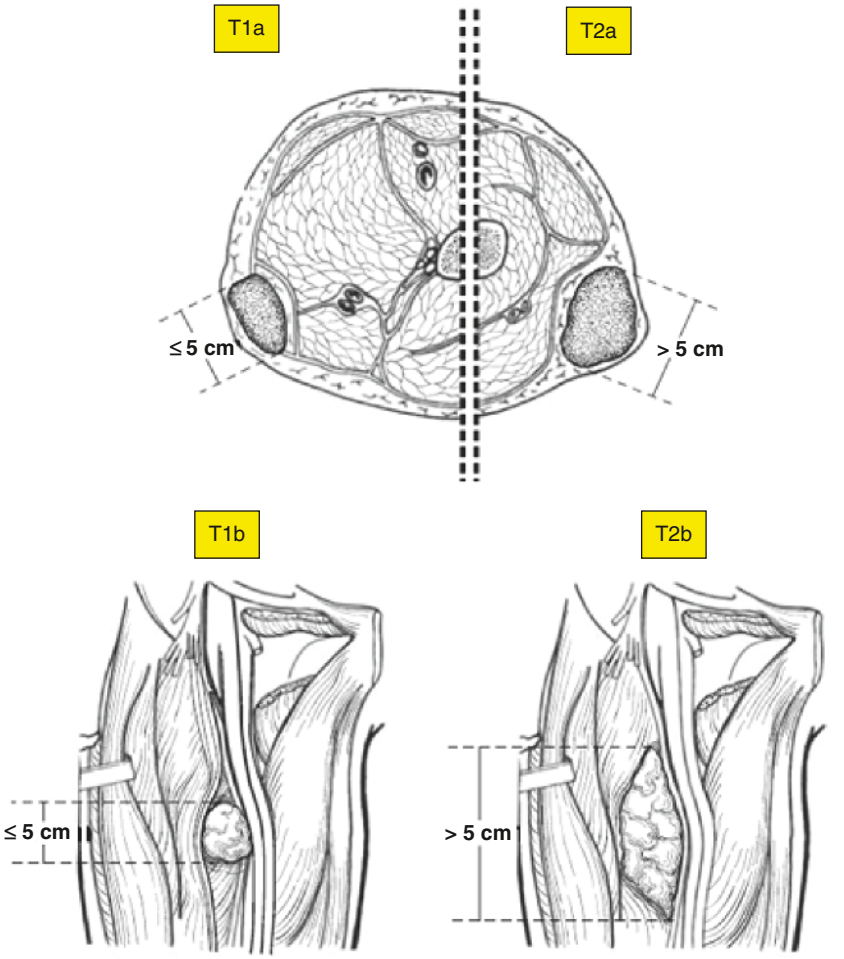

Fig. 11.1 T staging in soft tissue sarcomas (from [19], pp 193, 194, Figs. 22.1, 22.3, and 22.4, reproduced with the permission from the American Joint Committee on Cancer)

Primary Tumor (T) (Fig. 11.1)

TX: Primary tumor cannot be assessed
T0: No evidence of primary tumor
T1: Tumor 5 cm or less in greatest dimension*
  T1a: Superficial tumor
  T1b: Deep tumor
T2: Tumor more than 5 cm or larger in greatest dimension*
  T2a: Superficial tumor
  T2b: Deep tumor

*Superficial tumor is located exclusively above the superficial fascia without invasion of the fascia; the deep tumor is located either exclusively beneath the superficial fascia, or is superficial to the fascia with invasion of or through the fascia, or yet both superficial beneath the fascia. Retroperitoneal, mediastinal, and pelvic sarcomas are classified as deep tumors.

Regional Lymph Nodes (N)

NX: Regional lymph nodes cannot be assessed
N0: No regional lymph node metastasis
N1: Regional lymph node metastasis [*note*: presence of positive nodes (N1) is considered stage III]

Distant Metastasis (M)

MX: Distant metastasis cannot be assessed
M0: No distant metastasis
M1: Distant metastasis

AJCC stage groups

Stage Ia
GX, G1, T1a, N0, M0
GX, G1, T1b, N0, M0

Stage Ib
GX, G1, T2a, N0, M0
GX, G1, T2b, N0, M0

Stage IIa
G2, G3, T1a, N0, M0
G2, G3, T1b, N0, M0

Stage IIb
G2, T2a, N0, M0
G2, T2b, N0, M0

Stage III
G3, T2b, N0, M0
Any G, Any T, N1, M0

Stage IV
Any G, Any T, Any N, M1

Five-Year Survival Rates According to Stage	
Stage I	90%
Stage II	81%
Stage III	56%
Stage IV	<20%

11.4 Treatment Algorithm

Stage I (extremity localization) [14]
Surgery (surgical margin (+) or close → postoperative RT)
Stage II–III [14] (extremity localization)
Surgery + postoperative RT or preoperative RT + surgery
Stage IV
Best supportive care, CT, palliative RT, ± palliative surgery

- If primary tumor is under control and there are ≤4 lung metastases, metastasectomy may be tried.

Special situations [14]
Retroperitoneal sarcomas
Surgery ± IORT (12–15 Gy) + postoperative RT (45–50 Gy)
Preoperative chemoradiotherapy + surgery + IORT boost
Desmoid tumors
Surgery

- Surgical margin (+): postoperative RT
  Inoperable, RT (56–60 Gy).
- Surgical approach should be "en bloc resection;" surgical margin should be ≥2 cm. Surgical clips are useful for determining the tumor bed in radiotherapy planning.
- Surgical scar and clips are included in RT portal.

11.5 Radiotherapy

RT field (Fig. 11.2): tumor/tumor bed, scar, and drain sites:
Up to 50 Gy:

- *Craniocaudal:* 5–7 cm
- *Mediolateral:* 2–3 cm

After 50 Gy (boost field) (Fig. 11.2):

- *Craniocaudal:* 2 cm
- *Mediolateral:* 2 cm

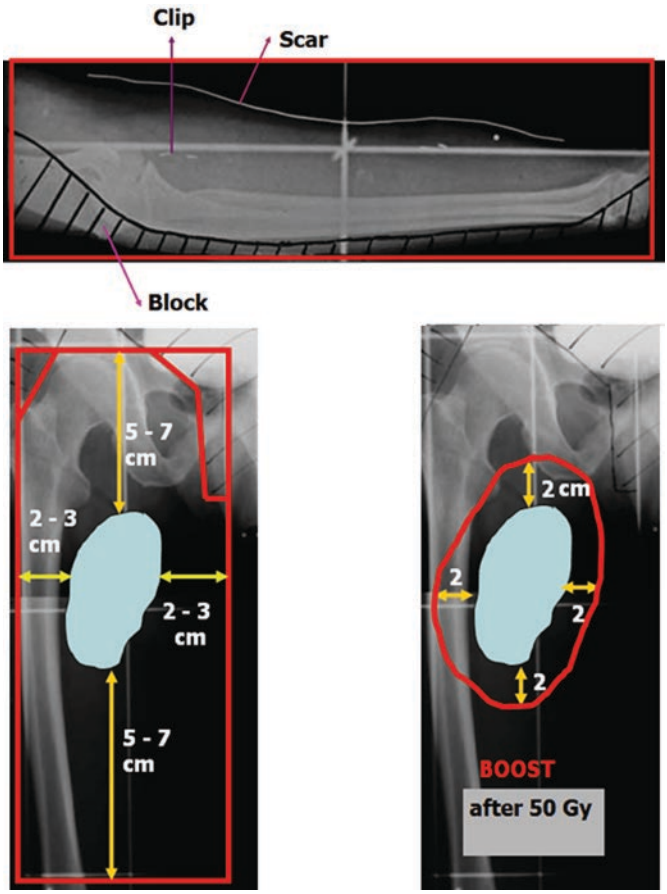

Fig. 11.2 Postoperative RT field for STS

Postoperative RT:

- Surgical margin (−) or microscopic residual (+); 60 Gy
- Surgical margin (+); 66 Gy
- Gross disease; 70–75 Gy
- RT starts 14–20 days after surgery

Preoperative RT:

- 2 Gy/day, total 50 Gy
- Surgery is performed after 3 weeks of RT

The entire circumference of any extremity should never be irradiated, and a margin of at least 1.5–2 cm to the skin should be provided on one side to protect lymphatic circulation/drainage.

- >20 Gy: epiphyseal plaques close prematurely in children [15].
- ≥40 Gy: pone marrow ablation is observed [16].
- ≥50 Gy: pone fracture and delayed scar healing is observed [17].
- >40–45 Gy: fibrotic bands are formed within joints.

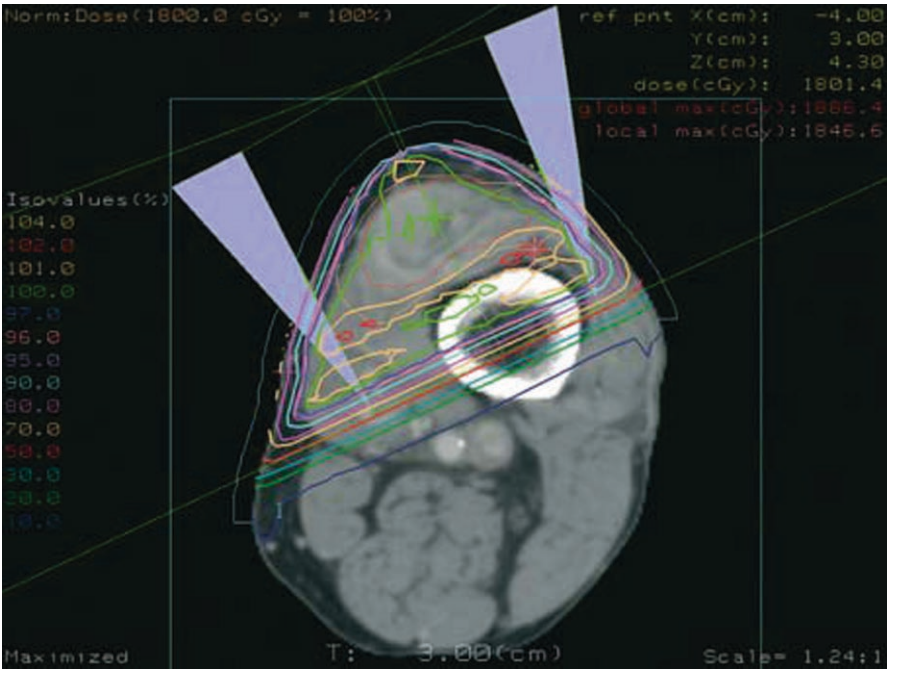

Fig. 11.3 Conformal RT volumes for STS [20], p 768, Fig. 30.7a

Conformal RT Volumes (Fig. 11.3) [18]
CTV: tumor + 5–7 cm in craniocaudal, 1.5 cm in mediolateral
PTV: CTV + 0.5 cm

11.6 Selected Publications

M.D. Anderson, 1981 (1963–1977) → 300 adults with STSs were treated by conservative surgical excision and postoperative radiotherapy. Five-year survival rate varied with anatomic site, histopathologic diagnosis, and stage of the lesion. The overall local recurrence rate was 22.3% (67/300). The incidence of lymph node metastases as the initial site of spread was only 2.7% (8/300), so elective treatment of the regional lymphatics was not indicated. The incidence of significant complications in extremities was low (6.5%). The combination of conservative surgery and postoperative radiation therapy allows the retention of a functional limb in 84.5% of patients with extremity lesions.

Lindberg RD et al (1981) Conservative surgery and postoperative radiotherapy in 300 adults with soft-tissue sarcomas. Cancer 47(10):2391–2397

National Cancer Institute, *1982* (1975–1981) → 43 adult patients with high-grade STSs of the extremities were prospectively randomized to receive either amputation or a limb-sparing resection plus adjuvant radiation therapy. The limb-sparing resection group received wide local excision followed by 50 Gy to the entire anatomic area at risk for local spread and 60–70 Gy to the tumor bed. Both randomization groups received postoperative chemotherapy with doxorubicin, cyclophosphamide, and high-dose methotrexate.

- Four local recurrences in the limb-sparing group and none in the amputation group ($p = 0.06$).
- No differences in disease-free survival rates (71 and 78% at 5 years) or overall survival rates (83 and 88% at 5 years).
- Patients with positive margins of resection had higher local recurrence than those with negative margins, even when postoperative radiotherapy was used.
- Conclusion: limb-sparing surgery (LSS), radiation therapy, and adjuvant chemotherapy appear capable of successfully treating the great majority of adult patients with STSs of the extremities.

Rosenberg SA et al (1982) The treatment of soft-tissue sarcomas of the extremities: prospective randomized evaluations of (1) limb-sparing surgery plus radiation therapy compared with amputation and (2) the role of adjuvant chemotherapy. Ann Surg 196(3):305–315

National Cancer Institute, *1998* (1983–1991) → patients with extremity tumors and a limb-sparing surgical option were randomized to receive or not receive postoperative adjuvant external-beam radiotherapy. Patients with high-grade sarcomas received postoperative adjuvant chemotherapy, whereas patients with low-grade sarcomas or locally aggressive nonmalignant tumors were randomized after surgery alone.

- Median follow-up of 9.6 years.
- A highly significant decrease in LR was seen with radiation, but no difference in OS was shown.
- Lower probability of LR in patients with low-grade STS receiving XRT, but again there was no difference in OS.
- Conclusion: although postoperative external-beam radiotherapy is highly effective at preventing LRs, selected patients with extremity STSs who have a low risk of LR may not require adjuvant XRT after LSS.

Yang JC et al (1998) Randomized prospective study of the benefit of adjuvant radiation therapy in the treatment of soft tissue sarcomas of the extremity. J Clin Oncol 16(1): 197–203

M.D. Anderson; 1998 → 453 patients with grade 2–3 STS. Median follow-up: 97 months. There were three groups: preoperative radiotherapy (median 50 Gy); postoperative radiotherapy (median 64 Gy) and RT alone (median 65 Gy and gross total excision at an outside center prior to referral). Gross disease treated with preop was controlled locally in 88% at 10 years, as compared to 67% with postop ($p=0.01$). Re-excision at MDACC (postop) resulted in enhanced 10-year local control over that with RT alone (88 vs. 75%, $p=0.06$), and was confirmed to be an independent predictor in multivariate analysis ($p=0.02$). Local control was highest with preop in patients presenting primarily with gross disease, and with postop in patients presenting primarily following gross total excision. 50 Gy was inadequate after gross total excision.

Pollack A et al (1998) Preoperative vs. postoperative radiotherapy in the treatment of soft tissue sarcomas: a matter of presentation. Int J Radiat Oncol Biol Phys 42(3):563–572

RTOG 95-14/Intergroup, 2006 (1997–2000) → 66 patients with high-grade STS (≥8 cm in diameter) of the extremities and body wall. Three cycles of neoadjuvant chemotherapy (CT; modified mesna, doxorubicin, ifosfamide, and dacarbazine), preoperative radiation therapy (RT; 44 Gy administered in split courses), and three cycles of postoperative CT. Seventy-nine percent of patients completed their preoperative CT and 59% completed all planned CT. Sixty-one patients underwent surgery. Fifty-eight of these were R0 resections, of which five were amputations. Three-year rates for disease-free, distant-disease-free, and overall survival were 56.6, 64.5, and 75.1%, respectively.

Kraybill WG (2006) Phase II study of neoadjuvant chemotherapy and radiation therapy in the management of high-risk, high-grade, soft tissue sarcomas of the extremities and body wall: Radiation Therapy Oncology Group Trial 9514. J Clin Oncol 24:619–625

NCI Canada, *2002* (1994–1997) → 94 patients assigned to preoperative radiotherapy (50 Gy in 25 fractions) and 96 to postoperative radiotherapy (66 Gy in 33 fractions). Median follow-up: 3.3 years. Wound complications were recorded in 31 (35%) of the 88 in the preoperative group and 16 (17%) of the 94 in the postoperative group ($p=0.01$). Tumor size and anatomical site were also significant risk factors in multivariate analysis. Overall survival was slightly better in patients who had preoperative radiotherapy than in those who had postoperative treatment ($p=0.0481$). Because preoperative radiotherapy was associated with a greater risk of wound complications than postoperative radiotherapy, the choice of regimen for patients with STS should take into account the timing of surgery and radiotherapy, and the size and anatomical site of the tumor.

