Renato G. Panizzon
M. Heinrich Seegenschmiedt *Editors*

Radiation Treatment and Radiation Reactions in Dermatology

Second Edition

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Renato G. Panizzon:

In memory of
Brigitta Pfister, who died tragically in an accident during her thesis work, and
Urs W. Schnyder, my first teacher in dermatologic radiotherapy

To Frederick D. Malkinson, my mentor and friend who wakened my interest in radiobiological research

M. Heinrich Seegenschmiedt:

"What do think is the most difficult of all, to see what lies before your eyes!" (J.W. Goethe)

For my children Sebastian, Johannes, Andreas,
Emanuel and ***Victoria***

Preface

The authors are highly enthusiastic to offer a new edition of this traditional book on dermatologic radiotherapy for dermatologists, radio-oncologists, related specialists, and trainees. It follows the interest of Herbert Goldschmidt's book issued in 1991 and our first edition in 2004.

For this edition, there have been further changes, starting with the new coeditor M. Heinrich Seegenschmiedt, who put an enormous effort into this edition. Several new authors with great expertise joined us such as Stephan Bodis, Reinhard Dummer, Gerald B. Fogarty, Michael Geiges, Wendy Jeanneret-Sozzi, Stephan Lautenschlager, René-Olivier Mirimanoff, Susanne J. Rogers, Sima Rozati, Lukas J.A. Stalpers, and Ulrich Wolf.

We added new chapters, e.g., the history of dermatologic radiotherapy, tumor staging, precancerous lesions, the Indian experience of lymphoma treatment, as well as a chapter on radiation accidents.

A significant effort has been made to include new findings and results, but also concerning the photographs and tables. We are especially indebted to the staff of Springer, Mrs. Ioanna C. Panos, Mr. Magesh Rajagoplan, Mrs. Ellen Blasig and others, who have made this second edition a reality.

We realize with pleasure a renaissance of dermatologic radiotherapy among the younger generation. This is due to the fact that new superficial radiotherapy equipment has been available on the market.

It is the express wish of the editors, contributors, and the publisher that the information compiled in this work greatly aids dermatologists, radio-oncologists, and allied specialists in facilitating the best patient care possible.

Lausanne, Switzerland — Renato G. Panizzon, MD
Hamburg, Germany — M. Heinrich Seegenschmiedt

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Our appreciation and thanks go to our families for their understanding and patience.

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History of Dermatologic Radiotherapy with a Focus on Zurich

1

Michael L. Geiges

Contents

1.1 Introduction

Wilhelm Conrad Röntgen studied engineering and physics in Zurich. Thanks to his good grades he was admitted to the Federal Polytechnic Institute (ETH) without passing an entrance exam and in spite of the fact that he was not admitted to study in his hometown Utrecht, and not having the necessary "abitura." In Zurich, he did not only obtain his diplomas but he also fell in love with Anna Bertha Ludwig, daughter of the innkeeper of the restaurant "Zum Grünen Glas" situated close to the University, taking her as his wife. It is well known that the first x-ray image of a human being pictures her hand (Fig. 1.1).

On the evening of November 8th 1895 Wilhelm Conrad Röntgen, at that time professor of physics in Würzburg, discovered a "new kind of rays", as he published in January 1896 in the "Sitzungsberichte der Würzburger Physikalisch-medizinischen Gesellschaft" [1].

The news about these miraculous rays spread very rapidly all over the world. At the same time, as Röntgens' article was published in Nature and Science, the fascinated public was already able to admire this curiosity in public demonstrations, for example, in a theater in Davos [2].

Immediately, many researches began to study x-rays, and the biologic effects of radiation became quickly apparent through signs of damage of the skin. Radiation-induced dermatitis was reported in March 1896 and depilation and pigmentation in April 1896 [3].

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Fig. 1.1 Wilhelm Conrad Röntgen with his wife Anna Bertha Ludwig and the coachman Emanuel Schmid who used to drive them regularly up to the Engadin in the Swiss Alps for summer vacation (Archive of the Institute for the History of Medicine, University of Zurich)

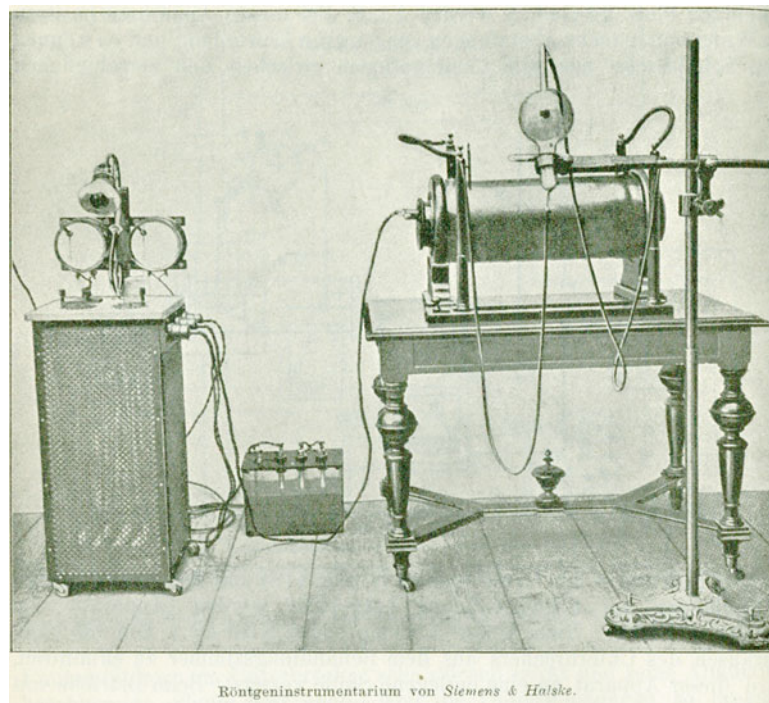

Fig. 1.2 "Röntgeninstrumentarium" (Freund L (1903) Grundriss der gesammten Radiotherapie, Urban & Schwarzenberg, Berlin Wien)

These reports led Leopold Freund, Dermatologist in Vienna, to use x-rays on a pigmented hairy nevus in November 1896. The treatment resulted in epilation and after 2 months in an ulcer which rapidly became deep and painful and ultimately gave rise to a carcinoma with metastases [4].

Freund described his experiences in 1903 in the book *Grundriss der gesammten Radiotherapie* for the practitioner [4]. After Freund's publication, x-rays were tested empirically on almost all skin affections. Among the very early indications for x-ray treatment was the treatment of fungal infections of the scalp, mainly favus and microsporia. Radiotherapy became the gold standard for the treatment of such indications up to 1958 when griseofulvin came on the market [5] (Figs. 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, and 1.8).

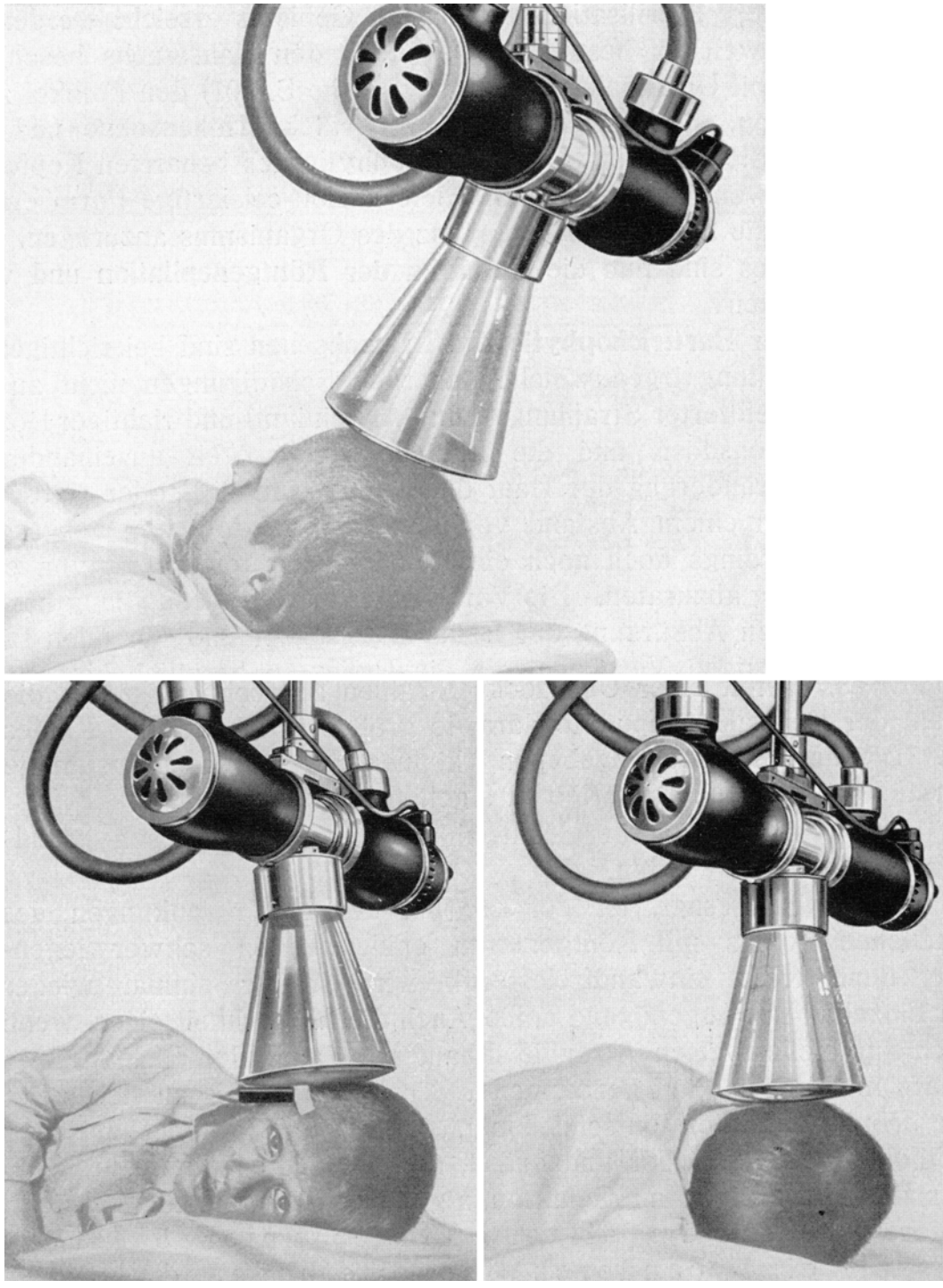

Fig. 1.3 Depilation treatment of trichophytia of the scalp (Blumenthal F, Böhmer L (1923) Strahlenbehandlung bei Hautkrankheiten. Karger, Berlin 1932)

1.2 Indications for X-Ray Treatment

The best results were achieved in the treatment of any kind of eczema and psoriasis. Children with mycosis of the scalp and with port-wine stains were treated successfully with x-rays.

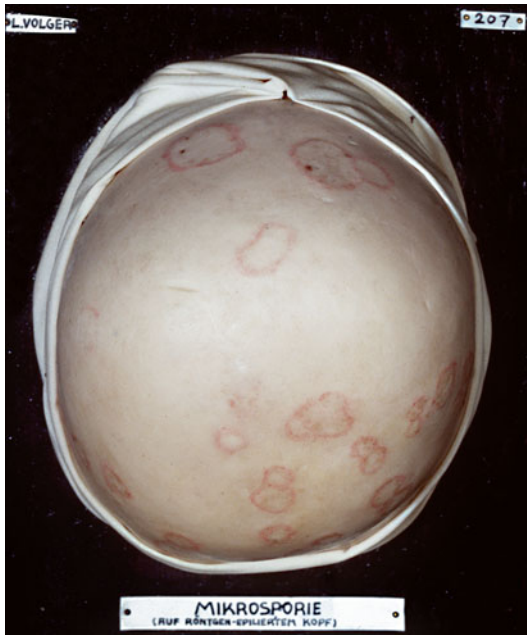

Fig. 1.4 Moulage No. 207: Radiodepilated scalp with microsporia. Made in 1918 by Lotte Volger, Dermatology Clinic Zurich (Museum of Wax Moulages, University and University Hospital Zurich)

Tuberculosis of the skin, also treated with the Finsen UV light, seemed to respond in most cases. But there were also warnings about the possible risk of developing lupus vulgaris carcinoma.

X-ray treatments against acne and rosacea did not work well. Case reports have been published of patients having been treated with x-rays of different quality and quantity for almost a year without improvement.

There was a debate about whether cancer of the skin should be treated with radiation. In 1899, Thor Stenbeck in Stockholm treated a patient with skin cancer of the nose with success when applying small doses of Röntgen rays in daily sessions over a period of several months [6]. On some types of epithelioma, what we call basal cell carcinoma today, x-rays seemed to work very well, while others were refractory [7].

One of the pioneering publishers on the subject of good outcomes in skin cancer treatment with x-rays was the dermatologist Guido Miescher. Together with Bruno Bloch, he had come from Basel to Zurich when the clinic was founded in 1916 and followed Bloch in 1933 as Director of the Clinic and ordinary professor for dermatology in Zurich (Fig. 1.9).

As assistant professor at the clinic of Bruno Bloch, he conducted various experiments with x-rays. Many of his experiments have been documented with wax moulages. They were made with a plaster cast molding the patient and

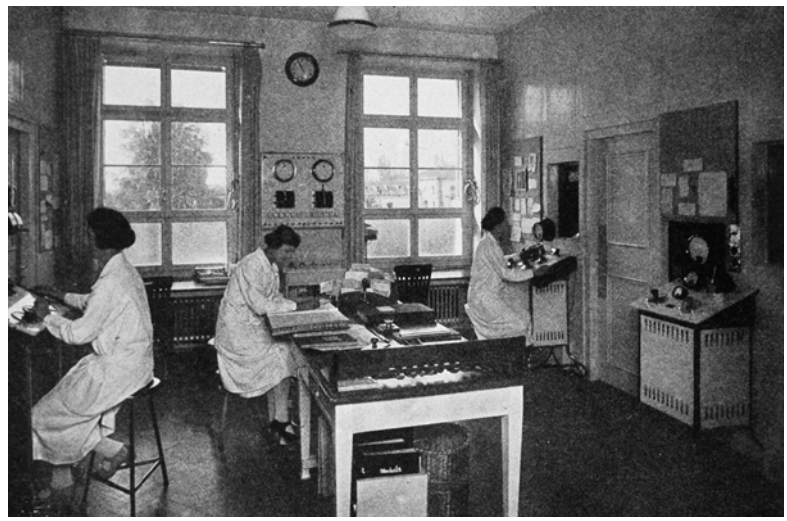

Fig. 1.5 Controlling room for radiotherapy at the clinic in Zurich in 1926 (Bloch B (1929) Die Dermatologische Universitätsklinik Zürich. Methods and Problems of Medical Education, The Rockefeller Foundation, New York)

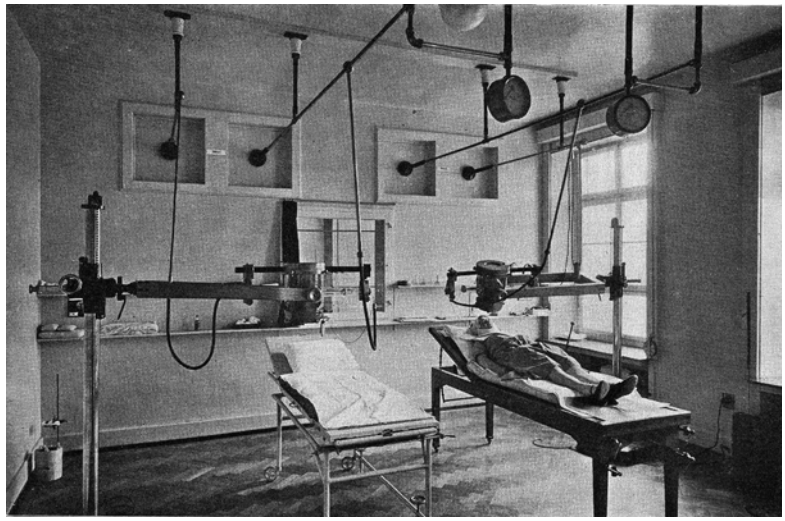

Fig. 1.6 Treating room for radiotherapy at the clinic in Zurich in 1926 (Bloch B (1929) Die Dermatologische Universitätsklinik Zürich. Methods and Problems of Medical Education, The Rockefeller Foundation, New York)

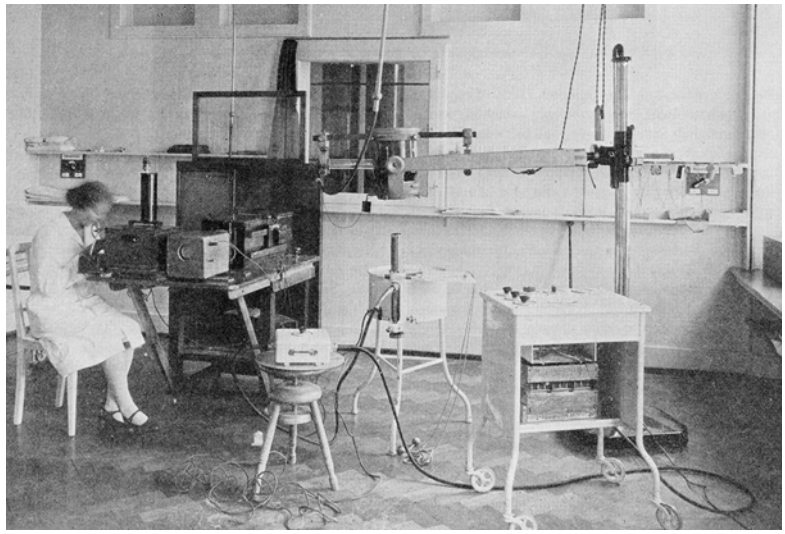

Fig. 1.7 Room for measuring Rx radiation at the clinic in Zurich in 1926 (Bloch B (1929) Die Dermatologische Universitätsklinik Zürich. Methods and Problems of Medical Education, The Rockefeller Foundation, New York)

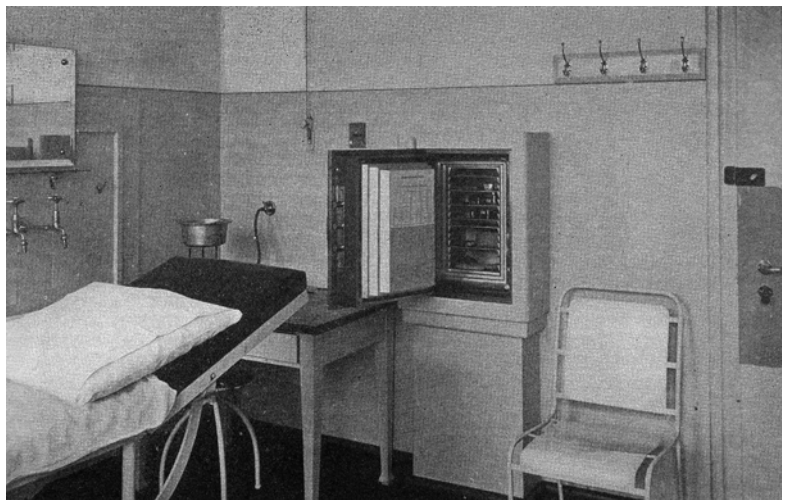

Fig. 1.8 Safe for the storage of radium at the clinic in Zurich in 1926 (Bloch B (1929) Die Dermatologische Universitätsklinik Zürich. Methods and Problems of Medical Education, The Rockefeller Foundation, New York)

Fig. 1.9 Guido Miescher giving a lecture: it is recognizable that Miescher had acquired a chronic radiodermatitis on the cheeks and the chin. It is verbally passed on that he had himself radioepilated either because he wanted to avoid arduous daily shaving or for medical reasons like a folliculitis (Department of Dermatology, University Hospital Zurich)

providing a three-dimensional view of the skin alterations. The coloring is so realistic that the model is almost lifelike. Some of the moulages have been used by Miescher to illustrate his scientific articles. For us, today, it is an extraordinary opportunity to have a look at these historical findings as if we were looking at the original patients themselves. There are moulages showing the comparison of fractional radiotherapy versus single-dose treatment on the upper lip of a patient with dermal cylindromas. Others show the successful treatment of a widespread lentigo maligna melanoma or the follow-up of an extended squamous cell carcinoma treated in 1928 with follow-ups every couple of years with the last one made 13 years later in 1941 [8] (Fig. 1.10).

Besides of x-rays brachytherapy with radium was commonly used. It was discovered by Henry Becquerel in 1898 [9]. In Zurich, radium was the private property of Bruno Bloch and was stored in a safe made of lead. It was applied close to the skin with the help of moulages (Fig. 1.11).

Very little was understood about the quality or the penetrating power of x-rays and its relation to dosage. Soft and oversoft rays with low kilovoltage, used by Frank Schulz in Berlin in 1910, provoked more erythema and were first regarded as more harmful than harder x-rays [7]. The usual treatment was done with 125 KV and aluminum filters. It took more than 10 years until Gustav Bucky, radiologist in Berlin, published in 1925 his article “superficial therapy with soft x-rays”, treating different dermatoses at 10 KV with very good results [10]. He called this radiation Grenz rays (border rays), as their characteristics resembled those of conventional x-rays in some ways and those of ultraviolet rays in others [11]. Today, they are also called Bucky rays.

1.3 Side Effects

X-ray diagnostics and especially radiation treatment was accompanied by many partly fatal problems. With such a powerful treatment tried out on almost every skin disease possible, many more or less serious injuries to both patients and operators resulted. This problem was of greater importance in the treatment of benign skin diseases. As mentioned above, filtration and fractioning of the dose were tried with varying degrees of success.

Over the years, the damage due to chronic irradiation became visible, and chronic radiodermatitis with ulcers and cancer was recognized as an occupational disease of radiotherapists [12, 13] (Fig. 1.12).