O'Sullivan B et al (2002) Preoperative versus postoperative radiotherapy in soft-tissue sarcoma of the limbs: a randomised trial. Lancet 359:2235–2241

Princess Margaret, 2002 → 55 patients with primary or locally recurrent retroperitoneal sarcoma (RPS) judged to be resectable were entered into a trial of combined therapy and observed prospectively. Forty-six patients underwent complete gross resection with curative intent. The 2-year overall survival and DFS for resected RPS were 88 and 80%, respectively. Significantly better two-year DFSs were achieved in patients with primary RPS and those with low-grade tumors (93 and 95%, respectively). Although preoperative XRT was very well tolerated, brachytherapy to the upper abdomen was associated with substantial toxicity.

Jones JJ et al (2002) Initial results of a trial of preoperative external-beam radiation therapy and postoperative brachytherapy for retroperitoneal sarcoma. Ann Surg Oncol 9(4):346–354

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Skin Cancer

12

Murat Beyzadeoglu, Gokhan Ozyigit, and Cuneyt Ebruli

Skin cancers are the most common type of cancer; they affect nearly one million people each year [1]. This chapter focuses on nonmelanoma skin cancers.

The skin consists of two layers: the epidermis and dermis (Fig. 12.1).
The upper layer is the epidermis, which is 0.4 mm in the eyelid and 1.5 mm thick in the base of the foot.
The dermis, which is located under the epidermis, has two layers.
Subcutaneous fat and connective tissue are found under the dermis.

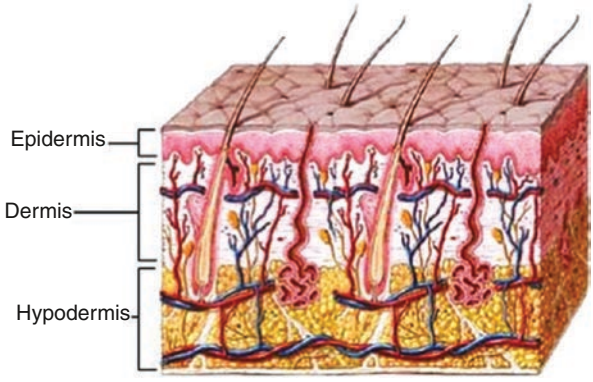

Fig. 12.1 Layers of the skin

The *epidermis* is a squamous epithelium layer that includes keratinocytes at various stages of differentiation. This layer has no blood vessels, so nutrition and excretion of waste products is achieved through diffusion.

- The epidermis includes melanocytes, Langerhans cells and Merkel cells.
- Melanocytes originate from neural crest cells and produce the pigment melanin. Melanin is collected in melanosomes, which are surrounded by keratinocytes.
- Langerhans cells originate from bone marrow and are located in the basal and granular layers of epidermis.
- Merkel cells originate from the mesoderm, and are associated with light touch sensation.

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The *dermis* consists of two layers, the superficial papillary layer and the deeper reticular dermis layer.

- Capillaries feed the papillary dermis, which is composed of elastic leaves, reticular leaves and collagen, as well as the avascular epidermis via diffusion.
- The reticular layer of the dermis includes fibroblasts, mast and other connective tissue cells, nerve ends, lymphatics and their epidermal branches.
- The main cell type is the fibroblast. Fibroblasts produce collagen, which makes up 70% of the weight of the dermis.
- The dermis also contains adipose glands, sweat glands, apocrine glands and hair follicles.
- Adipose glands are found all over the body except in the dorsum of the foot and the palmar regions.
- Sweat glands are found extensively in the palmar regions and the dorsum of the foot, in contrast to the adipose glands.

The *hypodermis* is located under the dermis, and includes subcutaneous adipose and connective tissues.

- Connective tissue elements form superficial and deep facial systems between bones and skin. These spaces are filled by adipose tissue, muscle and tendons, nerves, arteries, veins and lymph vessels.

12.1 Pathology/General Presentation

Malignant tumors of the skin [1]

- Basal cell carcinoma (BCC) (65–70%)
- Squamous cell carcinoma (SCC) (30–35%)
- Malignant melanoma (1.5%)
- Merkel cell carcinoma
- Malignant sweat gland tumors

BCC [2]. This is the most common type of cancer according to USA data.

- BCC originates from pluripotent epithelial cells of the epidermal basal layer or external root sheaths of hair follicles.
- BCC rarely metastasizes (<0.1%), but it is a locally aggressive tumor that invades and destroys underlying tissues.
- BCC does not develop from premalignant lesions, unlike SCC.
- The most frequent subtype is noduloulcerative BCC (50%). This ulcerates during growth as a result of tissue destruction. Characteristically, such lesions form rodent ulcers (i.e., a central ulcer surrounded by a pearl-like periphery).

- The second most common subtype is superficial BCC (33%), which extends into the epidermis without presenting dermal invasion. BCCs are patchy tumors that can be multiple, hypopigmented and erythematous.
- The most prominent feature of morpheaform (sclerosing) BCC is persistent surgical margin positivity after simple surgical excisions.
- The basosquamous form is rare and most commonly seen in face skin. Its rate of metastasis is similar to that of SCC (~5%).

Squamous cell cancer (SCC) [3]. This is the second most common type of cancer. It originates from the keratinocytes of the epidermis.

- SCC is most commonly seen on the dorsal surfaces of the hands and forearms, and the interdigital regions.
- The major etiological factor is solar radiation.
- There are two subtypes of SCC. The slow-growing type is low grade and has a verrucous and exophytic appearance. Verrucous carcinoma has a high tendency for metastasis. The second type is nodular and indurated; it grows rapidly and ulcerates early.
- Since SCC has a high potential for metastasis and regional lymph node involvement, a detailed physical exam should be done that focuses in particular on the lymph nodes (well-differentiated SCCs exhibit a nodal involvement rate of 1%; poorly differentiated, recurrent, tumors of size >3 cm and invasion depth >4 mm as well as lip-localized SCC have a nodal involvement rate of 10%. SCCs that develop on burn scars and with osteomyelitis show a nodal involvement rate of 10–30%.
  - The rate of distant metastasis is 2%, and the most frequent metastatic regions are the lungs, liver and bones.

Perineural invasion:

- Approximately 1% in BCC; it is generally seen in recurrent or locally advanced cases.
- Two to fifteen percent in SCC; frequently related with nodal involvement and the cranial base. Recurrent SCC involves perineural invasion unless proven by pathological evaluation.
- Perineural invasion is commonly asymptomatic. However, clinical signs may include paresthesia, pain, dysesthesia, numbness and paralysis.

Bowen's disease [4]

- This is a preinvasive form of SCC, and is also known as skin carcinoma in situ. Full-thickness dysplasia of the epidermis is seen histologically without invasion. It results in clinically well-demarcated, erythematous plaques.
- Treatment: surgery, cryotherapy, topical 5-FU or 40 Gy RT at 2 Gy/day.

Queyrat disease/erythroplasia [5]

- This is Bowen's disease of the penis, and is characterized by erythematous, shiny plaques caused by human papillomavirus (HPV).

Marjolin's ulcer [6]

- This is an SCC that develops at the base of a burn scar.

Merkel cell carcinoma [7]. Merkel cell carcinoma is a rare tumor that originates in the basal layer of the skin, and is related to the terminal axons.

- Merkel cell carcinoma is a neuroendocrine carcinoma of the skin.
- Merkel cell carcinoma is aggressive (~75% local recurrence, ~35% mortality). This mortality rate is higher than that of malignant melanoma.
- Lymphatic involvement is ≥25%, and 50–60% of patients have developed distant metastases within 10 months of diagnosis.
- Treatment: sentinel lymph node dissection (if SLND (+), complete regional lymph node dissection) + wide local excision + RT ± chemotherapy.

Malignant sweat gland tumors [8]. These are aggressive tumors that generally metastasize to regional lymph nodes. Distant metastases occur by a hematogenous route. Malignant eccrine sweat gland tumors are locally aggressive and destructive tumors. Most are seen in the palmar regions of the hands, and they are slow-growing, painless, nodular masses.

- Treatment: local wide excision + therapeutic lymph node dissection. The roles of radiotherapy and chemotherapy are not clear due to the rarity of these tumors.

12.2 Staging

T Staging for Cutaneous Squamous Cell/Other Cutaneous Carcinoma (Fig. 12.2) [9]

T0: No evidence of primary tumor
Tis: Carcinoma *in situ*
T1: Tumor 2 cm or less in greatest dimension with less than two high risk features**
T2: Tumor greater than 2 cm in greatest dimension or tumor any size with two or more high risk features*
T3: Tumor with invasion of maxilla, mandible, orbita, or temporal bone

T4: Tumor with invasion of skeleton (axial or appendicular) or Perineural invasion of skull base
*Excludes cSCC of the eyelid
**High risk features for the primary tumor (T) staging:
– Depth/invasion: >2 mm thickness, Clark level ≥ IV, Perineural invasion
– Anatomic location: primary site ear, primary site hair bearing lip
Differentiation: poorly differentiated or undifferentiated

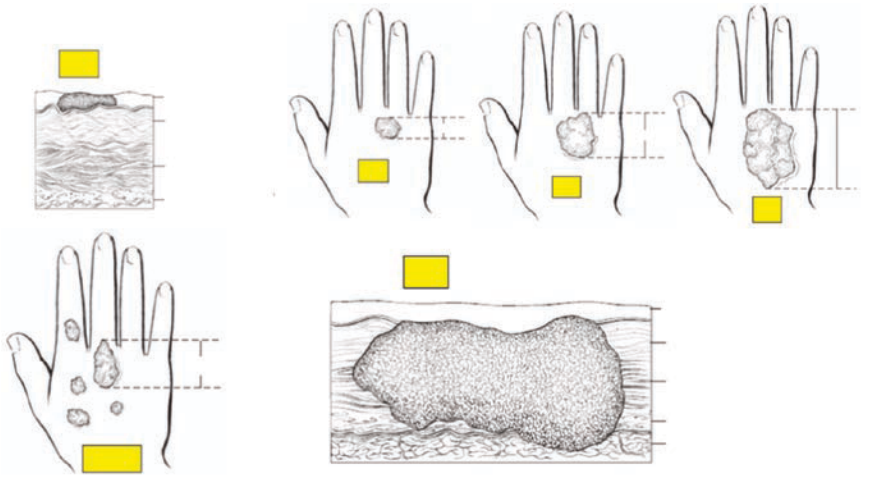

Fig. 12.2 T staging in nonmelanoma skin cancers (from [14], pp 200–202, Figs. 23.4–23.9, reproduced with the permission of the American Joint Committee on Cancer)

N Staging (Fig. 12.3) [9]

N0: No regional lymph node metastasis
N1: Metastasis in a single ipsilateral lymph node, 3 cm or less in greatest dimension
N2a: Metastasis in a single ipsilateral lymph node, more than 3 cm but not more than 6 cm in greatest dimension
N2b: Metastasis in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension
N2c: Metastasis in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension
N3: Metastasis in a lymph node, more than 6 cm in greatest dimension

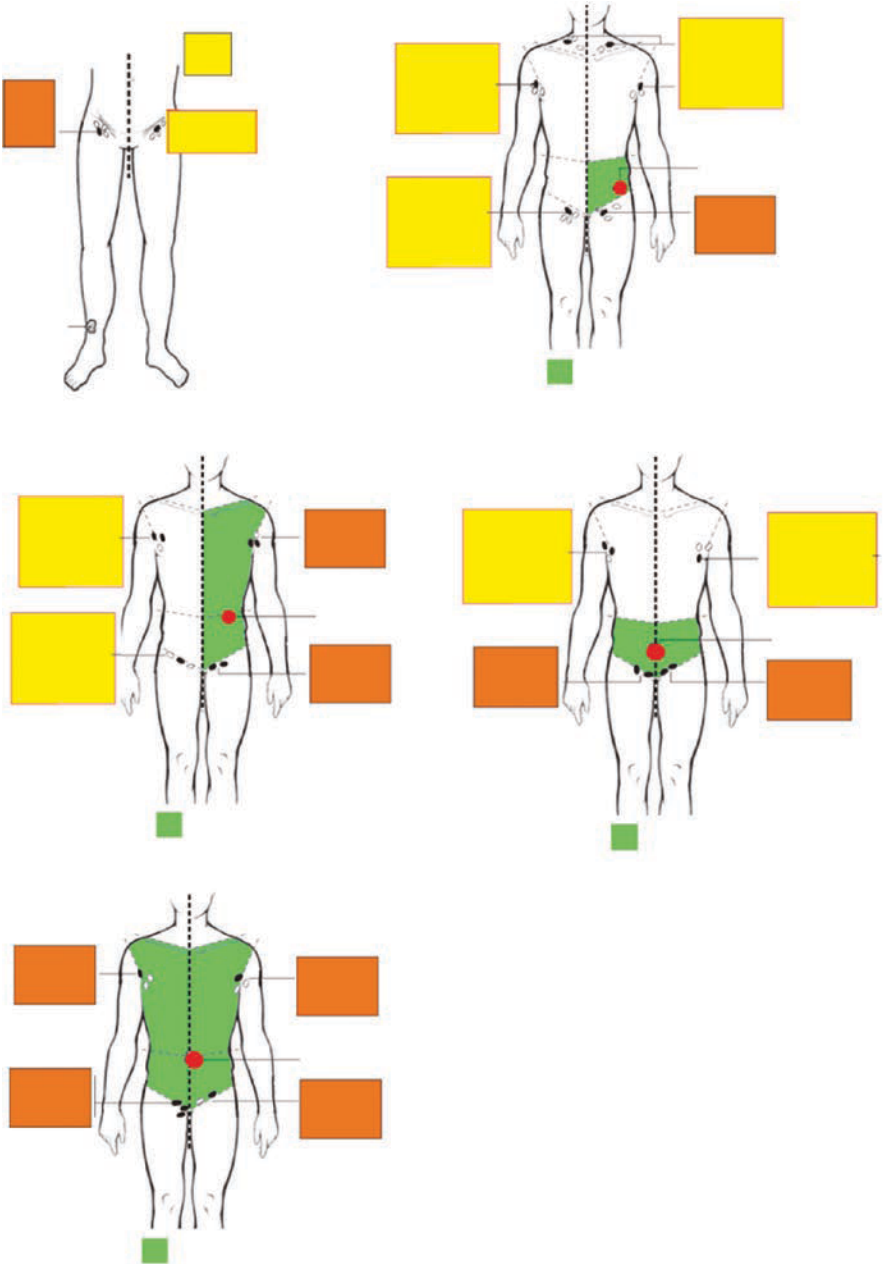

Fig. 12.3 Lymphatic involvement and tumor localization, and theireffect on staging in nonmelanoma skin cancers (from [14], pp 202–204, Figs. 23.4, 23.10–23.14, reproduced with the permission of the American Joint Committee on Cancer)

AJCC Stage Groups

Stage 0: TisN0M0
Stage I: T1N0M0
Stage II: T2N0M0
Stage III: T3N0M0; T1N1M0; T2N1M0; T3N1M0
Stage IV: T1N2M0; T2N2M0; T3N2M0; Any T, N3, M0; T4, Any N, M0; Any T, Any N, M1

12.3 Treatment Algorithm

The major therapeutic approaches utilized in the management of nonmelanoma skin cancers are: cryotherapy, curettage + electrodesiccation, chemotherapy, surgical excision, Mohs micrographic surgery and radiotherapy.

Cryotherapy [10]:

- ≤2 cm, superficial BCC therapy.
- Well-differentiated SCC therapy (margin: <3 cm tumors, 0.5–1 cm; ≥3 cm tumors, 1 cm).
- Cryogenic liquid nitrogen is most commonly used. The temperature should be at least −30°C to kill malignant cutaneous tissues.
- Advantages: high cure rate; ability to protect tissue; ability to treat multiple lesions.
- Disadvantages: long period of scar healing; hypopigmentation; poor scar tissue.

Curettage and electrodesiccation:

- Same indications as for cryotherapy, except for tumor localization on the skin of scar/cartilage/bone.
- Recurrent tumors with the same features.
- This type of therapy is associated with a high incidence of recurrence, and no samples are taken for pathological evaluation.

Topical 5-FU [11]:

- This is only used for tumors that are limited to the epidermis (superficial BCC and Bowen's disease).
- It can be used in the management of premalignant lesions related to SCC. However, it is contraindicated in nodular or infiltrative BCC and invasive SCC.

Surgical excision:

- This provides total excision of the lesion and histopathological evaluation.
- It is usually preferred for tumors that are >5 mm in size.
- Surgical margin: 0.5–1 cm for tumors <3 cm; 1 cm for tumors ≥3 cm.
- Reconstructive surgery may also be performed according to the localization and size of the tumor.
- Cure rate ~90%.

Mohs micrographic surgery [12]:

- A fixative (zinc chloride paste) is applied into the tumor in this technique. Serial excision is performed after fixation. Tumor mapping is done by evaluating the tumor histologically, and re-excision is performed from the areas of residual disease. Thus, the tumor is excised in a controlled manner, and the normal tissues are protected. Cure rate is 96–99%.
- Indications: BCC with high-risk localization (postauricular, mid-face and eye lids etc.), morpheaform or infiltrative-type BCC, recurrent BCC, verrucous carcinoma, and malignant sweat gland tumor.

12.4 Radiotherapy

Radiotherapy is used in the management of both primary and recurrent skin cancers. A margin of 0.5–2 cm is used, according to the size and histology of the tumor.

Primary radiotherapy in skin cancers [13]:

- Face skin: lesions >5 mm (particularly eyelids, tip of nose, nose wings, lips)
- Ear and forehead: lesions >2 cm
- Hairy scalp

Postoperative RT indications [13]:

- Surgical margin (+)
- Perineural invasion
- Primary tumor >3 cm
- T4 tumors
- SCC on skin of parotid glands

- Recurrent or morpheaform BCC: 0.5–1 cm margin.
- High-risk SCC (>3 cm, poorly differentiated or infiltrative–ulcerative SCC): 2 cm margin.
- Regional lymph nodes may be included in the RT portal for high-risk SCCs.

Photons or electrons with suitable energy are used according to tumor depth. Single RT field is used in the management of skin cancers.

- Dose prescription: D_{max} dose for photons, 95% isodose for electrons
- Total dose: 50 Gy for BCC, 60–66 Gy for SCC

Bolus may be used to increase the surface dose.

- Minimum bolus thickness for 6 and 9 MeV: 1 cm
- Minimum bolus thickness for 12 MeV: 0.5 cm

12.5 Selected Publications

12.5.1 Radiotherapy Alone (Retrospective)

University of Florida, 1987 → 100 patients with previously untreated (56) or recurrent (44) T2–T4 carcinomas of the skin of the head and neck who were treated with radical irradiation. Fifty-five patients had SCCs, 42 had BCCs, and 3 had basosquamous carcinomas. Eighty-four percent of the recurrences were noted within 2 years of radiation therapy, and 97% within 5 years of treatment.

Mendenhall WM et al (1987) T2–T4 carcinoma of the skin of the head and neck treated with radical irradiation. Int J Radiat Oncol Biol Phys 13(7):975–981

Washington University, 2001 (1966–1997) → 389 BCCs and 142 SCCs, 167 of which were recurrent tumors. Median follow-up was 5.8 years. Electron beam irradiation was used in 19%, superficial X-rays in 60%, a combination of electron beam and superficial X-rays in 20%, and megavoltage photons in <2%. The overall local tumor control rate was 89%; it was 93% for previously untreated lesions and 80% for recurrent lesions. Patients with BCC had a 92% overall control rate; patients with SCC 80%. Multivariate analysis showed that local failure was related to the daily dose fractionation. The maximal diameter of the lesion and the pathologic tumor type were also significant ($p = 0.01$). Overall, 92% of the treated population with cosmesis data had excellent or good results. The overall complication rate was 5.8%, consisting primarily of soft-tissue necrosis. Recurrent lesions fared worse, and therefore treatment at the earliest possible stage was strongly recommended.

Locke J et al (2001) Radiotherapy for epithelial skin cancer. Int J Radiat Oncol Biol Phys 51(3):748–755

Milan, 2003 → 405 basal and SCCs treated by kilovoltage radiotherapy in the period 1972–2002. The total dose of ionizing radiation administered ranged from 40 to 85 Gy, with different dose fractionations, according to the technique employed. The 5-year cure rate was 88.6%. Cosmetic results were evaluated as "good" or "acceptable" in 96.13% of the treated lesions in complete remission.

Caccialanza M et al (2003) Radiotherapy of carcinomas of the skin overlying the cartilage of the nose: results in 405 lesions. Eur J Dermatol 13(5):462–465

12.5.2 Perineural Invasion

Universtiy of Florida, 2003 → Radiotherapy alone or combined with surgery was used to treat 135 patients with microscopic or clinical evidence of perineural invasion of skin carcinoma. The 5-year local control rates without salvage therapy were 87% with microscopic perineural invasion and 55% with clinical perineural invasion. Overall, 88% of the local failures occurred in patients with positive margins. Almost half of the recurrences in patients with microscopic perineural invasion were limited to the first-echelon regional nodes. Radiotherapy in patients with skin cancer with clinical perineural invasion should include treatment of the first-echelon regional lymphatics. The risk of regional node involvement is also relatively high for patients with SCC with microscopic perineural invasion.

Garcia-Serra A et al (2003) Carcinoma of the skin with perineural invasion. Head Neck 25(12):1027–1033

12.5.3 Hypofractionation

Centre François Baclesse, France, 1989 → 675 cases of cutaneous epidermoid carcinomas of the face were treated with superficial irradiation therapy according to an original dose and time schedule (three fractions of 1,020 R over 14 days). The failure rate was low (less than 4%). Ninety percent of recurrences appeared within 3 years; they were central and most frequently observed in nasal locations and BCCs. Complications were rare (fewer than 3% of cases), and the majority were cured by medical treatment. Cosmetic results were satisfactory in over 90% of cases.

Abatucci JS et al (1989) Radiation therapy of skin carcinomas: results of a hypofractionated irradiation schedule in 675 cases followed more than 2 years. Radiother Oncol 14(2):113–119

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Lymphomas and Total Body Irradiation 13

Murat Beyzadeoglu, Cuneyt Ebruli, and Gokhan Ozyigit

Lymphomas originate from immune system cells in various stages of differentiation. They cause several morphological, immunological and clinical situations according to their origins.

All lymphoid cells originate from hematopoietic progenitor cells. These progenitor cells are divided into two subgroups: lymphoid and myeloid precursor cells. Lymphoid stem cells differentiate into B and T lymphocytes, which are the final products.

- B cell origin: 75% of lymphoid leukemias and 90% of all lymphomas [1].

Lymphoma classification changes frequently (see for example Rapaport in 1966, Lukes/Collins in 1974, Working Formulation in 1982, REAL in 1994 and WHO in 2001). The WHO classification is the most recent valid system for lymphomas (Table 13.1) [2].

13.1 Hodgkin's Lymphoma

Hodgkin's lymphoma (HL) is histologically characterized by the presence of various numbers of diagnostic multinucleated giant cells (Reed–Sternberg cells) within a mixed inflammatory infiltrate, and it originates from the lymphoid system. This disease was first defined by Thomas Hodgkin in 1832. Old terms for this disease are lymphogranulomatous lymphadenoma and malignant granuloma [3].

- HL constitutes 14% of all lymphomas and 1% of all malignancies.

13.1.1 Pathology/General Presentation

It is pathognomonic to find multinucleated or multilobulated giant cells called Reed–Stenberg [CD15+, CD30+] cells in biopsy material. Similar cells may be seen in infectious mononucleosis and non-Hodgkin lymphoma (NHL). These cells are surrounded by normal lymphocytes, plasma cells and eosinophils.

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Table 13.1 WHO lymphoma classification [2]

B cell NHL	T cell NHL	HL
Precursor B neoplasms	Precursor T neoplasms	Nodular lymphocyte predominant HL
Precursor B lymphoblastic leukemia/lymphoma	Precursor T lymphoblastic leukemia/lymphoma	Classical HL
Mature B cell neoplasms	Mature T cell neoplasms	Nodular sclerosing
B-CLL/small lymphocytic lymphoma	T cell prolymphocytic leukemia	Lymphocyte-rich HL
B prolymphocytic leukemia	T cell granular lymphocytic leukemia	Mixed cellular HL
Lymphoplasmocytic lymphoma	Aggressive NK cell leukemia	Lymphocyte-depleted HL
Splenic marginal zone B cell lymphoma	Adult T cell leukemia/ lymphoma	
Nodal marginal zone lymphoma	Extranodal NK/T cell lymphoma, nasal type	
MALT-type extranodal marginal zone lymphoma	Enteropathy-type T cell lymphoma	
Mantle cell lymphoma	Hepatosplenic gamma/delta lymphoma	
Follicular lymphoma	Subcutaneous panniculitis-like lymphoma	
Hairy cell leukemia	Mycosis fungoides/Sézary syndrome	
Plasma cell myeloma	Anaplastic large cell, primary cutaneous type	
Diffuse large B cell lymphoma	Peripheral T cell lymphoma	
Burkitt's lymphoma/ leukemia	Angioimmunoblastic T cell lymphoma	
	Anaplastic large cell, systemic type	

NHL non-Hodgkin lymphoma; *HL* Hodgkin's lymphoma

HL is classified into two groups according to the presence of fibrosis, collagen bands, necrosis and malignant reticular cells (WHO classification) [4].

1. Nodular lymphocyte predominant HL (2–5%)
2. Classical HL (~95%):
   - Nodular sclerosing HL (~65%).
   - Lymphocyte-rich HL (~10%).
   - Mixed cellular HL (~20%).
   - Lymphocyte-depleted HL (<5%).

13.1.2 Clinical Signs

Lymphadenopathy: lymph nodes are rubber-like and painless. They grow slowly. The most common site for LAP is the cervical region (80%). Axilla and inguinal region involvement is rare. An anterior mediastinal mass is frequently seen (50%). Hepatosplenomegaly is rare.

B symptoms:

- Fever (due to increases in interleukins 1 and 2; should be of unknown origin and above 38°C)
- Drenching night sweats (due to increases in interleukins 1 and 2)
- Weight loss (≥10% in the last 6 months; due to TNF increase)

In addition, itching and pain after alcohol intake may be observed. The most common symptom presented is a cervical mass (80%) [5]. B symptoms are present in one-third of all cases. Splenic involvement is seen in nearly all cases with bone marrow and hepatic involvement [5].

Nodular lymphocyte predominant HL: CD15 (−), CD30 (−), CD45 (+), CD20 (+) [5].

- This type is seen after 40 years of age. Mediastinal involvement is usually not observed. The most common presentation is lymphadenopathies in peripheral lymph node regions. Generally, late relapses are observed. Survival is excellent.

Nodular sclerosing HL: mediastinal involvement is common.
Mixed cellular HL: such cases are usually at advanced stages, and even early-stage supradiaphragmatic cases commonly have microscopic abdominal disease.
Lymphocyte-depleted HL: these cases are rarely seen, and usually occur in older patients. Most of them have B symptoms. This type has poor prognosis and is associated with HIV.

13.1.3 Staging

Cotswolds Lymphoma Staging 1989 (Modified Ann Arbor) [6]

Stage I
The involvement of a single lymph node region (I) or localized involvement of a single extralymphatic organ or site (IE).
Stage II
The involvement of two or more lymph node regions on the same side of the diaphragm (II) or the localized involvement of a single associated extralymphatic organ or site and its regional lymph node(s) with or without the involvement of other lymph node regions on the same side of the diaphragm (IIE). *Note*: the number of lymph node regions involved can be indicated using a subscript.
Stage III
The involvement of lymph node regions on both sides of the diaphragm (III), which may also be accompanied by localized involvement of an associated extralymphatic organ or site (IIIE), by involvement of the spleen (IIIS), or by involvement of both

(*continued*)

(continued)

(IIIE + S). Stage III disease may be subdivided according to the anatomic distribution of abdominal involvement or the extent of splenic involvement. Stage III (1) indicates involvement that is limited to the upper abdomen above the renal vein. Stage III (2) indicates the involvement of pelvic and/or paraaortic nodes. Five or more visible splenic nodules on a cut section constitutes extensive splenic involvement. Zero to four nodules is classified as minimal splenic disease.

Stage IV

Disseminated (multifocal) involvement of one or more extralymphatic organs, with or without associated lymph node involvement, or isolated extralymphatic organ involvement with distant (nonregional) nodal involvement.

Bulky disease [6] → massive mediastinal involvement (thoracic ratio of maximum transverse mass diameter of 33% or more of the internal transverse thoracic diameter measured at the T5/6 intervertebral disc level on chest radiography) or lymph node ≥10 cm (Fig. 13.1) [7].

B symptom (−): A (e.g., stage IIIA).

B symptom (+): B (e.g., stage IIIB).

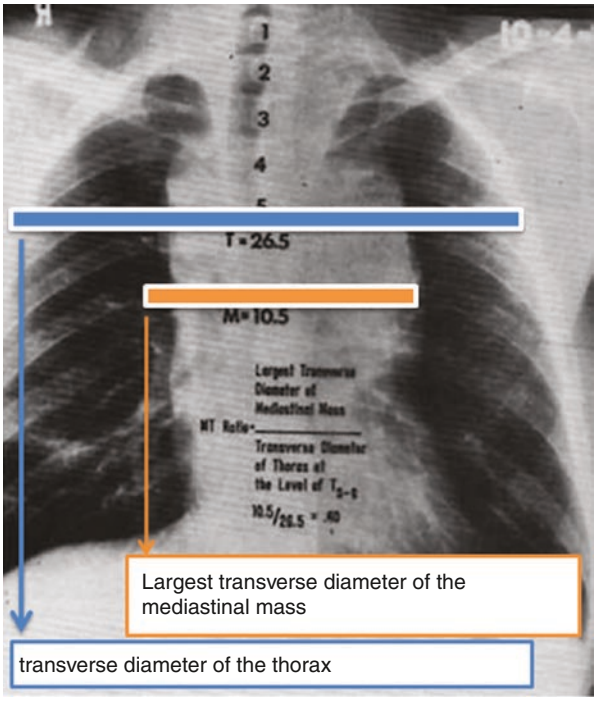

Fig. 13.1 Mediastinal bulky disease (from [23], p 806, Fig. 32.1, reproduced with the permission from Springer Science and Business Media)

Risk Groups for HL

Early favorable: clinical stage I or II without any risk factors.
Early unfavorable: clinical stage I or II with one or more of the following risk factors:
- Large mediastinal mass
- Extranodal involvement
- Elevated ESR (>30 mm/h for B stage, >50 mm/h for A stage)
- Involvement of ≥3 lymph node areas
- B symptoms

Advanced favorable: clinical stage III or IV with 0–3 of the adverse risk factors listed below.
Advanced unfavorable: clinical stage III or IV with ≥4 of the adverse risk factors listed below.
- Albumin level of less than 4.0 g/dL
- Hemoglobin level of less than 10.5 g/dL
- Male sex
- Age of 45 years or older
- Stage IV disease
- White blood cell (WBC) count of at least 15,000/mm^3

Absolute lymphocytic count of less than 600/mm^3 or a lymphocyte count that was less than 8% of the total WBC count

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13.1.4 Treatment Algorithm

Treatment Algorithm for HL [8]

Favorable stage IA–IIA (bulky (−), involvement of ≤3 LN regions, ESR <50
Four cycles ABVD + involved field RT (IFRT)

- RT dose in subclinical disease, 20 Gy
- RT dose in clinical disease, 30–36 Gy

(*continued*)

(continued)

- IFRT alone in nodular lymphocyte predominant HL

Poor prognostic factors (−), alternative → extended-field RT (EFRT) (20–36 Gy)
Unfavorable stage IA–IIA (bulky (+), involvement of >3 LN regions, ESR >50); stage IB–IIB
Four to six cycles of ABVD + IFRT [20–36 Gy]
Stage III–IV
Restaging after four cycles of ABVD

- Complete response

  Two cycles of ABVD + 20–36 Gy IFRT for residual/bulky regions
- Partial response

Two to four cycles of ABVD + 30–36 Gy IFRT for residual/bulky regions

Special Situations [8]

Primary refractory disease
High-dose chemotherapy + stem cell transplantation
Relapse
CT or CT + RT

- Previous RT (+): 15–20 Gy RT
- Previous RT (−): 30–40 Gy RT
- Relapse in stage III–IV cases → autologous bone marrow transplantation (BMT) or stem cell transplantation

ABVD → adriamycin (doxorubicin), bleomycin, vinblastine, dacarbazine.