In retrospect, it is astonishing to us how unreservedly x-rays were used over the decades. It’s difficult to understand that, e.g., so-called pedoscopes were used in shoe-selling stores up to the 1970s. With this apparatus, the client was able to monitor whether her/his shoes fit well. The advertisement invited the consumers to

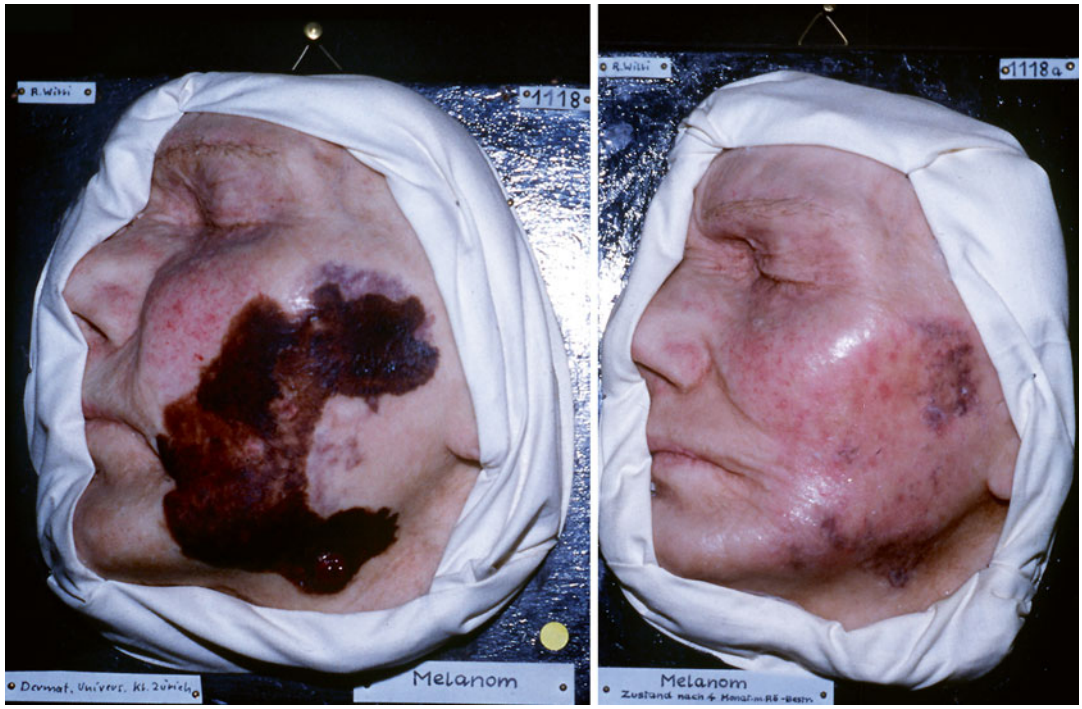

Fig. 1.10 Moulage No. 1118, Rx treatment of lentigo maligna, Moulage made by Ruth Willi in 1950, Dermatology Clinic Zurich (Museum of Wax Moulages, University and University Hospital Zurich)

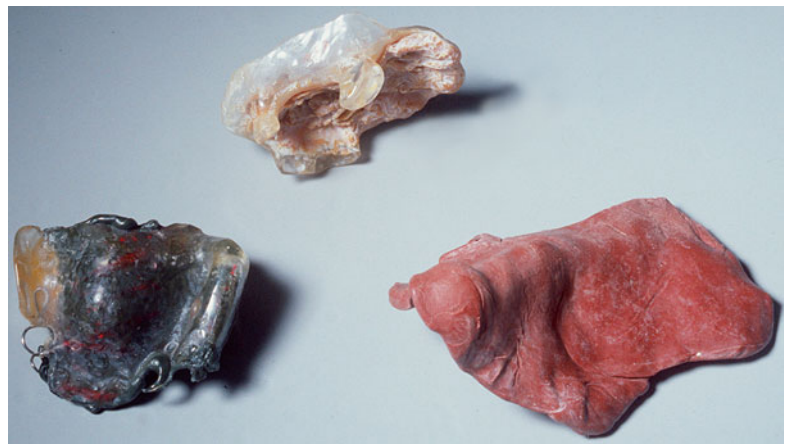

Fig. 1.11 Moulages as placeholders for the brachytreatment with radium (Institute and Museum for the History of Medicine, University of Zurich)

check their shoes as often as possible, because "nothing would be more harmful than ill-fitting shoes" [2] (Fig. 1.13).

There were two major problems when treating with x-rays. Firstly, the apparatus was a fragile construction sending out rays of changing quality and quantity depending on the temperature, time of use, and many other technical details.

Secondly, there was no reliable method of measuring the amount of radiation. Most commonly, chemical dosimeters were used. The "radiometer" according to Holzknecht was followed in 1904 by the Radiomètre developed by Sabouraud and Noiré. The Sabouraud–Noiré pastille consisted of barium platinocyanide that changed its color with exposure to radiation from

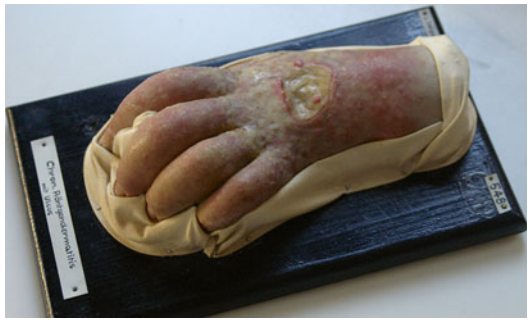

Fig. 1.12 Moulage No. 548, radiodermatitis with ulcers. Made by Lotte Volger in 1924, Dermatology Clinic Zurich (Museum of Wax Moulages, University and University Hospital Zurich)

Fig. 1.13 Advertisement for a pedoscope used in a shoe-selling store in Zurich (Archive of the Institute for the History of Medicine, University of Zurich)

bright green to yellow–brown. The so-called Teinte B corresponded to the maximum dose that could be applied before the skin reacted with erythema, radiodermatitis, or irreversible alopecia.

Others used the biology of the skin as an indicator to find the right dose. They compared the erythema induced by radiation with a standard colored scale like the one developed by Theodor Schreus [14] (Figs. 1.14 and 1.15).

But even these advances were very unreliable as some persons showed stronger reactions on x-rays than others. This brought up a discussion whether there might be a kind of idiosyncrasy or allergy against x-rays [15, 16].

In 1924, Guido Miescher stated that the Röntgen erythema was an important indicator for all radiotherapists but that there was no clear definition or profound research on what the erythema exactly was. Therefore, he conducted experiments on healthy skin of about 100 patients, comparing the erythema provoked with colored wax moulages used as benchmarks.

Miescher was able to show a broad range of individual differences and a wavelike change of erythema and pigmentations over time, later called the Miescher waves [17] (Fig. 1.16).

1.4 The Twentieth Century Up to Now

Radiation therapy reached its peak in the 1950s. Already in 1929, the 5th volume of the handbook of Jadassohn contained 500 pages on radiation therapy [18]. In its addendum, published in 1959 by Alfred Marchionini and Carl Gustav Schirren, more than 1,000 pages dealt with radiotherapy [19].

In 1936, the Swiss dermatologists decided that training in radiology must be compulsory for every dermatologist including the following topics:

- Physics of radiation
- Biology of radiation
- Knowledge of the construction of the apparatus
- Theoretical and practical basis of measurements
- Dose calculation
- Technique of surface therapy
- Indications of radiation therapy

The first course, lasting 1 week, took place in 1938 in Zurich, and an additional practical training lasting 3–6 months in a radiological institute was required in order to obtain the specialist title for dermatology [20].

In the second half of the twentieth century, antibiotics, retinoids, steroids, UV light therapy with psoralen, and other modalities offered new

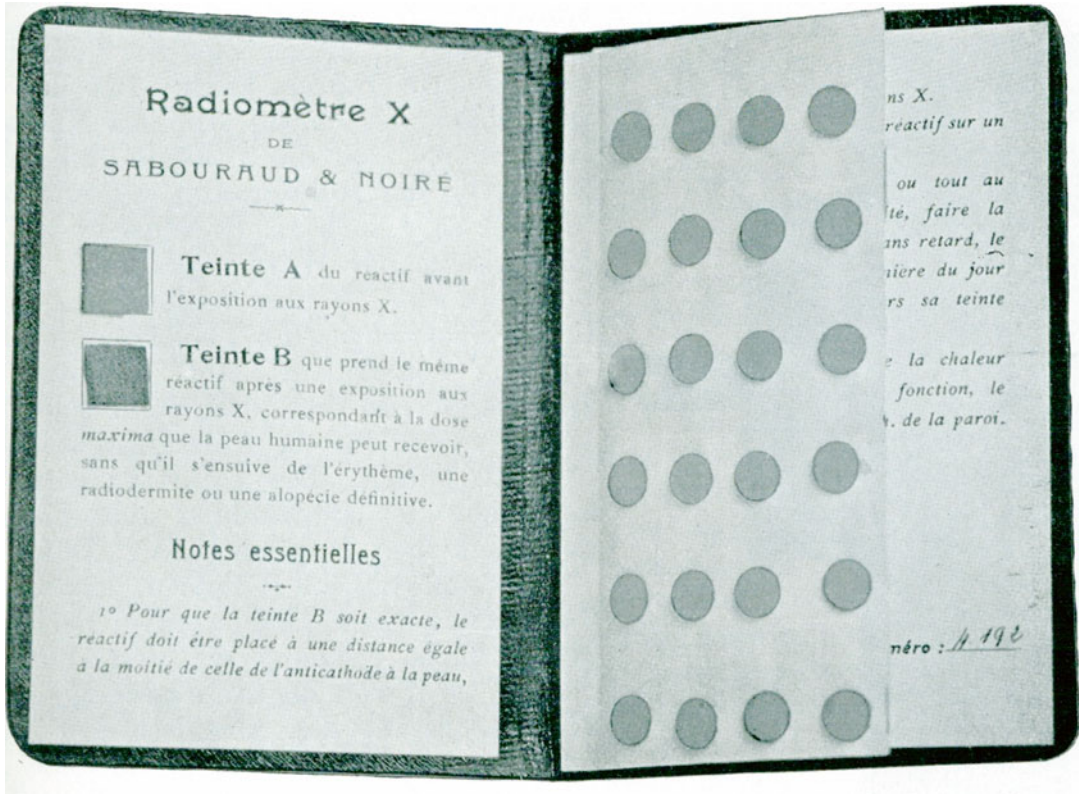

Fig. 1.14 Radiomètre of Sabouraud – Noiré Jadassohn [18]

possibilities in treating dermatoses. X-ray treatment still kept the reputation of being dangerous, despite an enormous improvement and perfection. Almost as fast as radiation treatment has gained attention, it then lost its momentum and, in recent decades, was relegated to being a very secondary dermatological therapeutic option. In 1991, Renato Panizzon, Privatdozent at the dermatology clinic in Zurich, together with Herbert Goldschmidt from the University of Pennsylvania in Philadelphia, published the book *Modern Dermatologic Radiation Therapy*. He stated in the preface: "Radiation therapy of cutaneous cancers and other dermatologic disorders is not covered adequately in many current textbooks of dermatology and radiation oncology. This book is intended to fill that gap" [21].

This book fulfilled this promise and became a standard work at the end of the last century. Radiotherapy still offers a practical treatment with very few side effects and usually an extremely good cosmetic outcome. In certain situations, it can be the only effective treatment to an individual patient avoiding distorting scaring. However, it needed and still needs advertisement. Today, skin cancer has become an epidemic, but at the same time it is more difficult and more expensive for dermatologists to use x-rays in their private practice because of harsher legal requirements. Luckily, new x-ray machines have become available at reasonable prices comparable to laser techniques. It is interesting to note that the younger generation starts to detect this modality again under research, practical, and reimbursement issues.

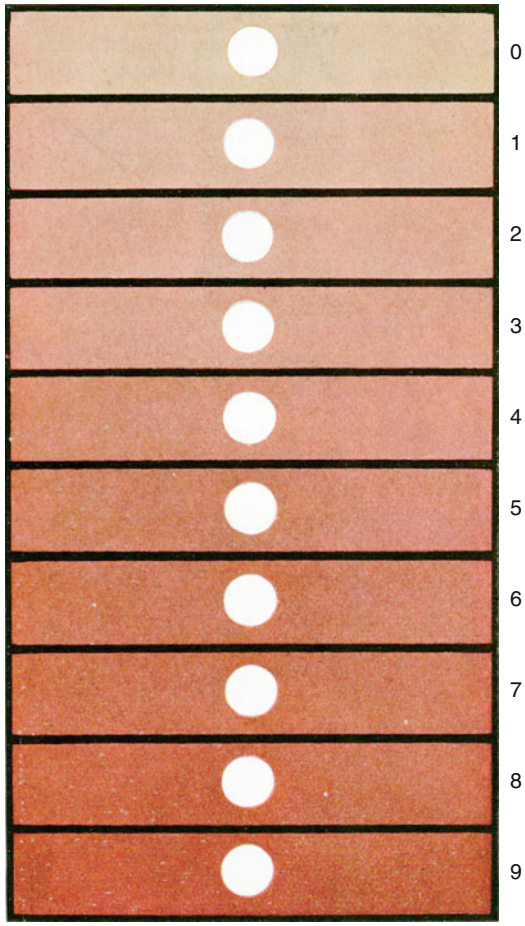

Fig. 1.15 Standard scale for measuring erythema by Theodor Schreus Jadassohn [18]

Fig. 1.16 Moulage No. 1074 documenting experiments on Rx erythema. Made by Lotte Volger around 1923, Dermatology Clinic Zurich (Museum of Wax Moulages, University and University Hospital Zurich). These experiments took several months. Female patients with syphilis were asked to participate as test persons because they were staying for many weeks in a closed section of the clinic receiving salvarsan treatment, as they were considered to be prostitutes dangerous for the male public

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Radiophysical Principles

2

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Contents

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2.1 Structure of Matter and Radioactivity

Atoms as the fundamental components of matter consist of two main parts: the core (usually called atomic nucleus), where most of the atomic mass is located, and a cloud of electrons surrounding it. The electrons move on orbits around the nucleus. These permitted orbits are also called electron shells and are named alphabetically with capital letters starting with K. The atomic nuclei are made up of an integral number of protons and neutrons. While the protons carry a positive charge, the neutrons are electrically neutral. Electrons and protons carry the same charge but of opposite sign. This charge is called elementary charge e:

$$e = 1.602 \times 10^{-19} C.$$

Since the number of negatively charged electrons is equal to the number of protons in the nucleus, the atom itself is electrically neutral.

The electron shells are characterised by discrete amounts of the binding energy. Transitions of electrons between these energy levels or orbits are accompanied with emission or absorption of discrete portions of energy. Since the Coulomb attraction between the negative electrons and the positive nucleus decreases with increasing distance, the inner electrons are more tightly bound, i.e. they have a higher binding energy. The number of protons Z equals the atomic number and

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thus determines the chemical element of the atom as well as the structure of the electron shells. The number of protons in the nucleus is the same for all atoms of a given element, but the number of neutrons may vary. These atoms, with a different number of neutrons, but the same number of protons, are called isotopes.

Since the number of the elementary particles in the nucleus is responsible for the atomic weight, we can define the mass number A as

$$A = Z + N \tag{2.1}$$

While the chemical behaviour of an atom is only determined by its atomic number, the properties of the atomic nucleus depend on the number of neutrons too. In nuclear physics a certain nucleus is denoted as follows:

$${}^{A}_{Z}X$$

with A, Z, and X being the mass number, the atomic number, and the chemical symbol of the element, respectively. Examples are ${}_{9}{}^{19}\mathrm{F}, {}_{29}{}^{60}\mathrm{Co}, {}_{92}{}^{238}\mathrm{U}$ denoting isotopes of the elements fluorine, cobalt, and uranium with 19, 60, and 238 nucleons, respectively. Because the atomic number Z and the chemical element provide redundant information, the subscript often is omitted. Atomic nuclei can be stable as well can disintegrate, thereby forming new nuclei with different properties. This behaviour of an atomic nucleus to decay within a given time is what we call radioactivity. We know different types of the radioactive decay, each characterised by the emission of specific particles: α-, β^--, and β^+-particles.

The α-decay is usually observed for heavy nuclei with a big neutron excess. α-particles are atomic nuclei of helium, consisting of two protons and two neutrons. The equation for the α-decay can be written as

$${}^{A}_{Z}X \rightarrow {}^{A-4}_{Z-2}Y + {}^{4}_{2}\mathrm{He} + E_{kin} \tag{2.2}$$

Typical examples are the decay of ^{235}U to ^{231}Th as well as ^{226}Ra to ^{222}Rn.

The β^-- and the β^+-decay occur for medium-weight isotopes with neutron or proton excess respectively. To describe the β^--decay, the following equations apply:

$${}^{A}_{Z}X \rightarrow {}^{A}_{Z+1}Y + \beta^- + \overline{\nu} + E_{kin} \tag{2.3}$$

$${}^{A}_{Z}X \rightarrow {}^{A}_{Z-1}Y + \beta^+ + \nu + E_{kin} \tag{2.4}$$

β^- and β^+ indicate an electron and a positron, respectively; the positron is the anti-particle of the electron with the same mass but an electrical charge of opposite sign. ν and ν– denote the neutrino and the antineutrino, respectively, which are particles without mass and charge, and a very low probability to interact with matter. Radionuclides emitting β-radiation are, for example, ^{90}Sr which decays to ^{90}Y by emission of β^--radiation and the positron emitting ^{19}F. The daughter nucleus originating as a result of an α or β-decay might exist in an excited energy state. To return to the ground state, the nucleus has to de-excite which usually happens by emitting discrete amounts of energy as γ-radiation. From the physical point of view, γ-radiation is electromagnetic radiation with a very high frequency, but can also be regarded as particles – so-called γ-quanta – having no rest mass and no electric charge. γ-emitting radionuclides are widely used as radiation sources in radiotherapy.

Radioactive nuclei decay randomly. If we have a sample of nuclei, and we consider a time interval short enough to assure that the population of atoms did not change significantly by decay, then the proportion of atoms decaying in our short time interval will be proportional to the length of the interval. The number of nuclei N which have not yet decayed after an arbitrary time interval t follows an exponential law:

$$N = N_0 \cdot e^{-\lambda \cdot t} \tag{2.5}$$

where N_0 is the number of radioactive nuclei at time 0 and λ is known as the radioactive decay constant characteristic for the particular decay. The rate of disintegration of any radioactive substance is commonly designated by its half-life $T_{½}$, which is the time required for one-half of a given quantity of the substance to decay. Depending on the element, a half-life can be as short as a

fraction of a second or as long as several billion years. Substituting the decay constant by the half-life according to

$$T_{1/2} = \frac{1}{\lambda} \cdot \ln 2 \tag{2.6}$$

we get

$$N = N_0 \cdot e^{-\frac{t \cdot \ln 2}{T_{1/2}}} \tag{2.7}$$

The activity A is the physical quantity used to measure the rate of disintegration. The unit of activity is 1/s (s^{-1}) which means one decay per second and is called Becquerel (Bq). For instance, in a sample of an activity of 1 MBq, 1,000,000 nuclei decay in every second. Since the number of decaying nuclei, i.e. the activity, is proportional to the number of radioactive nuclei, we can express the exponential law of decay also in terms of activity by simply substituting N by A.

2.2 The Nature of Ionising Radiation

Atoms in general – as stated above – are electrically neutral. When an atom or molecule is ionised, it acquires or loses one or more electrons. Ionisation by removing electrons can among other things be caused by bombarding atoms with charged particles like α- and β-particles as well as by uncharged particles like neutrons or γ-quanta. In general, radiation means energy that is radiated or transmitted in the form of rays or waves or particles. Ionising radiation is high-energy radiation capable of producing ionisation in the substances through which it passes.

If the energy lost by the incident radiation is not sufficient to detach an electron from the atom, but is used to raise an electron from its energy level to a higher one, this process is called excitation.

Table 2.1 summarises different types of ionising radiation. Since all charged particles ionise atoms by themselves, they are called direct ionising radiation. Uncharged particles like neutrons and photons, i.e. electromagnetic radiation at high energies, ionise matter by charged particles produced by only a few interactions with atomic electrons or nuclei. These secondary particles actually detach the prevailing majority of electrons from the atoms. That is the reason why we call uncharged particles also indirect ionising radiation. From the point of view of radiotherapy, photons are the most important indirect ionising radiation. As mentioned above, photons are electromagnetic radiation. We know electromagnetic waves from our daily life, e.g. as radio waves, microwaves, visible, and ultraviolet light.

Table 2.1 Possible classification of ionising radiation

Ionising radiation		
Indirect (uncharged)		Direct (charged)
γ-rays, X-rays (photons)	Neutrons	Electrons, positrons (β-particles) α-particles, protons, ions
Rest mass = 0	Rest mass >0	
Electromagnetic waves or quantum radiation	Particle radiation	

Waves are characterised by their frequency f, their wavelength λ, and their velocity of propagation c (which is the speed of light for electromagnetic waves) according to the following relation:

$$c = \lambda \cdot f \tag{2.8}$$

However, they can also be regarded as particles with a defined energy E and a rest mass being zero:

$$E = h \cdot f \tag{2.9}$$

The factor h is known as Planck's constant. The production of which will be explained later, and the γ-radiation emitted by excited nuclei are electromagnetic waves at very high frequencies.

The unit to measure the energy of elementary particles, electrons, and photons is the *electron volt* (eV). It is the energy gained by a particle which carries one elementary charge as it traverses a difference in electrostatic potential of one volt in vacuum. The electron volt is a very small unit:

$$1\,\text{electron volt}(\text{eV}) = 1.602 \cdot 10^{-19}\,\text{J}$$

Since mass is a form of energy, the masses of elementary particles are sometimes expressed by electron-volts; e.g. the mass of the electron, the lightest particle with measurable rest mass, is 511 keV/c^2, where c is the speed of light.

The eV is a useful energy unit when discussing atomic processes as its magnitude is adapted to the low energy levels involved.

In the following, the essential interactions of ionising radiation with matter will be discussed.