- Risks of sterility and secondary malignancy are lower than with the MOPP regimen (MOPP: mechlorethamine, vincristine, procarbazine, prednisolone).

Poor prognostic factors [8] → male gender, age >45, stage IV, Hb <10.5, WBC >15,000, lymphocyte <6,000, albumin <40 g/dL, ESR >50

Ninety percent of children and 80% of adults at all anatomical stages and with all histological subtypes are cured with modern therapeutic approaches.

13.1.5 Radiotherapy

Favorable early-stage HL (IA–2A) can be classically treated with EFRT alone. However, combined chemotherapy and IFRT is preferred due to late effects of EFRT.

Extended-Field RT Types

- EFRT fields without chemotherapy for supradiaphragmatic HL [with no poor prognostic factors, favorable early stage (IA–2A)]
  Mantle, mini mantle, modified mantle
- EFRT fields without chemotherapy for infradiaphragmatic HL [with no poor prognostic factors, favorable early stage (IA–2A)]
  Inverse Y, subtotal nodal irradiation (STNI), STNI + splenic RT

Total nodal irradiation (TNI) → mantle + inverse Y

Mantle RT Simulation [9]

- Bilateral cervical, supraclavicular, infraclavicular, hilar, mediastinal and axilla lymphatics are included (Fig. 13.2a, b).
- Simulation is performed in the supine position with maximum extension of the head and arms above the head or arms at a 90° angle towards the side, or in the anatomical position with hands on the waist (akimbo position) (Fig. 13.3) [9].

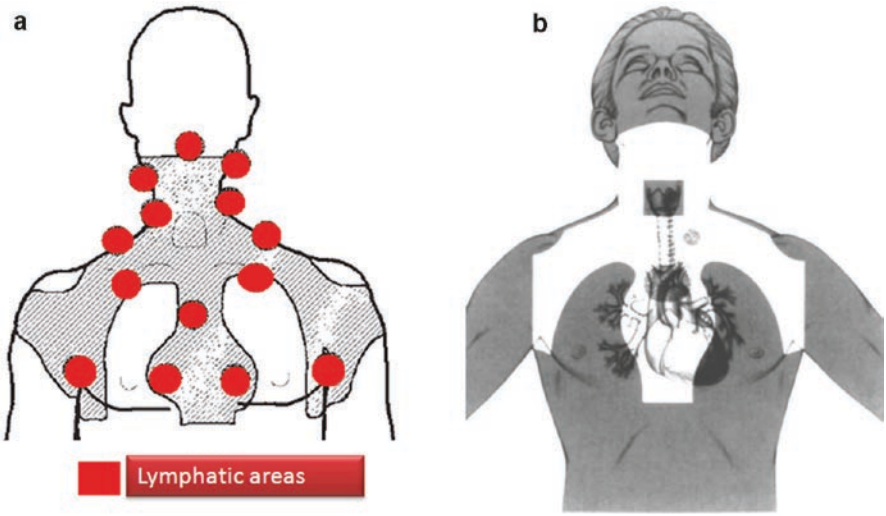

Fig. 13.2 (**a**) Lymphatics included within mantle field; (**b**) mantle field (from [10], p 663, Fig. 30.1, reproduced with the permission from Springer Science and Business Media)

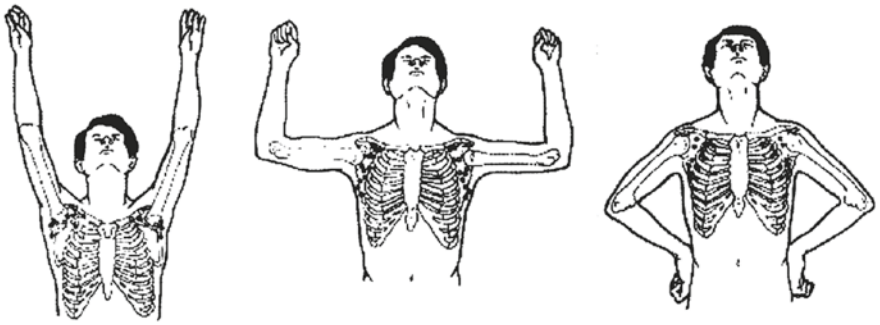

Fig. 13.3 The positions of the arms in mantle radiotherapy (from [23], p 818, Fig. 32.5a–c, reproduced with the permission from Springer Science and Business Media)

Neck should be at maximum extension.

- Extension should be in a position where the chin is in the same plane as the mastoid process and external occipital protuberance (Fig. 13.4) [9].
- This ensures the exclusion of the oral cavity and teeth from the RT fields, and decreases the dose to the mandible.

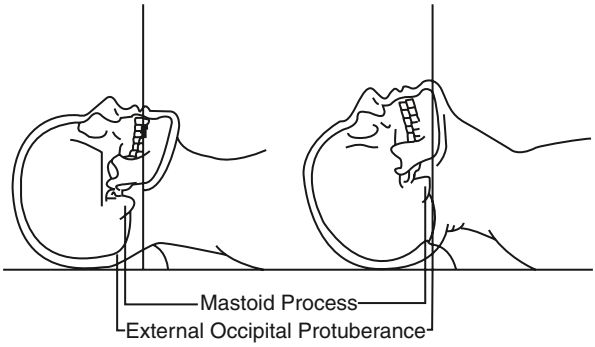

Fig. 13.4 Head position in mantle RT (from [23], p 819, Fig. 32.6, reproduced with the permission from Springer Science and Business Media)

Borders of Mantle RT (Fig. 13.5) [9, 10]

- *Superior*: chin–mastoid process tip line
- *Inferior*: T9–10 or T10–11 intervertebral space (diaphragmatic dome) [pericardial involvement or epicardial LAP (+) → T11–T12 intervertebral space]
- *Lateral*: includes axilla

All palpable lymph nodes should be marked with wires.

- Planning is usually performed at SSD = 100 cm. However, if the field size is more than the maximum field size of the treatment machine, the SSD can be increased during simulation.

- Central axis is usually at the sternal notch or close to it.
- Central axis and the points 10 cm to the right and left of it and the inferior border should be marked with a tattoo to check during the daily set-up and to allow for the possibility of infradiaphragmatic RT at later stages.

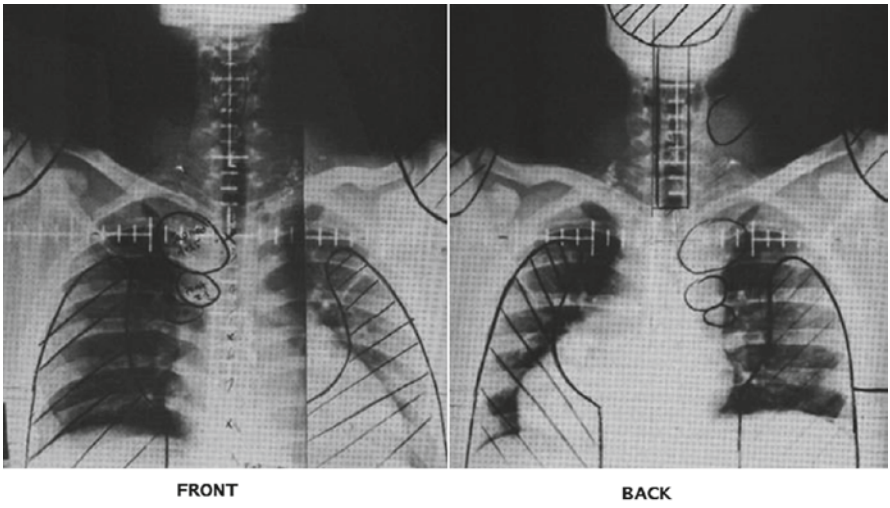

Fig. 13.5 Anterior and posterior simulation films of mantle RT (from [23], p 820, Fig. 32.9a, b, reproduced with the permission from Springer Science and Business Media)

Mantle RT field shielding blocks [9]: these blocks should be individualized focalized blocks after simulation (Fig. 13.6).

- *Lung blocks*: made separately for anterior and posterior.

Upper border in anterior: 2 cm below the medial clavicle, and a thin lung band is left at the lateral clavicle.
Upper border in posterior: a thin band is left under the clavicle since the infraclavicular LNs are located anteriorly.
Lateral borders: a 1 cm band is left in costal curves which extends until the fifth to the sixth costa and finishes horizontally in the chest wall.
Medial borders: bilateral hilar regions and mediastinal lymphatics are included (mediastinal enlargement should be included).

- Humeral heads are shielded both anteriorly and posteriorly.
- Larynx is shielded.
- Heart below hilar level is shielded without including the mediastinal region both anteriorly and posteriorly.
- Spinal cord is shielded in the midline.
- A small block is put at the inferior border to the spinal cord posteriorly.
- Oral cavity is protected if the superior border includes the oral cavity.

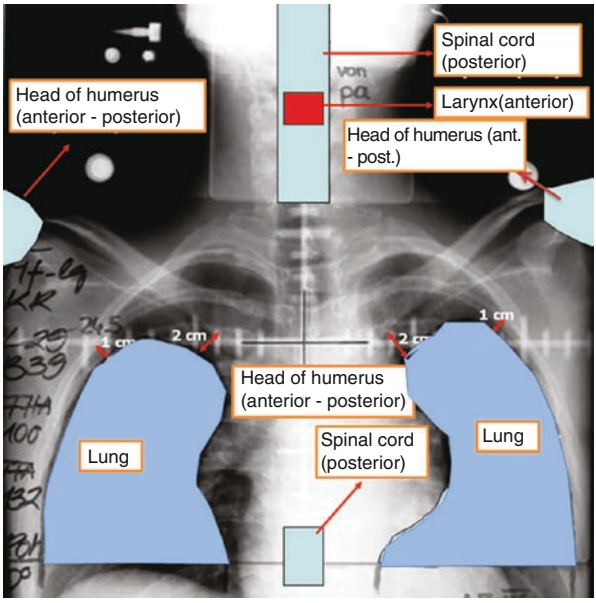

Fig. 13.6 Shielding blocks in mantle RT (from [23], p 820, Fig. 32.9a, b, reproduced with the permission from Springer Science and Business Media)

Mini mantle: mediastinal and hilar regions are not included (Fig. 13.7a).
Modified mantle: axillary lymph nodes are not included (Fig. 13.7b).

Inverse Y (Fig. 13.8) [9]

- Paraaortic, bilateral pelvic, and bilateral inguinal–femoral lymphatics are included. Splenic lymphatics are also included in cases where there is involvement.
- Rarely used (→ usually in TNI).

Superior: dome of diaphragm/above T11 vertebra.

- A gap is provided in cases with previous mantle or mediastinal RT.

Inferior: includes inguinal lymph nodes.
Lateral: iliac spines.

- If the spleen is irradiated, the paraaortic field is enlarged at the upper left [9, 10].
- Paraaortic field width is nearly 9–10 cm if no LAP is present, and limited to the transverse processes of vertebrae.

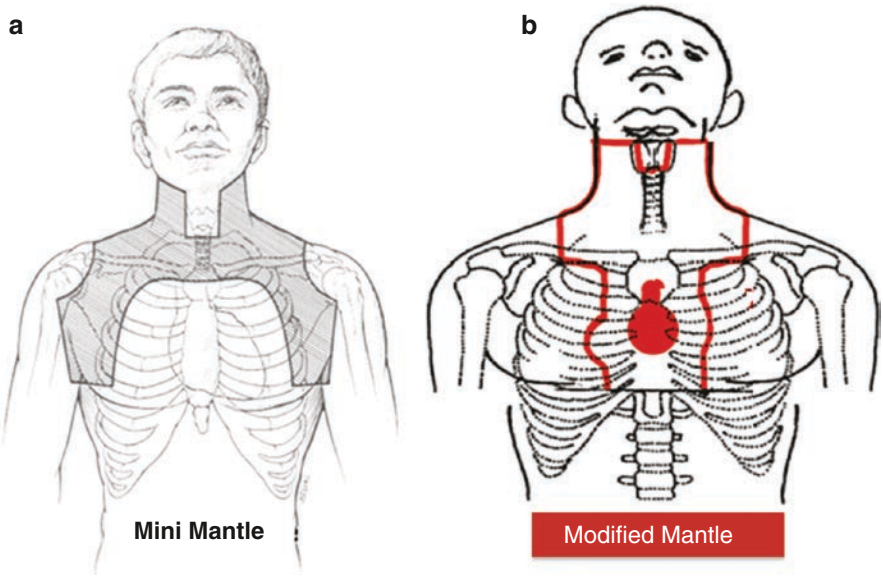

Fig. 13.7 (**a**) Mini mantle; (**b**) modified mantle (from [23], p 827, Fig. 32.20, reproduced with the permission from Springer Science and Business Media)

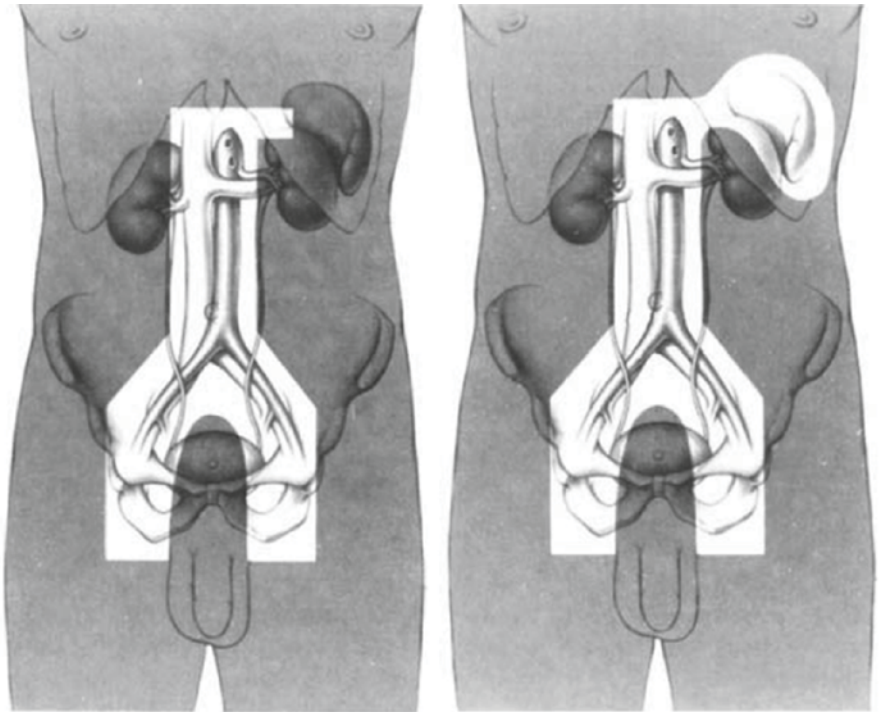

Fig. 13.8 Inverse Y and inverse Y + splenic RT fields (from [10], p 663, Fig. 30.2, reproduced with the permission from Springer Science and Business Media)

IV contrast is used for the visualization of the kidneys. Two AP and PA simulation films are taken. Shielding areas are marked at the level of the kidneys, iliac wings and sacrum (midline block). A testis shield should be used. The ovaries should be transported surgically to outside of the field, or marked with clips and shielded during radiotherapy.