2.2.1 Interaction of Charged Particles with Matter

If any *charged particles* such as electrons penetrate matter, they produce ionisation by collision with the atoms. Charged particles interact with the orbital electrons as well as with the electromagnetic field of the atomic nucleus. The radius of the nucleus is about 10^{-14} m, and the radius of the electron orbits is about 10^{-10} m. For this relation of size, we can imagine that the probability that any charged particle travelling through matter interacts with an orbital electron is bigger than hitting the nucleus. The energy of the incident particle is transmitted to many atoms in a large number of collisions along the particle track through the medium. Thus, the primary particle will lose its energy by a large number of small increments.

As the incoming particle interacts with the orbital electrons, it causes ionisation or excitation. These interactions are mediated by the Coulomb force between the electric field of the moving particle and the electric field of the orbital electrons. When the path of the incoming particle is deflected by the electrostatic attraction of the nucleus, it results in an energy loss of the incident particle with the lost energy being emitted as electromagnetic radiation. Because of the underlying mechanism, this radiation is called *bremsstrahlung,* which is a German word and means "braking radiation". Both electronic collisions and the production of bremsstrahlung cause a decrease of the kinetic energy of the charged particles, as the depth of the penetrated tissue grows, until they stop. As a consequence, charged particles have a limited range in matter. The physical quantity that describes the process of slowing down of charged particles is the stopping power S. The stopping power is defined as the ratio of lost energy per path length. To eliminate the influence of the mass density especially for compound materials, usually the mass stopping power S_ρ is used:

$$S = -\frac{\mathrm{d}E}{\mathrm{d}x}, S_\rho = \frac{S}{\rho} = -\frac{\mathrm{d}E}{\rho \mathrm{d}x} \qquad (2.10)$$

Because of their different masses, electrons, protons, and heavier particles have different ranges in matter. It can be seen that for the penetration of several centimetres into water which is equivalent to soft tissue protons must have kinetic energies of several hundred MeV, whereas a few MeV are sufficient for electrons. Electrons of such energy can be generated with reasonable effort by linear accelerators, which will be discussed later, whereas the production of protons with therapeutically relevant ranges requires huge particle accelerators. Therefore, electrons are the most commonly charged particle radiation used for radiotherapy.

The collision of high-energy electrons and heavy charged particles like protons, deuterons, or α-particles with atomic nuclei can lead to nuclear reactions, too. Since this kind of interaction is of no importance for the objective of this book, it will not be considered further on.

2.2.2 Interaction of Uncharged Particles with Matter

2.2.2.1 Basic Effects

Uncharged particles are also denoted as indirectly ionising radiation (cf. Table 2.1) because they generally ionise matter in two steps. Since photon radiation is the only indirectly ionising radiation used for the radiotherapy of benign diseases, just the interactions of photons with matter will be discussed in the following. The primary interaction of photons with matter is characterised by the release of electrons with kinetic energies big enough to ionise atoms directly. These

secondary electrons behave like primary electrons, i.e. they are slowed down by electronic collisions and bremsstrahlung production and have a limited range depending on their kinetic energy as shown above. The kinetic energy itself depends on the energy of the primary photon as well as on the type of the interaction. For photon radiation with energies in the range from about 10 keV up to several MeV, which are relevant for radiotherapy, the following effects are of importance:

- Rayleigh or coherent scattering
- Photoelectric effect
- Compton effect or incoherent scattering
- Pair production

Photo disintegration, where photons release neutrons or protons from atomic nuclei, is observed for photons with energies greater than about 10 MeV, only, and is of less importance in radiotherapy [1].

Coherent or Rayleigh scattering means that only the direction of the primary photon is influenced as a result of the interaction with bound electrons. There is no energy transferred to the interacting atom; hence the energy of the incident photon remains unchanged. In compound materials, consisting of elements with low atomic numbers like biological tissue, coherent scattering occurs mainly for photons with energies below about 20 keV.

The *photoelectric effect* or photoabsorption is observed when the incoming photon detaches an inner shell electron. The incident photon disappears, thereby dividing its energy into two parts: one part is used to release the bound electron and the other part is given as kinetic energy to it. The created inner shell vacancy is filled by an electron from an outer shell whereby the excessive binding energy is emitted as electromagnetic radiation. The energy of these monoenergetic photons depends on the difference in the binding energies of the two involved electron shells. Because the binding energies of the electron shells are characteristic for the particular atom, i.e. for the particular element, the emitted radiation is referred to as characteristic photon radiation. If the energy of this photon is transferred to an outer shell electron, then a so-called Auger electron will be ejected. The probability to undergo photoabsorption strongly increases with the atomic number and decreases with photon energy. The photoelectric effect is the dominating interaction in biological materials for photon radiation with energies up to about 50 keV.

In the *Compton effect*, individual photons collide with single electrons that are free or loosely bound in the atoms. Incident photons transfer a part of their energy and momentum to the electrons, which in turn recoil. In the instant of the collision, new photons of less energy are produced that scatter at angles, the size of which depends on the amount of energy lost to the recoiling electrons. These deflections of the primary photons, accompanied by a change of their energy, are known as Compton scattering. The probability of the occurrence of the Compton effect has only a very weak dependence on the atomic number and decreases slightly with the photon energy. The Compton effect dominates in light elements like biological tissue in the energy range from about 50 keV up to several MeV.

If the energy of the incident photon exceeds 1,022 keV, then an electron and a positron together can be created in the strong Coulomb field of the atomic nucleus. The rest mass of an electron and a positron, respectively, is equivalent to an energy of 511 keV each. Hence, this *pair production* can only occur if the photon has an energy which at least amounts to twice that mass equivalent. The difference between the photon energy and that threshold energy of 1,022 keV is converted into kinetic energy of the electron and the positron. After the positron has been nearly stopped, it annihilates with an arbitrary electron under emission of two radiation quanta with an energy of 511 keV each. Pair production, like the photoelectric effect, exhibits a strong increase in the interaction probability with atomic number, but tends to increase with photon energy, too. Pair production must be taken into account for photon energies above several MeV especially for heavy elements.

2.2.2.2 Exponential Attenuation Law

As a consequence of the photon interactions described above, not only secondary electrons that ionise additional atoms are being produced, but the properties of the incident photon field are

being altered, too. Either the primary photon disappears completely (photoabsorption, pair production) or it is scattered with (incoherent) or without (coherent) energy loss. In other words, the primary photon beam is attenuated. This attenuation depends on photon energy and on the following material parameters: thickness, density, and atomic number. For narrow, monoenergetic photon beams the attenuation can be described by an exponential law given in the following equation:

$$I = I_0 \cdot e^{-\mu x} \tag{2.11}$$

where

I Intensity of the photon beam after passing through the material with thickness x

I_0 Intensity of the photon beam before passing through the material

x Material thickness

μ Linear attenuation coefficient.

Dividing the linear attenuation coefficient by the mass density, we obtain the mass attenuation coefficient μ/ρ which does not depend on density. However, in the above formula the linear thickness has to be replaced by the mass thickness ρx:

$$I = I_0 \cdot e^{-\frac{\mu}{\rho} \cdot \rho x} \tag{2.12}$$

The total mass attenuation coefficient μ/ρ is composed of the individual coefficients for the single processes described above:

$$\frac{\mu}{\rho} = \frac{\sigma_R}{\rho} + \frac{\tau}{\rho} + \frac{\sigma_c}{\rho} + \frac{\chi}{\rho} \tag{2.13}$$

$\sigma P/\rho$ is the attenuation coefficient for the coherent scattering, τ/ρ for the photoelectric effect, σ_X/ρ for the Compton effect, and χ/ρ for pair production. As mentioned above, all these effects depend on the atomic number of the attenuation material and on the energy of the photon beam. This means that one or two effects dominate the attenuation processes for a given combination of matter and energies. Since photon radiation between a few tens of keV and several MeV is used for radiotherapy, the Compton effect is obviously predominant except for low photon energies. The total attenuation coefficient varies only slightly with photon energy within the interval between 1 and 10 MeV and is nearly independent on the material. Photon attenuation is dependent of energy – the curves become more flat with increasing energy, indicating a decreased attenuation.

2.2.3 Inverse-Square Law

Any point source which spreads its influence equally in all directions without a limit to its range will obey the inverse-square law. This follows from the law of conservation of energy, because the flux of radiation through a spherical surface imagined around a radiation source has to be constant (no energy is created or lost outside the source, i.e. there are no interactions with matter). Being strictly geometric in its origin, the inverse-square law applies to ionising radiation as well. As the surface of a sphere of radius r is given by $4\pi r^2$, the radiation intensity has to decrease with $1/r^2$ so that energy is conserved. Correspondingly, the amount of radiation received by an object at a distance r decreases with $1/r^2$, i.e. the inverse square of the distance from the source. Thus, the inverse-square law can be written as

$$I \propto \frac{1}{r^2} \; or \; \frac{I_1}{I_2} = \frac{r_2^2}{r_1^2} \tag{2.14}$$

with I_1, I_2 being the intensity of radiation at distances r_1 and r_2, respectively.

2.2.4 Dosimetric Quantities

In the preceding paragraphs, we concentrated on the basic interactions of radiation. The energy lost by radiation of any kind travelling through matter is transferred directly or indirectly via charged secondary particles to a large number of atoms. This physical process of energy deposition is the origin of all chemical, biochemical, and biological alterations in biological tissue.

To quantify the biological consequences of ionising radiation, a measure is needed which provides a sufficiently reliable relation between the amount of applied radiation and the biological effects and which can be determined reproducibly. The quantity that fulfils these requirements is the energy dose. The energy dose D is defined as the ratio of the energy dE deposited by ionising radiation in matter per unit mass dm:

$$D = \frac{\mathrm{d}E}{\mathrm{d}m} \tag{2.15}$$

The SI unit for the energy dose is J/kg which we also call a Gray (Gy):

$$1\mathrm{Gy} = 1\frac{\mathrm{J}}{\mathrm{kg}}$$

An older unit is rad:

$$1\mathrm{Gy} = 100\mathrm{rad} = 100\mathrm{cGy} \tag{2.16}$$

The dose rate defined as dose per unit time describes the time behaviour of the dose:

$$\dot{D} = \frac{\mathrm{d}D}{\mathrm{d}t} \tag{2.17}$$

The dose rate is measured in Gy/s, mGy/min, µGy/h, or similar units. If the variation of the dose rate with the time is known, then the dose can easily be calculated by integrating the dose rate over a given time. For a constant dose rate, the calculation is further simplified to a multiplication:

$$D = \dot{D} \cdot t \tag{2.18}$$

A radiation dose of 1 Gy can have a remarkable biological effect, e.g. the dose per single irradiation for the curative treatment of a tumour is in the same order of magnitude. However, the amount of energy deposited in matter by a dose of 1 Gy is very small compared to other processes of daily life, e.g. to boil a cup of tea by ionising radiation would require a dose of about 100,000 Gy. This is the reason why the energy dose cannot be determined by calorimetric methods in a clinical environment. Hence, dose measurements are performed by utilising other effects caused by ionising radiation. The most important effect is the ionisation of matter which can best be measured in gases, e.g. in air. Thus, the main measuring devices in dosimetry are air-filled ionisation chambers – small cylindrically shaped or parallel plate probes which make up capacitor-like devices with volumes usually less than 1 cm^3.