Subtotal Nodal Irradiation (Fig. 13.9) [9]

- Sequential mantle + paraaortic field + splenic irradiation

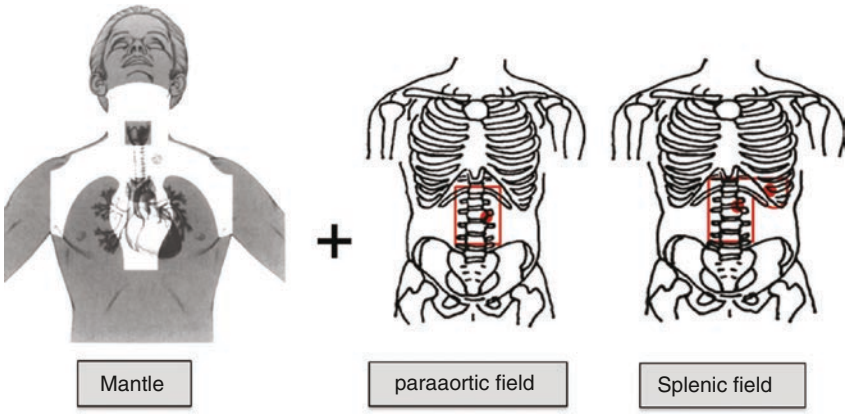

Fig. 13.9 Subtotal nodal irradiation field (from [10], p 663, Fig. 30.1 and [23], p 828, Fig. 32.21; reproduced with the permission from Springer Science and Business Media)

Total Nodal Irradiation (TNI) (Fig. 13.10) [9]

- Sequential mantle + inverse Y ± splenic irradiation

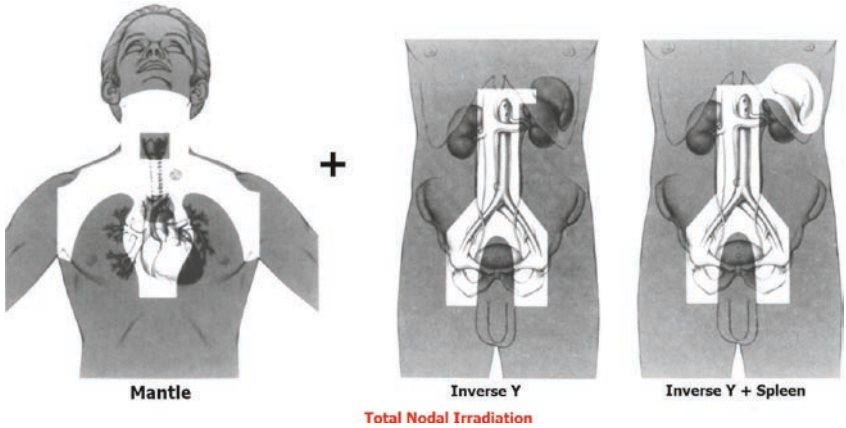

Fig. 13.10 Total nodal irradiation field (from [10], p 663, Figs. 30.1 and 30.2, reproduced with the permission from Springer Science and Business Media)

Involved Field RT Examples (Fig. 13.11a–c)

Unilateral cervical LN ± supraclavicular LN involvement:
Superior: upper cervical LN (+), 1.5–2 cm above mastoid process; middle/lower cervical LN (+), mastoid process
Inferior: 2 cm below clavicle
Medial: supraclavicular LN (−), inner side of vertebral corpus; supraclavicular LN (−), contralateral transverse process of vertebra
Lateral: two-thirds of clavicle

- Larynx is shielded.

Bilateral cervical LN ± supraclavicular LN involvement:
Superior: upper cervical LN (+), 1.5–2 cm above mastoid process; middle/lower cervical LN (+), mastoid process
Inferior: 2 cm below clavicle
Lateral: two-thirds of clavicle

- Larynx is shielded.
- Spinal cord is shielded.

Mediastinal, cervical, axillary LN involvement:
Superior: upper cervical LN (+), 1.5–2 cm above mastoid process; middle/lower cervical LN (+), mastoid process
Inferior: 2–3 cm below prechemotherapy mediastinal mass
Medial: two-thirds of clavicle
Lateral: includes involved axilla

- Larynx is shielded.
- Spinal cord is shielded.
- Humeral head is shielded (Table 13.2).

Table 13 2 Lymphatic regions for involved field radiotherapy

Lymph node	Radiotherapy fields (IFRT)
Preauricular and submandibular	Preauricular, cervical, supraclavicular LN, Waldeyer field LN
Upper cervical	Bilateral cervical/preauricular, supraclavicular LN
Lower cervical, supraclavicular, infraclavicular	Bilateral cervical/supraclavicular/infraclavicular
Axilla	Ipsilateral axilla/supraclavicular/infraclavicular
Cubital	Cubital and ipsilateral axilla LN
Epitrochlear	Epitrochlear and ipsilateral axilla LN
Mediastinal	Hilar, mediastinal
Hilar	Hilar, mediastinal

(*continued*)

Table 13.2 (continued)

Lymph node	Radiotherapy fields (IFRT)
Paraaortic	Paraaortic, splenic, portal LN
Iliac	Ipsilateral iliac/inguinal
Inguinal/femoral	Ipsilateral inguinal/femoral
Popliteal	Ipsilateral popliteal/inguinal/femoral LN

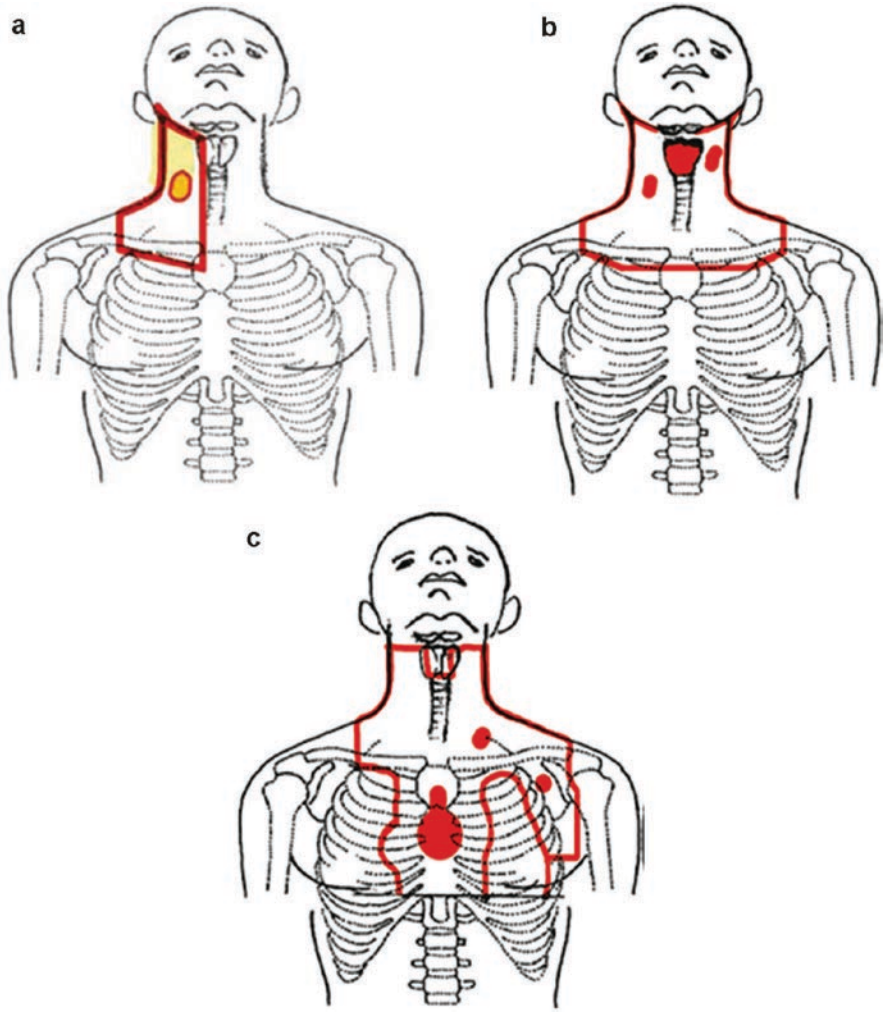

Fig. 13.11 (**a–c**) IFRT samples (from [23], p 827, Fig. 32.20, reproduced with the permission from Springer Science and Business Media)

- If upper cervical LN is bulky in cases receiving mantle RT, the cervical part of the mantle field may be planned with the Waldeyer RT portal. A gap is left with the mantle (Fig. 13.13).

Waldeyer Field RT (Fig. 13.12) [10]

- IFRT used for involvement of the Waldeyer lymph nodes, preauricular LN involvement, cervical lymph node at the thyroid notch level.

  Two lateral fields:
  Superior: includes sphenoidal sinus + 1 cm above the zygomatic arch
  Posterior: spinal processes
  Anterior: anterior to second molar tooth
  Inferior: thyroid notch (above hyoid bone)

- Brain, teeth and maxillary sinus within field is shielded.
- Single field may be used in cases of unilateral preauricular LN involvement.

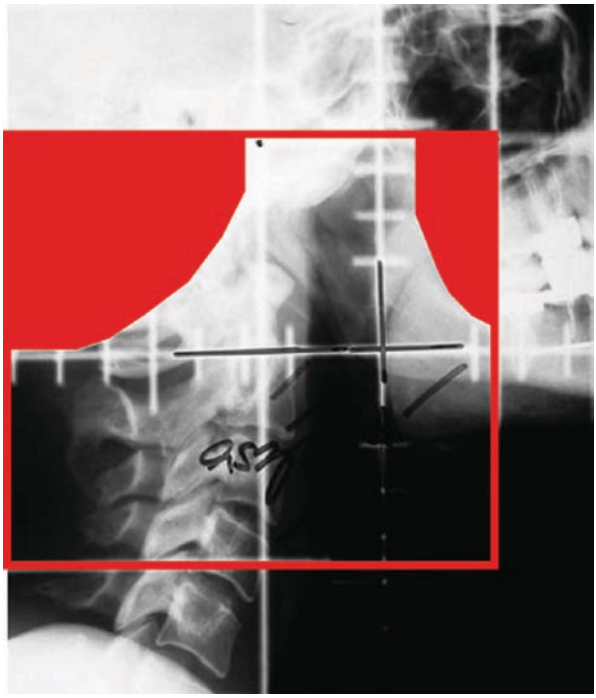

Fig. 13.12 Waldeyer RT field (from [10], p 689, Fig. 30.5, reproduced with the permission from Springer Science and Business Media)

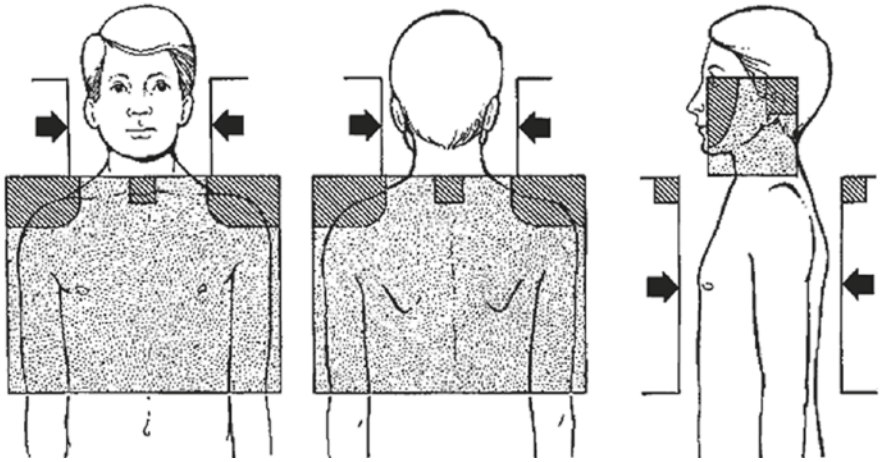

Fig. 13.13 Mantle RT together with Waldeyer field (from [23], p 825, Fig. 32.16, reproduced with the permission from Springer Science and Business Media)

13.2 Selected Publications

H7, 1994 → patients with stage I or II HL were stratified into two groups, favorable and unfavorable, based on the following four prognostic factors: age, symptoms, number of involved areas, and mediastinal–thoracic ratio. The experimental therapy consisted of six cycles of epirubicin, bleomycin, vinblastine, and prednisone (EBVP) followed by IFRT. It was randomly compared, in favorable patients, to STNI and, in unfavorable patients, to six cycles of mechlorethamine, vincristine, procarbazine, prednisone, doxorubicin, bleomycin, and vinblastine (MOPP/ABV hybrid) and IFRT. Median follow-up time of the 722 patients included was 9 years.

- In 333 favorable patients, the 10-year event-free survival rates (EFS) were 88% in the EBVP arm and 78% in the STNI arm ($p = 0.0113$), with similar 10-year overall survival (OS) rates (92 vs. 92%, respectively; $p = 0.79$).
- In 389 unfavorable patients, the 10-year EFS rate was 88% in the MOPP/ABV arm compared with 68% in the EBVP arm ($p < 0.001$), leading to 10-year OS rates of 87 and 79%, respectively ($p = 0.0175$).
- A treatment strategy for early-stage HL based on prognostic factors leads to high OS rates in both favorable and unfavorable patients. In favorable patients, the combination of EBVP and IFRT can replace STNI as standard treatment. In unfavorable patients, EBVP is significantly less efficient than MOPP/ABV.

Noordijk EM et al (2006) Combined-modality therapy for clinical stage I or II Hodgkin's lymphoma: long-term results of the European Organisation for Research and Treatment of Cancer H7 randomized controlled trials. J Clin Oncol 24(19):3128–3135

H8, 2007 → 1,538 patients (age, 15–70 years) who had untreated stage I or II supradiaphragmatic Hodgkin's disease with favorable prognostic features (the H8-F trial) or unfavorable features (the H8-U trial). In the H8-F trial, three cycles of mechlorethamine, vincristine, procarbazine, and prednisone (MOPP) combined with doxorubicin, bleomycin, and vinblastine (ABV) plus involved-field radiotherapy were compared with subtotal nodal radiotherapy alone (reference group). In the H8-U trial, three regimens were compared: six cycles of MOPP-ABV plus involved-field radiotherapy (reference group), four cycles of MOPP-ABV plus involved-field radiotherapy, and four cycles of MOPP-ABV plus subtotal nodal radiotherapy. The median follow-up was 92 months.

- In the H8-F trial, the estimated 5-year EFS rate was significantly higher after three cycles of MOPP-ABV plus involved-field radiotherapy than after subtotal nodal radiotherapy alone (98 vs. 74%, $p<0.001$). The 10-year OS estimates were 97 and 92%, respectively ($p=0.001$).
- In the H8-U trial, the estimated 5-year EFS rates were similar in the three treatment groups: 84% after six cycles of MOPP-ABV plus involved-field radiotherapy, 88% after four cycles of MOPP-ABV plus involved-field radiotherapy, and 87% after four cycles of MOPP-ABV plus subtotal nodal radiotherapy. The 10-year OS estimates were 88, 85, and 84%, respectively.
- Chemotherapy plus involved-field radiotherapy should be the standard treatment for Hodgkin's disease with favorable prognostic features.
- In patients with unfavorable features, four courses of chemotherapy plus involved-field radiotherapy should be the standard treatment.

Ferme C (2007) Chemotherapy plus involved-field radiation in early-stage Hodgkin's disease. N Engl J Med 357(19):1916–1927

German HD8, 2003 → 1,204 patients with newly diagnosed early-stage unfavorable HD were randomly assigned to receive cyclophosphamide, vincristine, procarbazine, and prednisone (COPP) + doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) for two cycles followed by radiotherapy of 30 Gy EF + 10 Gy to bulky disease (arm A) or 30 Gy IF + 10 Gy to bulky disease (arm B). The median follow-up time was 54 months.

- Survival rates at 5 years after start of radiotherapy revealed no differences between arms A and B, respectively, in terms of FFTF (85.8 and 84.2%) and OS at 5 years (90.8 and 92.4%).
- There were no differences between arms A and B, respectively, in terms of complete remission (98.5 and 97.2%), progressive disease (0.8 and 1.9%), relapse (6.4 and 7.7%), death (8.1 and 6.4%), and secondary neoplasia (4.5 and 2.8%).
- Radiotherapy volume size reduction from EF to IF after COPP + ABVD chemotherapy for two cycles produces similar results and less toxicity in patients with early-stage unfavorable HD.

Engert A et al (2003) Involved-field radiotherapy is equally effective and less toxic compared with extended-field radiotherapy after four cycles of chemotherapy in patients with early-stage unfavorable Hodgkin's lymphoma: results of the HD8 trial of the German Hodgkin's Lymphoma Study Group. J Clin Oncol 21(19):3601–3608

Italy, 2007 → among 260 patients treated with induction chemotherapy for bulky HL, 160 patients achieved negative residual masses at 2-[18F]fluoro-2-deoxy-D-glucose positron emission tomography (FDG-PET) scans. They were randomly divided into two well-matched groups to receive either 32 Gy radiotherapy to bulky area or no further therapy. Median follow-up: 40 months.

- Histology showed a malignancy in 14% of patients in the chemotherapy-only group and in 4% of patients in the chemotherapy + radiotherapy group ($p = 0.03$). All the relapses in the chemotherapy-only group involved the bulky site and the contiguous nodal regions. Thus, the overall diagnostic accuracy of FDG-PET to exclude future relapses in the patients not protected by radiotherapy was 86%, with a false-negative rate of 14%.
- The addition of irradiation helps improve EFS in HL patients with postchemotherapy FDG-PET-negative residual masses.

Picardi M (2007) Randomized comparison of consolidation radiation versus observation in bulky Hodgkin's lymphoma with post-chemotherapy negative positron emission tomography scans. Leuk Lymphoma 48(9):1721–1727

NCI Canada/ECOG, 2005 → 399 patients with nonbulky clinical stage I–IIA Hodgkin's lymphoma were stratified into favorable and unfavorable risk cohorts. Patients allocated to radiation-containing therapy received subtotal nodal radiation if favorable risk or combined-modality therapy if unfavorable risk. Patients allocated to ABVD received 4–6 treatment cycles. Median follow-up was 4.2 years.

- Five-year freedom from disease progression was superior in patients allocated to radiation therapy ($p = 0.006$; 93 vs. 87%); no differences in EFS ($p = 0.06$; 88 vs. 86%) or OS ($p = 0.4$; 94 vs. 96%) were detected.
- In a subset analysis comparing patients stratified into the unfavorable cohort, freedom from disease progression was superior in patients allocated to combined-modality treatment ($p = 0.004$; 95 vs. 88%); no difference in OS was detected ($p = 0.3$; 92 vs. 95%).
- In patients with limited-stage Hodgkin's lymphoma, no difference in OS was detected between patients randomly assigned to receive treatment that includes radiation therapy or ABVD alone. Although 5-year freedom from disease progression was superior in patients receiving radiation therapy, this advantage is offset by deaths due to causes other than progressive Hodgkin's lymphoma or acute treatment-related toxicity.

Meyer RM et al (2005) Randomized comparison of ABVD chemotherapy with a strategy that includes radiation therapy in patients with limited-stage Hodgkin's lymphoma: National Cancer Institute of Canada Clinical Trials Group and the Eastern Cooperative Oncology Group. J Clin Oncol 23(21):4634–4642

HD1 (German Hodgkins Study Group), 1995 → 288 patients with stage IIIB or IV HD received induction chemotherapy with 3× (COPP + ABVD). Patients achieving CR were eligible for randomization to either 20 Gy radiotherapy to initially involved fields (RT-arm) or to an additional 1× (COPP + ABVD) (CT arm). Patients with nodal PR were allocated to more intense radiotherapy (IRT arm: 20 Gy IF, 40 Gy to persisting tumor).

- 171 (59%) achieved CR after induction chemotherapy. Of these, 100 patients were successfully randomized to RT or CT. In the CT arm, relapses were observed in 10 of 49 patients compared with 13 of 51 patients in the RT arm (p = n.s.).
- No differences in treatment efficacy were detected between 20 Gy IF radiotherapy and 1× (COPP + ABVD) chemotherapy following CR after six cycles of alternating chemotherapy in patients with advanced-stage HD.

Diehl V et al (1995) Further chemotherapy versus low-dose involved-field radiotherapy as consolidation of complete remission after six cycles of alternating chemotherapy in patients with advanced Hodgkin's disease. German Hodgkins' Study Group (GHSG). Ann Oncol 6(9):901–910

SWOG 7808, 1994 → 278 adults with clinical or pathologic stage III or IV Hodgkin's disease, who achieved complete responses after six cycles of MOP-BAP (nitrogen mustard, vincristine, prednisone, bleomycin, doxorubicin, and procarbazine).

- Remission duration, relapse-free survival, and OS were similar for the two groups ($p = 0.09$, $p > 0.2$, and $p = 0.14$, respectively).
- Low-dose radiation improved remission duration in the subgroups of patients with nodular sclerosis and bulky disease. For all patients with bulky disease, the 5-year remission duration estimate was 75% for the low-dose radiation group and 57% for the no further treatment group ($p = 0.05$).
- No difference in OS was noted between low-dose radiation and no further treatment in all patients or major subgroups.
- Low-dose involved field radiation after MOP-BAP chemotherapy in patients with stage III or IV Hodgkin's disease did not prolong remission duration or OS in randomized patients.

Fabian CJ et al (1994) Low-dose involved field radiation after chemotherapy in advanced Hodgkin disease. A Southwest Oncology Group randomized study. Ann Intern Med 120(11):903–912

EORTC 20884, 2003 → 739 stage III–IV HL cases were treated with 6–8 cycles of mechlorethamine, vincristine, procarbazine, prednisone/doxorubicin, bleomycin, and vinblastine hybrid chemotherapy. Patients in complete remission (CR) after chemotherapy were randomized between no further treatment and (IFRT). Those in PR after six cycles received IFRT (30 Gy to originally involved nodal areas and 18–24 Gy to extranodal sites with or without a boost). Median follow-up was 7.8 years.

- The 8-year EFS and OS rates for the 227 patients in PR who received IFRT were 76 and 84%, respectively. These rates were not significantly different from those for CR

patients who received IFRT (73 and 78%) or from those in CR who did not receive IFRT (77 and 85%).
- Patients in PR after six cycles of mechlorethamine, vincristine, procarbazine, prednisone/doxorubicin, bleomycin, vinblastine treated with IFRT had 9-year EFS and OS rates similar to those of patients in CR, suggesting a definite role for RT in these patients.

Aleman BM et al (2007) Involved-field radiotherapy for patients in partial remission after chemotherapy for advanced Hodgkin's lymphoma. Int J Radiat Oncol Biol Phys 67(1):19–30

Germany, 1998 → data on 1,740 patients treated in 14 different trials that included 16 relevant comparisons were analyzed.

- Additional RT showed an 11% overall improvement in tumor control rate after 10 years ($p=0.0001$). No difference could be detected with respect to OS ($p=0.57$).
- When combined-modality treatment was compared with CT alone in the parallel-design trials, no difference could be detected in tumor control rates ($p=0.43$), but OS was significantly better after 10 years in the group that did not receive RT ($p=0.045$).
- There were significantly fewer fatal events among patients in continuous complete remission (relative risk, 1.73; $p=0.005$) if no RT was given.
- Combined-modality treatment in patients with advanced-stage Hodgkin's disease overall has a significantly inferior long-term survival outcome than CT alone if CT is given over an appropriate number of cycles. The role of RT in this setting is limited to specific indications.

Loeffler M (1998) Meta-analysis of chemotherapy versus combined modality treatment trials in Hodgkin's disease. International Database on Hodgkin's Disease Overview Study Group. J Clin Oncol 16(3):818–829

13.3 Non-Hodgkin Lymphoma

NHLs are malignancies of the lymphoid–reticular system, like HL. They are usually observed in older patients and show more extranodal involvement than HLs. They also do not show contagious LN extension patterns, unlike HL. NHLs exhibit different responses to treatment modalities [11].

Extranodal involvement is commonly seen in the head–neck region, particularly in the Waldeyer ring, nasal cavity, paranasal sinus, oral cavity, larynx and orbita. The most commonly involved extralymphatic localizations are the liver, lungs and bone marrow.

13.3.1 Pathology/General Presentation

The Rappaport, Lukes/Collins, International Formulation, and Kiel classifications are not used anymore. The current NHL classification system is the WHO system, which was the REAL in 2001 [2].

B cell NHLs constitute 80% of all NHLs [11]
Diffuse B cell lymphoma (DLBCL), 31%
Follicular lymphoma, 22%
MALT-type extranodal marginal zone B cell lymphoma, 5%
B-CLL/small lymphocytic lymphoma, 6%
Mantle cell lymphoma, 6%
T cell NHLs constitute 13% of all NHLs [11]
T/NK cell lymphoma, peripheral T cell lymphoma, 6%
Mycosis fungoides/Sézary syndrome, <1%
Anaplastic large cell lymphoma, 2%
Low-grade NHL [11].
Follicular lymphoma (grade I–II)
B-CLL/small lymphocytic lymphoma
MALT-type extranodal marginal zone B cell lymphoma
Mycosis fungoides/Sézary syndrome
Moderate-grade NHL [11]
Follicular lymphoma (grade III)
Mantle cell lymphoma
Diffuse large B cell lymphoma (DLBCL)
T/NK cell lymphoma, peripheral T cell lymphoma
Anaplastic large cell lymphoma
High-grade NHL [11]
Lymphoblastic lymphoma
Burkitt's lymphoma

- DLBCL is presented at stage I–II in 30–40% of cases, and is commonly associated with extranodal disease.
- Follicular lymphoma is presented at stage IV in 60% of cases (21% in stage I–II, 19% in stage III).
- MALT-type extranodal marginal zone B cell lymphoma is generally seen in the stomach, ocular adnexae, skin, thyroid, parotids, lungs and breasts. Most cases are at stage I–II (65–70%).
- Mantle cell lymphoma is generally presented as disseminated disease, and together with spleen, bone marrow and GIS involvement.

B symptoms are more common in HL.

13.3.2 Staging

Staging is the same as HL [5].

Limited-stage NHL

- Stage I–II (≤3 lymphatic region involvement), B symptom (−), bulky disease (−)

Advanced-stage NHL

- Stage II and >3 lymphatic region involvement, stage III–IV, B symptom (+), bulky disease (+)

International Prognostic Index (IPI) [11]

- IPI estimates the prognosis in low- to high-grade NHL.
- It consists of five elements:
  - Age: <60 or ≥60
  - Serum LDH level (normal or high)
  - ECOG performance status (0–1 or 2–4)
  - Stage (I–II or III–IV)
  - Extranodal involvement number (0–1 or >2)
- Five-year recurrence-free survival and OS for IPI ≥2: 50%
- Five-year OS: IPI 0–1, 73%; IPI 2, 51%; IPI 3, 43%; IPI, 4–5 26%

13.3.3 Treatment Algorithm

Treatment Algorithm for NHL [12]

Low-grade B cell lymphoma

Limited stage

IFRT

RT → 1.5–1.8 Gy/day, 25–36 Gy

Median OS → 10–15 years

Ten-year DFS → 40–50%

Transformation rate to diffuse B cell lymphoma → 10–15%

Advanced stage

Asymptomatic → surveillance

Symptomatic → CT or RT

CT → chlorambucil, CVP, fludarabine

RT → 8 Gy in single fraction

Median OS → 10–15 years

Recurrence

High-dose CT + stem cell transplantation, or

Radioimmunotherapy

Transformed disease

Treated as low-grade NHL

Radioimmunotherapy → the application of monoclonal antibodies (MAb) conjugated with radioisotopes.

- *Drugs used:* I-131-anti CD 20 MAb (tositumomab; Bexxar®) and yttrium-90 anti-CD 20 MAb (ibritumomab; Zevalin®)

Moderate-grade B cell lymphoma [12]

Limited stage
IPI 0–1 → four cycles of CT + IFRT
CT → CHOP–rituximab
RT → IFRT, 25–36 Gy
IPI ≥2 → 6–8 cycles of KT + IFRT
CT → CHOP–rituximab
RT → IFRT, 25–36 Gy

Advanced stage
6–8 cycles of CT ± IFRT
CT → CHOP
(CHOP-R in diffuse B cell lymphoma)
RT → IFRT, 25–36 Gy for bulky disease

Recurrence
High-dose CT + stem cell transplantation

Palliation
Solitary recurrence → RT (20 Gy in ten fractions or 4 Gy in two fractions)
Diffuse recurrence → CT (rituximab, etoposide, etc.)
Nasal NK/T cell lymphoma → RT is recommended as primary therapy (RT dose >50 Gy); consolidation CT is used for stage IIE and IPI >2

High-grade B cell lymphoma
Stage I–II
Chemotherapy ± RT (bulky disease, residual disease)
Stage III–IV
Chemotherapy

Gastric MALT-type extranodal marginal zone B cell lymphoma (MALTOMA)
Stage IAE
Two weeks of proton pump inhibitor + bismuth salicylate + tetracycline + metronidazole
Complete response → 97–98%
Other stages
Chemotherapy (alkylating agents)

Recurrence or resistance to antibiotics
IFRT
RT → 30 Gy in 2 Gy/day, (stomach + perigastric LN)
Local control → >95%

13.3.4 Radiotherapy

RT planning in NHL is similar to that in HL.

13.3.5 Selected Publications

SEER Data, 2008 → 13,420 patients with localized diffuse large B-cell lymphoma (DLBCL). The Surveillance, Epidemiology, and End Results database was queried for all patients diagnosed with stage I, IE, II, or IIE DLBCL between 1988 and 2004. 5,547 (41%) had received RT and 7,873 (59%) had not.

- RT was associated with a significant DSS (hazard ratio, 0.82, $p < 0.0001$) and OS benefit that persisted during the 15 years of follow-up.
- Elderly patients, defined as either >60 or >70 years old, had significantly improved DSS and OS associated with RT.
- On multivariate analysis, RT was significantly associated with increased DSS and OS.
- This analysis presents the largest detailed dataset of stage I–II DLBCL patients. RT is associated with a survival advantage in patients with localized DLBCL, a benefit that extends to elderly patients.

Ballonoff A et al (2008) Outcomes and effect of radiotherapy in patients with stage I or II diffuse large B-cell lymphoma: a surveillance, epidemiology, and end results analysis. Int J Radiat Oncol Biol Phys 72(5):1465–1471

JAROG; 2007 → 37 patients with MALT lymphoma. The median tumor dose was 30.6 Gy (range, 30.6–39.6 Gy). The median follow-up was 37.3 months.

- Moderate-dose RT was highly effective in achieving local control with acceptable morbidity in 37 patients with MALT lymphoma.

Isobe K (2007) A multicenter phase II study of local radiation therapy for stage IEA mucosa-associated lymphoid tissue lymphomas: a preliminary report from the Japan Radiation Oncology Group (JAROG). Int J Radiat Oncol Biol Phys 69(4):1181–1186

Italy, 2007 → 53 patients with primary mediastinal large B-cell lymphoma. Planned treatment consisted of induction chemotherapy (I-CT; prednisone, methotrexate, doxorubicin, cyclophosphamide, etoposide–mechloroethamine, vincristine, procarbazine, prednisone (ProMACE-MOPP) in the first two patients, MACOP-B in the next 11, and VACOP-B in the last 40) followed by IFRT. Median follow-up: 93.9 months.