Radiotherapy means the application of dose to a certain volume; consequently, not only the dose to a single point has to be determined for the description of radiation fields, but the knowledge of the spatial dose distribution is necessary, too. While the dose profile across the radiation beam should be flat, the variation of dose with growing depth depends strongly on the type and energy of radiation as well as on the distance between the radiation source and the irradiated volume.

The most common types of radiation used for radiotherapeutical purposes are photons with energies from some tens of keV up to several MeV and electrons with energies in the range between 4 and about 20 MeV.

All curves exhibit the expected exponential decrease with growing depth. However, the curves become more flat as the energy increases because of the lessened photon attenuation. For photon energies from ^{60}Co radiation (about 1.25 MeV) and higher, the location of the maximum dose is shifted away from the surface towards greater depths. This so-called build-up effect could be explained as follows. If a photon radiation enters any matter, it starts to produce secondary electrons which deposit their energy as a radiation dose along their pathways. The energy of these secondary electrons increases with the energy of the primary photons. For photon energies of about 1 MeV, the range of these electrons reaches several millimetres. Hence, the photon energy will be transported into depth [2–6]. Since the number of secondary electrons rises with depth, the deposited energy, i.e. the dose, will increase until the electrons from the surface are slowed down to rest. This distance depends on the energy of the incoming primary radiation and reaches about 3 cm for a 15 MV photon beam

from a linear accelerator. Beyond the depth of maximum dose, the number of secondary electrons which are stopped and the number of electrons set in motion are in equilibrium; hence, the depth-dose curve shows the typical exponential-type decrease. The dose build-up allows skin sparing when irradiating deep-seated tumours, but sometimes it is not wanted, if surface lesions have to be treated.

Depth-dose curves for electrons are different in shape. Beyond a region with constant or slightly increasing dose, a steep dose drop due to the limited electron range in matter can be seen. The steepness of the curve decreases with increasing energy of the electron beam because the electrons undergo more scattering events [6]. The dose build-up near the surface is a consequence from lateral scattering which is more pronounced for electrons with lower energies. With increasing electron energy, there is a growing background below the tails of the curves, preventing them from coming down to zero. This background arises from bremsstrahlung photons that are mainly produced at some beam-defining parts of the electron accelerator being passed by the electron beam.

Currently, there is an increasing interest in using protons for radiotherapy. Protons exhibit a depth-dose distribution with a steep dose increase at the end of their range – the so-called Bragg peak. Hence, a high degree of dose conformity to the target can be achieved by varying the proton energy accordingly allowing an excellent sparing of healthy tissue. Though, the costs for proton therapy are about ten times higher than for treatments at recent medical electron linacs which prevents their broad application.

2.3 Sources of Ionising Radiation

In radiotherapy, the intended biological effects are reached by applying the prescribed dose to a volume what we will call target volume. To avoid unwanted side effects in the surrounding healthy tissue, it is necessary to keep the radiation dose within certain limits. This is done by selecting an appropriate radiation quality and by choosing an irradiation technique that will best fulfil the initial constraints set up by the medical intention.

Despite dedicated technical equipment that exists, intended to be used only for the treatment of skin lesions, most irradiations are done with standard radiotherapy devices. In the following, an overview about radiation sources and treatment techniques with special emphasis put to their application for the treatment of skin diseases will be given.

Depending on the size, shape, and location of the lesion target, the radiation therapy can be realised as brachytherapy with one or multiple radiation sources in close contact with the target or by external irradiation where the radiation source is far outside the patient.

For brachytherapy (BPAXΎΣ [Greek] means brief or short) usually radionuclides that emit β^-- or γ-radiation are used. While the dose distribution around γ-sources is dominated by the inverse-square law and only weakly depends on energy, in case of β^--sources the energy of the emitted electrons determines their range and thereby has great influence on the shape of the dose distribution. Because of their very limited range β-emitters are used only for very special applications like the irradiation of the vessel walls of the coronary arteries to prevent restenosis after dilatation and for the treatment of tumours of the sclera.

Brachytherapy can be done by applying radiation for a limited time only or by permanent implantation of radioactive sources into the target volume. The dose applied to the target volume is controlled by an appropriate combination of the number, the activity, and the geometric distribution of sources and in case of permanent implants by the half-life of the selected radionuclide.

External beam therapy requires sources that emit radiation with suitable penetrative potential at a rather high level of intensity. Because of their physical properties, only photon sources or high-energy electrons and protons from particle accelerators can fulfil these requirements.

In the early days of radiotherapy, the only available radiation sources were X-ray tubes and naturally occurring radionuclides extracted from ores.

2.3.1 Radionuclides

For a long time the most important radionuclide was ^{226}Ra, a nuclide occurring in the ^{238}U decay chain and discovered by Marie and Pierre Curie by the end of the nineteenth century. ^{226}Ra and its daughter nuclides emit α- and β-particles as well as γ-radiation. The α-particles have a very limited range of only some 10 μm and are completely stopped in the walls of the capsules in which the radium is applied. Furthermore, also the β-particles having kinetic energies of several hundred keV did not contribute either to the dose around the capsules. Radium has a half-life of about 1600 years and was in widespread use for brachytherapy until the 1950s of the last century, when other isotopes produced by neutron activation in nuclear reactors or by extraction from burned out nuclear fuel became available. In Table 2.2 important radionuclides and their application in radiotherapy are summarised. In addition to the type of emitted radiation, their energy, the half-life, and the activity or specific activity, respectively, are essential parameters for their therapeutic application.

2.3.2 Gamma Ray Units

Although some of these machines used ^{137}Cs as radiation source in the past, most of these units are equipped with ^{60}Co sources. The main advantages of ^{60}Co as radionuclide for the source are the higher energy of the emitted gammas and the much greater specific activity allowing smaller geometric dimensions for the source. The high-energy gammas deliver a better dose distribution for treating deep-seated lesions, and the higher activity allows shorter treatment times and a bigger source to patient distance (source-skin distance – SSD) and hence a reduction of the influence of the inverse-square law on the depth-dose distribution. Together with the less attenuation of the cobalt gammas, the resulting depth-dose curves become more flat and the dose distribution in the patient can be improved for the treatment of deep-seated lesions. The source with a diameter of about 1–2 cm and a length of 2–4 cm is mounted on a support made from a material with very high density (e.g. depleted uranium) to achieve a high attenuation of the gammas when the source is not in the working position. The source assembly is surrounded by a container filled with lead to protect the environment from radiation. The collimation of the radiation is done by two pairs of independently movable collimators made from a high density material like lead or tungsten, too.

The maximum field size of modern cobalt units is 25 × 25 cm–40 × 40 cm and the source to axis distance (SAD) is 80 cm or 100 cm. There are one or two slots below the collimator into which special accessories can be inserted like wedge filters or shielding blocks to create

Table 2.2 Radionuclides and their use in radiotherapy

Nuclide	Decay	Half-life	$E\beta_{,\,max}$ (MeV)	$E\beta_{,\,mean}$ (MeV)	$E\gamma$ (MeV)	Application
^{60}Co	β^-	5.27a	0.331	0.095	1.173, 1.332	External, brachy
^{137}Cs	β^-	30.14a	0.51	0.16	0.662	External, brachy
^{226}Ra	α	1,600a	4.60, 4.73 (α)	–	0.186	Brachy (not longer used)
^{192}Ir	K, β^+, β^-	74 days	0.24–0.67	0.17	0.296–0.612	Brachy (afterloading)
^{106}Ru/^{106}Rh	β^-/β^-	368 days/2.2 h	0.04/3.54	0.01/1.43		Brachy (choroid melanomas)
^{125}J	β^-	59.3 days		0.035	0.027–0.035	Brachy (prostate seeds)
^{32}P	β^-	14.3 days	1.71	0.695		Brachy (intravasal)
^{90}Sr/^{90}Y	β^-/β^-	29.1a/64.1 h	0.546/2.28	0.196/0.933		Brachy (pterygia, intravascular)

irregularly shaped fields. The dose rate at the rotation axis for a SAD of 100 cm and a source activity of about 550 GBq (approx. 15 kCi) is approximately 2.5 Gy/min in the depth of the dose maximum in water. The dose delivered to a specific point is calculated by multiplying the dose rate with the treatment time. That means the treatment time for a single field is less than 1 min for a dose of 2 Gy near the surface. Due to the 63 months half-life of the ^{60}Co isotope, the sources have to be replaced after several years.

2.3.3 Afterloading Units

While in the early days of radiotherapy radioactive sources were applied by hand, today almost all brachytherapy treatments are carried out by the method of afterloading. Afterloading means that an inactive applicator is precisely placed at or near the treatment site and subsequently loaded with a radioactive source. The source tightly connected to the tip of a steel wire is driven to the applicator guided by a series of connecting tubes. This can be done manually or more commonly by a so-called remote afterloading unit that controls the delivery of the source to the applicator from the outside, thus providing radiation protection for the staff. The irradiation time and the positions of the source necessary to deliver the prescribed dose distribution are determined by treatment planning.

Various applicators can be used for the treatment of skin lesions. The so-called Leipzig applicator (Nucletron, Netherlands) consists of a cone-shaped tungsten collimator with a plastic protective cap. During treatment the ^{192}Ir source is positioned close to the focal spot of the collimator. The applicator set comprises cones with diameters of 10, 20, and 30 mm and with the longitudinal source axis oriented parallel or perpendicular to the treatment surface. The short source-to-surface distance of 16 mm provides a steep dose fall-off behind the skin surface, thereby allowing the irradiation of small tumours with an excellent sparing of healthy neighbouring tissue. Whereas these applicators are well suited for the treatment of rather small target volumes at plane surfaces, their design is disadvantageous for the irradiation of larger tumours at curved surfaces like the back of the nose. For those treatments the moulage technique can be applied. A brachytherapy moulage (French: casting, moulding) is made by moulding the body surface of the treatment area and subsequently embedding plastic catheters into the cast. The dwell times of the source at defined positions inside the catheters are calculated by a treatment planning system. Brachytherapy flab techniques initially developed for intraoperative radiotherapy can also be used for skin treatments. These flabs consist of flexible tissue equivalent rubber with a thickness around 10 mm or of plastic spheres arranged in a mesh-like pattern. They comprise plastic catheters evenly arranged in parallel with a distance in the order of 10 mm.

2.3.4 X-Ray Tubes

Electrons produce electromagnetic radiation when they interact with matter. This electromagnetic radiation is emitted as bremsstrahlung with a continuous spectrum as well as characteristic radiation (a line spectrum with energies typical for the emitting element). In an X-ray tube, a cathode which produces electrons by thermionic emission acts as electron source. These electrons, after being accelerated in a strong electric field, impinge on the positively charged anode. During slowing down the kinetic energy of the electrons is converted into X-radiation – characteristic radiation and bremsstrahlung. The anode is made of a material with high atomic number which has a large bremsstrahlung cross section (a high probability for producing bremsstrahlung). However, about 99 % of the kinetic energy of the electrons striking the anode is transformed into thermal energy. Therefore, metals with high heat capacity and conductivity are used for the anodes of X-ray tubes. Furthermore, the heat dissipated in the anode has to be removed by an efficient cooling system. X-ray tubes for diagnostic applications usually have a rotating anode to provide a small focus. Since the size of the focal spot is not as important as in diagnostic radiology, therapeutic

X-ray tubes can have a diameter of the focal spot of about 5–8 mm to reduce the thermal power per unit area on the rigid anode. The high voltage is supplied by a special generator capable of producing voltages up to 250 kV. Therefore, the maximum energy of the bremsstrahlung is usually limited to about 250 keV. Since these generators can only deliver a waveform that is close to DC, but still has some ripple, the maximum voltage as kilovolt peak (kVp) is given to characterise the X-radiation.