- The response rates after I-CT were complete response (CR) in 20 (37.73%) and partial response (PR) in 30 (56.60%); three patients (5.66%) were considered nonresponders. Among patients in PR after chemotherapy, 92% showed a CR after IFRT.
- IFRT had a pivotal role in inducing CR in patients in PR after chemotherapy.

Mazzarotto R (2007) Primary mediastinal large B-cell lymphoma: results of intensive chemotherapy regimens (MACOP-B/VACOP-B) plus involved field radiotherapy on 53 patients. A single institution experience. Int J Radiat Oncol Biol Phys 68(3): 823–829

MD Anderson, 2003 → low-dose IFRT (4 Gy) was found to be a valuable option in the management of relapsed disease in both indolent and aggressive lymphoma, and should be considered to palliate symptoms in patients with recurrent and/or chemotherapy refractory disease.

Seymour JF (2003) Long-term follow-up of a prospective study of combined modality therapy for stage I–II indolent non-Hodgkin's lymphoma. J Clin Oncol 21(11): 2115–2122

Haas RL (2005) 2005 Update: effective palliation by low dose local radiotherapy for recurrent and/or chemotherapy refractory non-follicular lymphoma patients. Eur J Cancer 41(12):1724–1730

British National Lymphoma Investigation, 2004 → 377 adults treated with RT alone for early-stage diffuse large cell lymphoma.

- Ten-year cause-specific survival in patients older than 60 years was poor and significantly inferior to that in younger patients (47 and 75%, respectively; $p < 0.001$).
- Short-course chemotherapy, with or without RT, is superior to RT alone in early-stage aggressive NHL in elderly as well as in younger patients.
- Increased age alone should not exclude patients from systemic treatment for early-stage aggressive NHL.

Spicer J (2004) Long-term follow-up of patients treated with radiotherapy alone for early-stage histologically aggressive non-Hodgkin's lymphoma. Br J Cancer 90(6): 1151–1155

Nissen NI, 1983 → 73 patients with non-Hodgkin lymphomas at clinical stage I or II were treated with extended field radiotherapy alone (RT) or RT plus adjuvant chemotherapy with vincristine, streptonigrin, cyclophosphamide and prednisone (RT + CT).

- 54% relapsed in the RT group vs. only 10% in the RT + CT group ($P < 0.01$).
- They recommended the use of adjuvant CT with RT in all stage I–II patients with unfavorable histology.

Nissen NI et al (1983) A randomized study of radiotherapy versus radiotherapy plus chemotherapy in stage I–II non-Hodgkin's lymphomas. Cancer 52(1):1–7

GELA LNH93-4, 2007 → patients older than 60 years with localized stage I or II histologically aggressive lymphoma and no adverse prognostic factors of the International Prognostic Index were randomly assigned to receive either four cycles of cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) plus involved-field radiotherapy or chemotherapy alone with four cycles of CHOP.

- Event-free and overall survival did not differ between the two treatment groups ($p = 0.6$ and $p = 0.5$, respectively).

- CHOP plus radiotherapy did not provide any advantage over CHOP alone for the treatment of low-risk localized aggressive lymphoma in elderly patients.

Bonnet C (2007) CHOP alone compared with CHOP plus radiotherapy for localized aggressive lymphoma in elderly patients: a study by the Groupe d'Etude des Lymphomes de l'Adulte. J Clin Oncol 25(7):787–792

GELA LNH93-1, 2005 → patients less than 61 years old with localized stage I or II aggressive lymphoma and no adverse prognostic factors according to the International Prognostic Index were randomly assigned to three cycles of cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) plus involved-field radiotherapy or chemotherapy alone with dose-intensified doxorubicin, cyclophosphamide, vindesine, bleomycin, and prednisone (ACVBP) plus sequential consolidation.

- Event-free and overall survival rates were significantly higher in the group given chemotherapy alone than in the group given CHOP plus radiotherapy ($p < 0.001$ and $p = 0.001$, respectively).
- In patients under 61 years of age, chemotherapy with three cycles of ACVBP followed by sequential consolidation is superior to three cycles of CHOP plus radiotherapy for the treatment of low-risk localized lymphoma.

Reyes F (2005) ACVBP versus CHOP plus radiotherapy for localized aggressive lymphoma. N Engl J Med 352(12):1197–1205

SWOG 8736, 1998 → 200 patients were randomly assigned to receive CHOP plus radiotherapy, and 201 received CHOP alone.

- Patients treated with three cycles of CHOP plus radiotherapy had significantly better progression-free survival ($p = 0.03$) and OS ($p = 0.02$) than patients treated with CHOP alone.
- Three cycles of CHOP followed by involved-field radiotherapy are superior to eight cycles of CHOP alone for the treatment of localized intermediate- and high-grade non-Hodgkin lymphoma.

Miller TP (1998) Chemotherapy alone compared with chemotherapy plus radiotherapy for localized intermediate- and high-grade non-Hodgkin's lymphoma. N Engl J Med 339(1):21–26

Miller TP (2001) 2001 update: CHOP alone compared to CHOP plus radiotherapy for early stage aggressive non-Hodgkin's lymphomas: updated of the SWOG Randomized Trial. Blood 98:724A, abstract 3024.

ECOG 1484, 2004 (1984–1992) → stage I (with risk factors) and II adults with diffuse aggressive lymphoma in CR after eight cycles of cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) were randomly assigned to 30 Gy IFRT or OBS. PR patients received 40 Gy RT.

- For patients in CR after CHOP, low-dose RT prolonged DFS and provided local control, but no survival benefit was observed.

Horning SJ (2004) Chemotherapy with or without radiotherapy in limited-stage diffuse aggressive non-Hodgkin's lymphoma: Eastern Cooperative Oncology Group Study 1484. J Clin Oncol 22(15):3032–3038

13.4 Cutaneous Lymphoma

Cutaneous lymphoma is a heterogeneous group of NHLs: 30% B cell, 70% T cell. They are rarely seen, with an incidence of 1–1.5/100,000. Cutaneous lymphomas are usually observed in older patients and are twice as common in males. They are usually presented with dermal lesions, and the period between symptoms and diagnosis is usually 5 years [13]. The finding of atypical T lymphocytes, termed Sézary cells, in peripheral blood is pathognomonic. Cutaneous lymphomas constitute 2% of all NHLs.

- Sézary syndrome = erythroderma + LAP + Sézary cells in peripheral blood
- Primary cutaneous lymphomas were classified by WHO-EORTC in 2000.

Cutaneous T Cell Lymphoma (70%) [13]
Indolent (good prognosis)
Mycosis fungoides (MF) (44%)
MF + follicular mucinosis
Pagetoid reticulosis
Primary cutaneous anaplastic large cell (8%)
Lymphomatoid papulosis (12%)
Aggressive (poor prognosis)
Sézary syndrome (3%)
Primary cutaneous T cell peripheral (aggressive) CD8 (+) (2%)
Cutaneous B Cell Lymphoma (30%) [13]
Indolent (good prognosis)
Follicular center lymphoma (11%)
Marginal zone B cell lymphoma (7%)
Moderately aggressive
Primary cutaneous large B cell lymphoma of leg (4%)
Other diffuse large B cell lymphomas (1%)

AJCC 2010 Staging System [14]

Stage IA → T1N0M0
Stage IB → T2N0M0
Stage IIA → T1-2N1M0
Stage IIB → T3N0-1M0
Stage IIIA → T4N0M0
Stage III B → T4N1M0
Stage IVA → T1-4N2-3M0
Stage IVB → T1-4N0-3M1

13.4.1 Treatment Algorithm

Stage IA [15]
Topical treatment (steroid, retinoid, nitrogen mustard)
Ultraviolet light therapies (PUVA, UV-B)
Local RT (electron)
Stage IB–IIA [15]

Topical therapies (steroid, retinoid, nitrogen mustard)
Ultraviolet light therapies (PUVA, UV-B)
Total skin irradiation (electron) (TSI)
Stage IIB [15]

Presence of only a few nodules
Local RT (electron) + topical nitrogen mustard
PUVA
Presence of many nodules
TSI (electron) + topical nitrogen mustard
PUVA + α-interferon
PUVA + retinoid (p.o.)
Other combination therapies
Stage IIIA–IIIB [15]

Extracorporeal photopheresis
PUVA
Retinoid (p.o.)
α-Interferon, methotrexate
Combined therapies
Stage IVA–IVB [15]

Topical therapies + chemotherapy
Combined systemic therapy
RT to symptomatic lesions
Bone marrow transplantation

RT in local therapies, 24–36 Gy with 6–9 MeV electron energies (with 0.5 cm bolus). Palliative RT: 15 Gy (3 × 5 or 5 × 3 Gy).

TSI: 1.5–2 Gy per fraction, 36 Gy with 2–7 MeV electrons (usually 6 MeV). In cases of prominent skin edema, TSI is stopped for 1 week.

13.4.2 Total Skin Irradiation (TSI)

The aim of TSI is the homogeneous irradiation of all of the skin on the body. Plaques of cutaneous lymphomas that can be found in skin locally or extensively are localized in the first 5 mm of skin depth. Therefore, electron energies should be used. In addition, palpable or visible tumors (nodules) are irradiated with a boost dose.

TSI Is Applied Using Two Main Techniques

- The treatment couch is moved manually or automatically while the patient is in the supine position.
- Three to six meters are left between the therapy machine and the patient (the Stanford 6 technique).

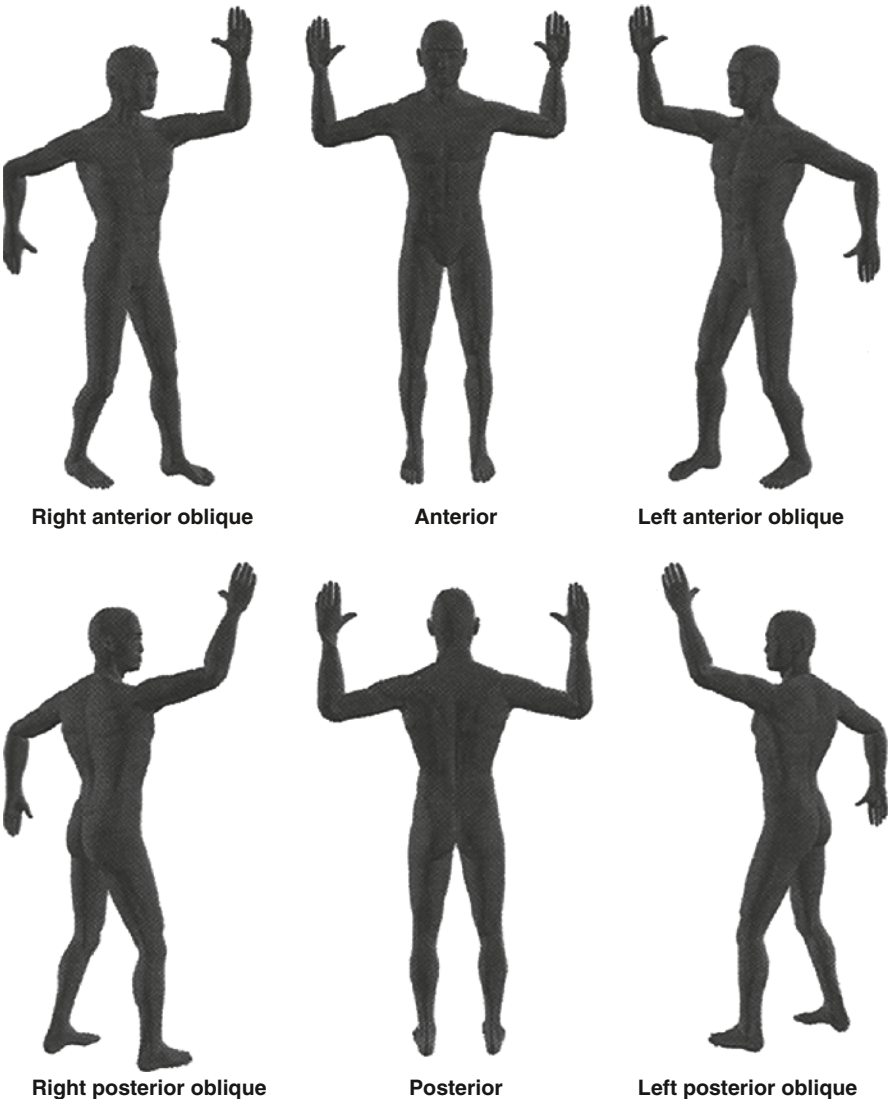

Fig. 13.14 Stanford 6 technique for total skin irradiation (from [24], p 818, Fig. 33, reproduced with the permission from Springer Science and Business Media)

Stanford 6 Technique (Fig. 13.14) [16]

The body is divided into six treatment fields:
Anterior, posterior, two posterior oblique, and two anterior oblique fields
On odd days (first day, third day, ...) during the TSI course, the anterior, left posterior oblique, and right posterior oblique fields are irradiated.
On even days (second day, fourth day, ...) during the TSI course, the posterior, left anterior oblique, and right anterior oblique fields are irradiated.

- The entire body is therefore covered every 2 days (one cycle = 2 days of TSI).
- TSI is applied 4 days each week, with a duration of 30 min for each fraction.
- SSD = 320 cm, gantry angle: 15–18°.
- The patient is treated on a special formica frame.
- Skin doses are measured with TLDs in all therapy fields or in the phantom prior to radiotherapy.
- A transparent plaque is placed approximately 30 cm away from the patient skin to block scattered electrons.

13.4.3 Selected Publications

Multifocal cutaneous lymphoma
Netherland, 1999 (1985–1997) → they evaluated the clinical behavior of and results of treatment for multifocal CBCL in 29 patients, and formulated therapeutic guidelines. The study group included 16 patients with primary cutaneous follicular center cell lymphoma (PCFCCL), eight with primary cutaneous immunocytoma (PCI), and five with primary cutaneous large B-cell lymphoma presenting on the legs (PCLBCL of the leg). Radiotherapy directed toward all skin lesions was as effective as multiagent chemotherapy. Patients with PCLBCL of the leg had a more unfavorable prognosis, particularly patients presenting with multifocal skin lesions. This last group should always be treated with multiagent chemotherapy.

Bekkenk MW et al (1999) Treatment of multifocal primary cutaneous B-cell lymphoma: a clinical follow-up study of 29 patients. J Clin Oncol 17(8):2471–2478

Primary cutaneous diffuse B cell lymphoma
Europe, Multicentric, 2001 (1979–1998) → 48 patients had a PCLBCL of the leg and 97 had a PCFCCL. Data from both groups were compared. Compared with PCFCCLs, PCLBCLs of the leg were characterized by an older age of onset, a more recent history of skin lesions, a more frequent predominance of tumor cells with round nuclei and positive bcl-2 staining, and a poorer 5-year disease-specific survival rate (52 vs. 94%; $p < 0.0001$). Round-cell morphology was an adverse prognostic factor in both PCLBCLs of the leg and in PCFCCLs, whereas multiple skin lesions were associated with a poor prognosis only in patients with PCLBCLs of the leg.

Grange F et al (2001) Prognostic factors in primary cutaneous large B-cell lymphomas: a European multicenter study. J Clin Oncol 19(16):3602–3610

RT + CT in cutaneous lymphoma

MD Anderson, 2001 → 46 patients, 27 males, with median age of 57 years. Treatment was radiotherapy in ten patients, doxorubicin-based therapy in 33 patients that was followed by radiotherapy in 25 patients, and another combination with radiotherapy in one patient. The complete response rate was 95%. PCNHL is rare, and its first relapse is exclusively cutaneous in 50% of patients. Patients with diffuse large B cell lymphomas are curable with doxorubicin-based regimens but not with radiotherapy.