X-ray tubes are enclosed in a housing made from a material with high density and high atomic number, which protects the environment from unwanted irradiation. After leaving the tube through the exit window which acts as a vacuum seal, the X-rays pass through an additional metal foil (copper, aluminium) that modifies the energy spectrum of the bremsstrahlung and thereby also decreases the total intensity of the X-ray beam.

It can be clearly seen that the bremsstrahlung continuum is significantly altered by filtration, whereas the lines of the characteristic X-radiation remain in the same position. Since high-energy X-rays are attenuated less than low-energy X-rays, the mean energy of the spectrum after this filtering will be shifted towards higher energies, and therefore the resulting depth-dose curves become more flat [7].

As we have seen, the photon spectrum determines the depth-dose distribution of the X-radiation. The accelerating potential, i.e. the operating high voltage at the X-ray tube, determines the maximum energy of the X-rays, but the shape of the spectrum is affected in a complex way by the material of the anode and the filtering of the radiation. Thus, it is not sufficient to characterise the penetrative quality of the radiation by the high voltage alone. A suitable parameter used in daily practice is the half value layer (HVL) of the radiation. The HVL gives the thickness of a material (aluminium up to approximately 120 kVp, copper for higher energies) that reduces the intensity of the X-rays in a narrow beam by 50 %. Since the spectrum will be changed further after travelling through the material, the HVL tends to increase because of beam hardening. The degree of alteration expressed as the ratio of the first (HVL_1) to the second HVL (HVL_2), which characterises the spectrum after passing the first HVL, is referred to as homogeneity index H of the radiation.

$$H = \frac{HVL_1}{HVL_2} \tag{2.19}$$

X-rays with $H > 0.9$ are called homogeneous; for monoenergetic radiation $H = 1$. Depending on the depth of the lesion to be irradiated, an appropriate energy of the X-ray beam is selected by choosing the operating high voltage and a suitable filter. Although arbitrary compositions of accelerating voltage and different filters were possible, only selected, experience-based combinations are available on recent X-ray units. In Table 2.3 the possible combinations for the Gulmay therapy unit are summarised [8].

As follows from the inverse-square law, the depth-dose distribution is influenced by the SSD too; smaller SSD increases the steepness of the dose descent with increasing depth. Radiation therapy with X-rays below 20 kVp was called Grenz ray therapy; from 40 to 50 kVp and SSDs around 2 cm, it is referred to as contact therapy; for radiation coming from X-ray tubes operated between 50 kV and 150 kV, the term superficial therapy; and above 150 kV, orthovoltage therapy are used [1].

It can be seen that the relations between kVp, filtering, and SSD are quite complex (e.g. the depth-dose curve for the 15 cm diameter applicator at 100 kVp has almost the same shape like the

Table 2.3 Combinations for kVp and filtration and resulting half value layers (HVL) for an X-ray therapy unit Gulmay 150

Filter #	High voltage in kVp	Filtration in mm	HVL in mm
1	20	0.1 Al	0.12 Al
2	30	0.4Al	0.29 Al
3	50	0.6 Al	0.58 Al
4	60	0.4 Al	
5	75		
6	80		
7	100	1.8 Al + 0.1 Cu	
8	120	1.1 Al + 0.3 Cu	
9	150	0.2 Al + 1.0 Cu	

one for the 10 cm applicator at 150 kVp for that particular machine), and therefore they shall be determined for the actual X-ray unit.

The physics of interaction of X-rays with matter shows that scattered radiation (due to coherent or incoherent scatter) is of great importance for the dose distribution in the irradiated material. The amount of scattered radiation increases with the volume irradiated. Consequently, the dose applied to a certain point depends on its depth, the material thickness behind this point, and on the field size. Although this information could be obtained from published data [9], they should be at least verified for the actual X-ray unit. If the reference dosimetry has been done under full backscatter conditions, i.e. a phantom of at least 20 cm thickness, then the reduced dose due to a lack of backscattered radiation in the case of thin irradiated objects (e.g. hands) has to be corrected for.

To delimit the size of the radiation field and to ensure a certain distance from the focus to the patient's skin, special metal applicators with rectangular or circular cross sections are attached to the tube. Further field shaping can be reached by the application of lead foils onto the skin surface to shield areas of healthy tissue from unwanted irradiation.

It follows that a separate dosimetry has to be available for every applicator. Furthermore, the influence of the reduced field size on the dose due to the application of additional shielding has to be taken into account. Required corrections can be obtained from measured curves as presented above.

2.3.5 Linear Accelerators

The attenuation of photon radiation emitted by conventional X-ray tubes is too high for treating deep-seated lesions with the prescribed dose. Therefore, the rapidly decreasing depth doses require relatively high doses near the surface at the entrance side of the beam. This problem can be solved by using radiation with higher penetrative quality, as can be generated by electrons with kinetic energies in the MeV range. However, for technical reasons, the accelerating potential of conventional X-ray tubes is limited to several hundred kV. Accordingly, other mechanisms are needed to produce electrons with MeV energies. Today, such MeV electrons usually are provided by particle accelerators. In modern linear accelerators (linac), electrons, emitted by an electron gun and pre-accelerated by a static electric field up to almost the speed of light, are injected into a special accelerating tube, often called wave guide. This tube consists of contiguous circular copper cavities into which electromagnetic waves are fed in by a powerful microwave generator operated by a magnetron or a klystron. The resulting very strong electric field in the cavities accelerates the electrons up to energies of several MeV. After leaving the wave guide, these electrons are deflected by an electromagnet and strike a metal block, called target. By being decelerated in the target the electrons produce bremsstrahlung like in the anode of an X-ray tube, but with a maximum energy which is about 100 times higher due to their high kinetic energy. Although the cross sections for producing bremsstrahlung are much higher for MeV electrons, which means that the photon radiation is generated more efficiently, target cooling is yet necessary to drain the dissipated thermal energy. To homogenise the intensity across the photon beam, a metal cone – the flattening filter – is inserted into the beam path behind the target. The dimensions of the photon field hitting the patient are determined by a collimator consisting of two pairs of moveable jaws, usually made of tungsten. Tungsten has a very high mass density of about 19.3 g/cm^3 and therefore is an excellent material for shielding high-energy photon radiation.

In recent linacs one pair of jaws usually consists of several single leaves, which can be moved independently of each other. With such multileaf collimators the contours of the photon beams can easily be confined to the shape of the volumes to be irradiated. Multileaf collimators are a much more elegant and efficient method for field shaping than the insertion of individually manufactured shielding blocks into the beam path using special accessory slots at the linac gantry. However, for very complex or very small lesions, the staircase-shaped outer contour delivered by a regular MLC with 1 cm leaf width might only give a coarse approximation of the target volume. Therefore, most recent linacs are equipped with MLCs with 0.5 cm leaves.

In most linacs, bremsstrahlung photons as well as high-energy electrons can be used for radiotherapy. In electron mode target and flattening filter are replaced by a thin metal foil used to widen the aperture of the narrow primary electron beam by electron scattering. A special electron applicator (electron tube) is inserted under the secondary photon collimator to collimate the spread electron beam near the patient's surface in order to provide flat, homogeneous treatment fields. Between the flattening filter or the first electron scattering foil and the collimator, the fluence of the photon and electron beams is measured by a thin, segmented ionisation chamber which can also detect deviations of the spatial intensity distribution of the radiation beam from preset values. Furthermore, there is a mirror behind the dose chamber which projects a light field with the same size and shape like the high-energy photon or electron field onto the patient's surface. Because of electron scattering, the mirror has to be removed from the beam path when the linac works in electron mode. All these components described above are mounted in the so-called gantry. The gantry is attached to a stand and can rotate around an axis in parallel with the floor.

Linacs deliver photon radiation with high energy and small penumbras at high dose rates. The total amount of radiation is controlled by the dose monitor – a counter triggered by the signals of the build-in dose chambers. Table 2.4 gives a short summary of typical dose rates from linacs, cobalt machines, and X-ray therapy units. Recently, there came linacs into the market without flattening filters, allowing dose rates of up to 20 Gy/min. These linacs can be used very efficiently for treating small fields or intensity modulated techniques for which the uneven profile does not matter.

The patient is positioned on a treatment table, moveable in the lateral, longitudinal, and vertical direction, and also capable of rotating around a vertical axis perpendicular to the rotational axis of the gantry. A wall-mounted laser system indicates the point where the perpendicular projection of the beam spot meets the rotational axis of the gantry. That point is assumed to be the origin of an accelerator-based coordinate system and is usually called isocentre. By means of skin marks, the patient could be placed in a definite and reproducible manner within this coordinate system.

Table 2.4 Typical dose rates and source-to-axis distances (SAD) and SSD, respectively, for various photon sources (measured in the depth of maximum dose at an SSD equal to the SAD for cobalt units and linacs and at the surface for the nominal SSD for X-ray units)

	Dose rate in Gy/min	SAD/SSD in cm
Linac	2–20	100
Cobalt machine	0.5–2.5	80–100
X-ray unit	0.5–10	10–50

2.4 Simulation and Treatment Planning

For complex cases, where the target volumes have to be defined individually, a three-dimensional model of the patient illustrating the target lesion and organs at risk has to be set up by means of X-ray computed tomography. In this model the radiooncologist determines the target volume and – if any – the organs at risk by drawing their contours into all relevant CT slices. A formalism has been published that takes into account the limited knowledge about the tumour spread and the precision of patient positioning [4–6].

The volume to be irradiated consists of the "gross tumour volume" (GTV) representing the extent of macroscopic disease. Around the GTV we find a region of certain or assumed microscopically tumour infiltration. Those volumes are referred to as "clinical target volume" (CTV). To allow for geometric uncertainties due to organ motion and the limited precision of patient positioning, a safety margin is added to the CTV leading to the "planning target volume" (PTV). Thus, to ensure that the prescribed dose is delivered to the CTV/GTV, the radiation fields have to be enlarged up to the PTV. However, because of complex shapes of the PTV, in many cases, only a limited degree of conformation of the high dose region to the PTV can be achieved. Therefore, the radiooncologist defines a dose level encompassing the PTV completely together with an unavoidable part of the surrounding tissue. This volume is called "treated volume" (TV). The "irradiated volume" (IV) contains all tissue within a dose level significant in comparison with normal tissue tolerance.

For the organs at risk (OAR), being organs or tissues in the vicinity of the PTV with a probability to develop radiation-induced morbidity that is

not negligible for the prescribed target dose, a similar formalism can be applied, leading to the so-called planning organ at risk volume (PRV).