Sarris AH et al (2001) Primary cutaneous non-Hodgkin's lymphoma of Ann Arbor stage I: preferential cutaneous relapses but high cure rate with doxorubicin-based therapy. Clin Oncol 19(2):398–405

Cutaneous lymphoma staging (review)

EORTC/ISCL, 2007 → these revisions were made to incorporate advances related to tumor cell biology and diagnostic techniques as pertains to mycosis fungoides (MF) and Sézary syndrome (SS) since the 1979 publication of the original guidelines, to clarify certain variables that currently impede effective interinstitution and interinvestigator communication and/or the development of standardized clinical trials in MF and SS, and to provide a platform for tracking other variables of potential prognostic significance.

Olsen E et al (2007) Revisions to the staging and classification of mycosis fungoides and Sézary syndrome: a proposal of the International Society for Cutaneous Lymphomas (ISCL) and the cutaneous lymphoma task force of the European Organization of Research and Treatment of Cancer (EORTC). Blood 110(6):1713–1722

Total skin irradiation

EORTC, 2002 → the European Organization for Research and Treatment of Cancer Cutaneous Lymphoma Project Group, in association with experts from radiotherapy centers in North America, reached a consensus on acceptable methods and clinical indications for TSEB in the treatment of MF.

Jones GW (2002) Total skin electron radiation in the management of mycosis fungoides: consensus of the European Organization for Research and Treatment of Cancer (EORTC) Cutaneous Lymphoma Project Group. Am Acad Dermatol 47(3):364–370

13.5 Total Body Irradiation (TBI)

TBI is used for a conditioning regimen prior to stem cell transplantation [17].

Diseases Requiring Stem Cell Transplantation

Acute myeloid leukemia (AML)
Acute lymphoblastic leukemia
Chronic myeloid leukemia (CML)

(*continued*)

(continued)

Chronic lymphocytic leukemia
Myelodysplasia
Lymphoma
Multiple myeloma
Aplastic anemia

- Idiopathic
- Fanconi
- Paroxysmal nocturnal hemoglobinuria

Congenital immune deficiencies
Autoimmune diseases

- Rheumatoid arthritis
- SLE
- Osteopetrosis

Leukoencephalopathy
Hurler syndrome
Sickle cell anemia
Thalassemia

Conditioning regimens for stem cell transplantation [18]

- Standard intensity regimens for leukemia

Cy/TBI (cyclophosphamide + TBI)
Bu/Cy (busulfan + cyclophosphamide)

- Standard intensity regimens for lymphoma

BEAM (BCNU/etoposide/ARA-C/melphalan)
CBV (BCNU/etoposide/cyclophosphamide)

- Standard intensity regimens for multiple myeloma

High-dose melphalan

TBI is used for bone marrow ablation, immune system suppression, and eradication of genetically damaged cells prior to stem cell transplantation.

Advantages of TBI compared to other conditioning regimens [17, 18]:
TBI affects sanctuary organs (testis, brain).
TBI does not cause a requirement for blood transfusion.
TBI is independent of hepatic and renal functions.
TBI does not cause cross-resistance with other agents.
TBI does not require metabolization, unlike chemotherapeutic agents.
Tumor cells are more sensitive to radiation, since transplantation cases usually do not have a previous history of radiotherapy.
The cyclophosphamide + TBI conditioning regimen has a reduced toxicity profile compared to the busulfan + cyclophosphamide regimen.
Disadvantages of stem cell transplantation:
Potential late side effects (sterility, cataract, growth retardation, neurological toxicity).

- TBI is usually applied after immunosuppressive chemotherapy. Cyclophosphamide is the most frequently used chemotherapeutic agent for a fractionated TBI regimen. Etoposide use is rapidly increasing in leukemia.
- TBI is applied with Co-60, 1–6 MV photon energies with a single fraction (8 Gy) or in fractionated doses. Immunosuppression and tumor cell eradication requires 8–12 Gy radiation doses.

Hydration and sedation should be done 2 h before fractionated TBI and 12 h before single-dose TBI (steroid and phenobarbital).

TBI Technique (Fig. 13.15) [18–22]

- Maximum field size for a SSD of 100 cm in most therapy machines is 40 × 40 cm. However, a field size of 120 × 120 can be achieved with an SSD of 300 cm due to divergence.
- Patients can be irradiated in the prone (pediatric), supine or leaning positions.

A compensator is required for the lungs, head–neck, and the lower extremities in the leaning position (Fig. 13.16).

TBI in the standing position: lung blocks are required (Fig. 13.16).

- Lung is the dose-limiting organ (maximum 10 Gy).

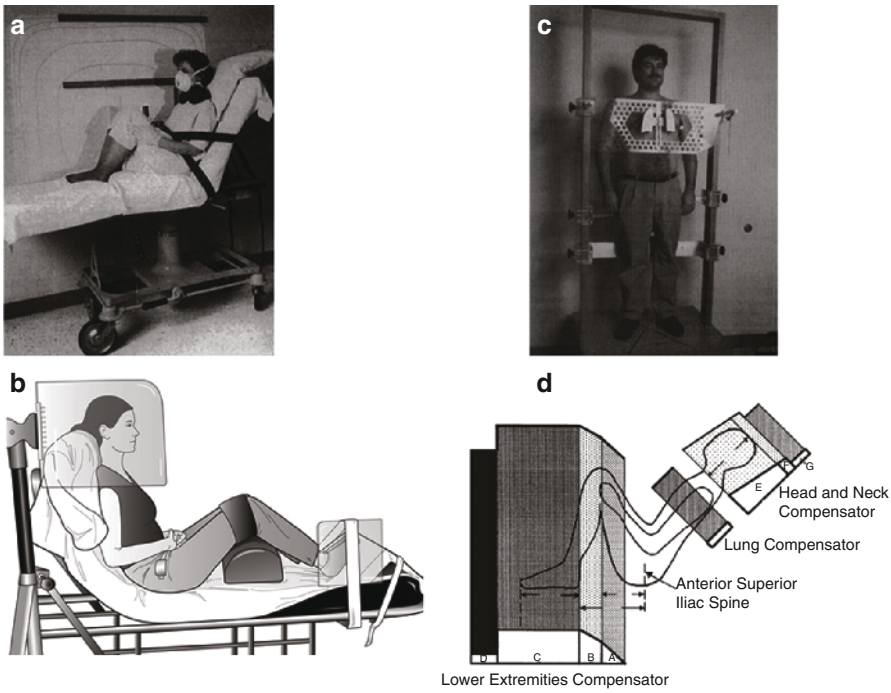

Fig. 13.15 (**a–d**) Patient positions in total body irradiation (from [25], p 789, 792, 797, Figs. 31.1, 31.5 and 31.12, reproduced with the permission from Springer Science and Business Media, with permission)

- In anterior–posterior TBI, bone marrow within costae under lung blocks are irradiated with the electron boost (6 Gy at D_{max}) [18, 20].
- An electron boost is also given to the testicles in all males (4 Gy at D_{max}, 90% isodose covers the posterior surface of the scrotum) [19, 20].
- TLD measurements should be done in the phantom and in the patient prior to the first fraction.
- After TBI, transplanted stem cells start proliferating at 2–3 weeks.

TBI doses in the standing position
First day (first, second and third fractions): 1.65 Gy/fraction with 6 MV, and 3 Gy electron boost to the testicles at the first fraction.
Second day (fourth, fifth and sixth fractions): 1.65 Gy/fraction with 6 MV.

Third day (seventh, eighth and ninth fractions): 1.65 Gy/fraction with 6 MV, and 3 Gy electron boost to the chest wall at the seventh fraction.
Fourth day (tenth and eleventh fractions): 1.65 Gy/fraction with 6 MV, and 3 Gy electron boost to chest wall at the tenth fraction.

TBI doses in the leaning position

First day (first and second fractions): 1.65 Gy/fraction with 18–25 MV.
Second day (third and fourth fractions): 1.65 Gy/fraction with 18–25 MV.
Third day (fifth and sixth fractions): 1.65 Gy/fraction with 18–25 MV.
Fourth day (seventh and eighth fractions): 1.65 Gy/fraction with 18–25 MV.

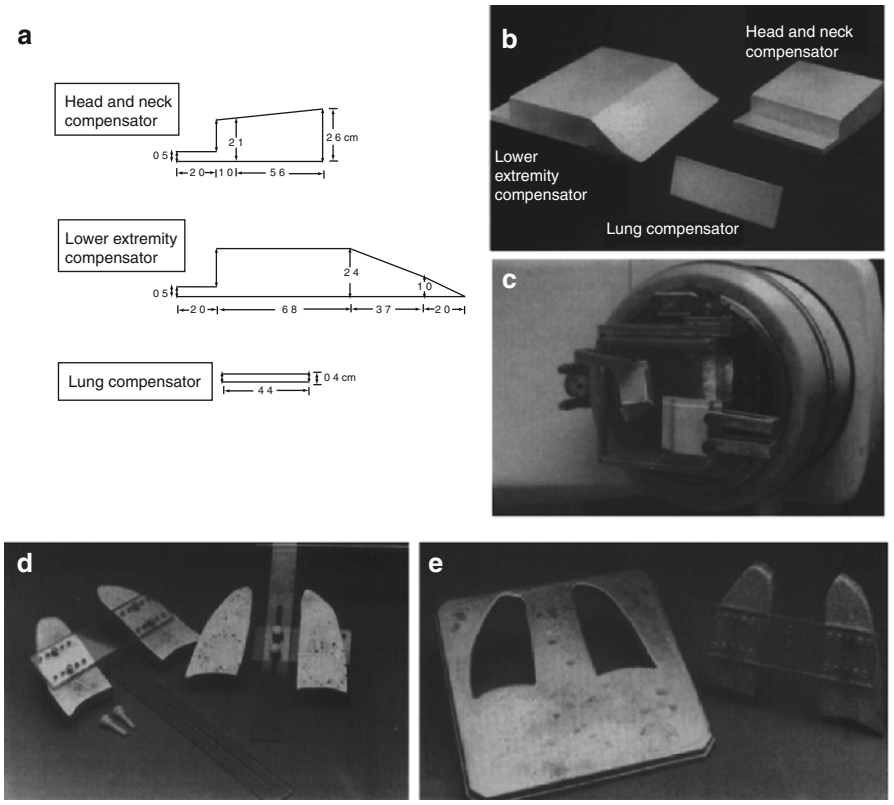

Fig. 13.16 Compensator and lung blocks used in TBI (from [25], p 793, 797, Figs. 31.6, 31.7a, b, and 31.11a, b, reproduced with the permission from Springer Science and Business Media)

13.5.1 Selected Publications

TBI (randomized trials)

Fred Hutchinson, 1994 (1988–1992) → 69 patients received 60 mg/kg of cyclophosphamide on each of two successive days, followed by six fractions of TBI each of 2.0 Gy (CY-TBI), and 73 patients received 16 mg/kg of busulfan delivered over 4 days followed by 60 mg/kg CY on each of two successive days (BU-CY). The BU-CY regimen was better tolerated than, and associated with survival and relapse probabilities that compare favorably with, the CY-TBI regimen.

Clift RA (1994) Marrow transplantation for chronic myeloid leukemia: a randomized study comparing cyclophosphamide and total body irradiation with busulfan and cyclophosphamide. Blood 84(6):2036–2043

1999 update: Clift RA (1999) Long-term follow-up of a randomized study comparing cyclophosphamide and total body irradiation with busulfan and cyclophosphamide for patients receiving allogenic marrow transplants during chronic phase of chronic myeloid leukemia. Blood 94(11):3960–3962

Nordic BMTG, 1994 (1988–1992) → 167 patients with leukemia receiving marrow transplants from HLA-identical donors and conditioned with cyclophosphamide (120 mg/kg) were randomized to additional treatment with either busulfan (16 mg/kg, $n=88$) or TBI (TBI; $n=79$). Patients treated with busulfan had more early toxicity and increased transplant-related mortality in patients with advanced disease. TBI was therefore the treatment of choice, especially in adults and patients with advanced disease. However, busulfan was an acceptable alternative for patients with early disease and for those in whom TBI is not feasible.

Ringden O (1994) A randomized trial comparing busulfan with total body irradiation as conditioning in allogeneic marrow transplant recipients with leukemia: a report from the Nordic Bone Marrow Transplantation Group. Blood 83(9):2723–2730

1999 update: 7-year leukemia-free survival (LFS) in patients with more advanced disease was 17% in the busulfan group vs. 49% in the TBI group ($p<0.01$). In patients with CML in the first chronic phase, 7-year LFS was 72% vs. 83% in the two groups, respectively.

Ringden O (1999) Increased risk of chronic graft-versus-host disease, obstructive bronchiolitis, and alopecia with busulfan versus total body irradiation: long-term results of a randomized trial in allogeneic marrow recipients with leukemia. Nordic Bone Marrow Transplantation Group. Blood 93(7):2196–2201

GEGMO, 1991 (1987–1990) → 101 patients with AML were randomized to be transplanted in first complete remission (CR1). A preparative regimen including Cytoxan (120 mg/kg) with TBI (CYTBI) ($n=50$) or busulfan (16 mg/kg) (BUSCY) ($n=51$) was followed by allogeneic BMT from an HLA-identical sibling. Besides the antileukemic effect of preparative regimens, this trial pointed out the progress accomplished in BMT management (transplant mortality = 8% in CYTBI) over the last 20 years, as well as the effectiveness of transplant in early first CR after CYTBI (DFS = 72% at 2 years).

Blaise D (1992) Allogeneic bone marrow transplantation for acute myeloid leukemia in first remission: a randomized trial of a busulfan–Cytoxan versus Cytoxan–TBI as

preparative regimen: a report from the Group d'Etudes de la Greffe de Moelle Osseuse. Blood 79(10):2578–2582

2001 update: Blaise D (2001) Long-term follow-up of a randomized trial comparing the combination of cyclophosphamide with total body irradiation or busulfan as conditioning regimen for patients receiving HLA-identical marrow grafts for acute myeloblastic leukemia in first complete remission. Blood 97(11):3669–3671

SWOG 8612, 1993 (1987–1991) → two regimens consisting either of fractionated TBI and etoposide (FTBI/VP-16) or high-dose busulfan with cyclophosphamide (BU/CY). Both regimens were well tolerated with no regimen-related deaths encountered during the 6-week period after BMT. The leading cause of treatment failure was leukemic relapse (45 of the 114 BMT recipients suffered a recurrence of their leukemia), whereas 38 patients died without evidence of relapse.

Blume KG (1993) A prospective randomized comparison of total body irradiation–etoposide versus busulfan–cyclophosphamide as preparatory regimens for bone marrow transplantation in patients with leukemia who were not in first remission: a Southwest Oncology Group study. Blood 81(8):2187–2193

TBI (meta-analyses)

Socie G → this study analyzed the long-term outcomes of 316 patients with CML and 172 patients with AML who participated in these four trials, with a mean follow-up of more than 7 years.

Bu-CY and CY-TBI provided similar probabilities of cure for patients with CML. In patients with AML, a nonsignificant 10% lower survival rate was observed after Bu-CY. Late complications occurred equally after both conditioning regimens (except for increased risk of cataract after CY-TBI and of alopecia with Bu-CY).

Socie G (2001) Busulfan plus cyclophosphamide compared with total-body irradiation plus cyclophosphamide before marrow transplantation for myeloid leukemia: long-term follow-up of 4 randomized studies. Blood 98(13):3569–3574

Hartman AR → the OSs, the disease-free survivals and the toxicities of BUCY vs. TBI-based regimens were compared by conducting a meta-analysis of five published, randomized, prospective trials comparing these regimens. Survival and disease-free survival were better with TBI-based regimens than with BUCY, but these differences were not statistically significant. TBI-based regimens cause less VOD than BUCY and were at least as good for survival and disease-free survival.

Hartman AR (1998) Survival, disease-free survival and adverse effects of conditioning for allogeneic bone marrow transplantation with busulfan/cyclophosphamide vs. total body irradiation: a meta-analysis. Bone Marrow Transplant 22(5):439–443

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