After the PTV and the PRV have been defined, the dosimetrist or the medical physicist develops a treatment plan for the individual case consisting of one or more different radiation beams that fulfil the requirements set by the radiooncologist. For that procedure, called physical treatment planning, a dedicated computer system is used. The software running on that system can create, visualise, and manipulate the patient model as well as generate suitable beam arrangements and calculate the dose distribution caused by them in three dimensions. A variety of dosimetric data from the treatment units have to be measured and transferred to the planning computer before performing these calculations. Depending on the physical algorithm used for dose calculation, these data consist of bunches of percentage depth-dose curves and dose profiles across the beam in different depths as well as absolute dose values to distinct points for various field sizes.

The approved treatment plan is then transferred first to the simulator where the patient gets appropriate skin marks and then to the computer control of the linac where all geometric and dosimetric parameters for the patient are set up automatically.

2.5 Treatment Techniques

After setting up the indication and defining the intention of radiotherapy, the radiooncologist has to specify what volume should be irradiated. Primarily this is made verbally; but a geometric description of the target volume is required to perform the irradiation. Depending on the site, the total dose, and the intention of the radiation treatment, this could be done either by simply placing the tube of the X-ray unit directly on the patient's skin or by creating a very precise three-dimensional patient model from computed tomography and outlining the target volume and the organs at risk, similar to the procedures used for treating malignant tumours according to the ICRU model described above. While the description of the location and the shape of target volumes and organs at risk as well as the definition of the desired dose and fractionation scheme for the target could be referred to as medical treatment planning, the design of the treatment technique including the selection of the radiation source; the beam quality; number, size, and shape of treatment beams; and the calculation of irradiation time or dose monitor settings belongs to the physical treatment planning.

In the following, an overview about the basic treatment techniques from the point of view of physical treatment planning will be given, with regard to typical applications of the radiotherapy of skin diseases.

2.5.1 Surface or Near Surface Lesions

Let's start with simple cases, where the lesion is located on or near the surface of the body with a reasonable assumption for the extent of the depth, like keloids, basalioma, skin lymphoma, etc. For these cases the target volume can be identified easily by visual inspection in combination with palpation. If available, single X-ray beams with energies up to 150 kVp as well as beams of MeV electrons from a linac are suitable for maximum depths of about 3 cm. The energy selection is made in accordance with the depth extent of the target. Electron fields, in particular at energies below 12 MeV, exhibit a reduced surface dose due to the characteristic dose build-up with depth. In order to increase the surface dose, sometimes tissue equivalent material is placed directly on the skin, thus shifting the isodoses towards the surface by the thickness of this so-called bolus. Simultaneously, a bolus decreases the energy of the electrons at the skin surface, thereby reducing the range of the electrons as well. So it can in principle be used to virtually provide electrons with energies less than the lowest one available at the linac.

The size and shape of the fields have to be adapted from the projection of the target volume perpendicular to the treatment field. In many cases simple rectangular fields can be used being defined by the size of the available standard tubes or electron applicators for the X-ray unit and for the linac, respectively. The protection of healthy tissue from unwanted radiation, i.e. the minimisation of the radiation risk, requires irregular

field shapes for many cases. So, special cut-outs made from lead or leaded rubber can be placed on the patient's surface below the applicator of the X-ray unit, or metal absorber plates can be inserted into the downstream diaphragm of the electron applicator.

Because the depth of the target volume does not exceed 3 cm, the use of orthovoltage therapy with 150 kVp is sufficient. Conformation to the target volume is reached by applying a cut-out made from leaded rubber with a thickness equivalent to 1 mm of lead.

For single fields the determination of the required irradiation time is based on the measurement of basic dosimetric quantities under reference conditions (kVp, filtration, SSD, applicator, depth, free in air or in phantom measurements, irradiation time). Corrections for different dose, the depth of dose prescription, thickness, and field size, relevant for the actual case, have to be applied. While the applicators of an X-ray unit are placed directly on the surface of the body, the distance from the distal end of an electron applicator to the skin may vary. Therefore, the SSD has to be taken into account when calculating the setting of the dose monitor of the linac.

Example 1 (X-Ray Therapy)

Dose prescription D	0.5 Gy to a depth of 2 cm, 150 kVp X-ray
Field size F	Circular applicator, 10 cm diam., about 1/3 covered by a cut-out
Thickness T	About 4 cm behind the prescription point
Reference dose rate DR_{ref}	1.5 Gy/min in 5 mm depth (measured in phantom for 10 cm diam. applicator)
Percentage depth dose PDD in 2 cm	86 %
Calculation of treatment time t	$t = D\dfrac{k(F)\cdot k(T)}{\mathrm{DR}_{\mathrm{ref}}\cdot \mathrm{PDD}}$ with $k(F)$ and $k(T)$ being correction factors for field size and thickness respectively

With $k(F)=1.1$ and $k(T)=1.05$ and PDD, we get a required irradiation time of $t=0.45$ min or approximately 27 s.

Example 2 (Electron Irradiation)

Dose prescription D	2 Gy to a depth d of 1.5 cm
Electron energy	6 MeV (depth of dose max 1.5 cm, 80 % in 2 cm)
Reference dose $\mathrm{DR}_{\mathrm{ref}}$	1 Gy/100 MU (MU: monitor unit) in depth of $d_{\max}$ at 100 cm SSD ($\mathrm{SSD}_{\mathrm{ref}}$)
SSD for treatment	105 cm
Calculation of monitor setting m	$m = D\dfrac{k(F)}{\mathrm{DR}_{\mathrm{ref}}\cdot \mathrm{PDD}}\left(\dfrac{\mathrm{SSD}+d}{\mathrm{SSD}_{\mathrm{ref}}+d_{\max}}\right)^2$

With an assumed cut-out factor $k(F)=1.05$ which accounts for the reduced field size and a percentage depth dose of 100 % (at $d_{\max}$), a calculated monitor setting of about 231 MU is obtained. The dose in a depth of 2 cm amounts to 1.6 Gy (80 %).

It should be noted that all corrections must be related to the reference conditions under which the basic dosimetry has been performed. Furthermore, the prescription and the recording of the radiation dose should follow the ICRU recommendations [4–6]. For instance, in X-ray and electron therapy, the dose specified in a depth quite in the middle of the target volume as well as the maximum and minimum dose to the target volume should be reported.

2.5.2 Deep-Seated Lesions

For larger extension of the target volume into depth, the dose homogeneity can be improved by increasing the energy of the applied radiation and the source-to-surface distance. Nevertheless, the potential to shape the dose distribution of a single field along the beam direction is very limited for photon radiation due to their exponential attenuation with depth. The only way out is to use multiple treatment fields coming from different directions. The simplest multiple field technique is a pair of opposing fields [11].

As expected, the higher the photon energy, the larger is the region where a homogeneous dose distribution can be achieved. For the first case with a thickness of 100 mm, 200 kVp gives

the best results, 150 kVp is still acceptable, and only for the 120 kVp the dose maximum exceeds 120 %. Increasing the thickness to 200 mm shows significant changes for the 150 kVp – the dose maximum exceeds 200 %. The use of the high-energy γ-radiation from a cobalt treatment unit or megavoltage X-rays from a linac give acceptable dose homogeneity across the volume and a remarkable skin sparing due to the dose build-up near the surface. However, even for the 15 MV photon radiation, almost all volume within the field apertures is irradiated with the therapeutic dose. The high dose volume can only be reduced by applying fields from oblique directions. It becomes obvious that with an increasing number of radiation beams a higher degree of conformation to a target volume can be achieved. On the other hand, the total irradiated volume increases. In comparison to other multiple field techniques, opposing fields deliver a large high dose volume but a small total volume of irradiated tissue.

To keep the potential for radiation-induced damage to the surrounding normal tissue as low as possible, the volume within the high dose region (TV) has to be conformed to the PTV as good as reasonably achievable [12]. This is done by inserting shielding blocks into the beam path or by creating a suitable beam shape with a MLC, thereby preventing normal tissue from being hit by the primary radiation.

An example is an isodose plan for the treatment of Graves' disease by a pair of opposing fields. To tailor the shape of the dose distribution to the PTV thereby minimising the volume of irradiated healthy tissue, individually designed shielding blocks are inserted in both fields.

The block contours visible in the beam's eye view determine the form of the isodoses in a plane perpendicular to the beam direction which fits satisfactorily to the target volume. The lenses of the eyes being organs at risk are located very closely to the field borders. Therefore, the uncertainties in patient positioning have great influence on the dose to the organs at risk.

To keep these placement errors as low as possible, the patients are fixated with special thermoplastic masks.

The calculation of treatment times or monitor settings for these multiple field techniques is more complex than for the single field cases described above. Moreover, to determine the dose distribution correctly, the spatial inhomogeneity of density has to be taken into account, too. This is not within the scope of this book, but further information can be found elsewhere [10, 13].

At this point, it should be pointed out that the dose specifications usually refer to water as reference material. As shown above, the physical interactions, leading to energy deposition by ionising radiation, depend on the particular material, i.e. on the elemental composition, and on the type and energy of radiation. For photon radiation with energies above 1 MeV and for MeV electrons, the doses absorbed by different biological materials deviate from the dose to water only by a few percent. However, low-energy photons as used for superficial and orthovoltage therapy have a strong dependence of photon absorption on the atomic number.

It can be clearly seen that for low energy photons the dose to bone which contains calcium and phosphorus as elements with high atomic numbers is much bigger than the dose to water in the same photon field. Since the elemental composition is usually unknown, it is impossible to calculate the actual dose distribution in the particular biological tissue for superficial and orthovoltage irradiations. Only Monte Carlo-based methods which model the relevant physics of interaction between radiation and matter can calculate dose precisely under the assumption of reasonable elemental compositions.

2.6 Summary

- Ionising radiation like photons, electrons, or other charged particles transfer energy to matter by passing through it.
- The physical quantity to measure this deposited energy is the dose being used as measure to quantify the biological effect of ionising radiation.
- Ionising radiation applied for radiation therapy like photons in the energy range from

20 keV up to 20 MeV and high-energy electrons can be produced by radioactive sources, X-ray tubes, and medical linear accelerators.

- Location, size, and shape of the lesion to be irradiated determine the kind of radiation and the applied irradiation technique.
- Single fields of X-rays or MeV electrons are used for the treatment of superficial or near superficial lesions.
- Short source-to-surface distance and low photon or electron energy provide a steep dose fall-off with depth
- Multiple fields of high-energy photons from linear accelerators are a common technique for treating deep-seated targets.
- Field shaping by radiation opaque cut-outs, by individually manufactured shielding blocks, or by multileaf collimators should be applied to minimise the volume of tissue exposed to radiation.

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Radiobiology of the Skin

3

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Contents

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3.1 Introduction

It is accepted that radiotherapy may be equally as effective as surgery in the management of epithelial skin cancers, whereas surgery is the more important modality for malignant melanoma which is generally accepted to be radioresistant. Radiobiology underlies the response (or lack of response) of a tumour to radiotherapy. The four key features that are considered to explain this response were itemised by Withers in 1975: repair, repopulation, reassortment and reoxygenation [1]. This list remains useful in academic and clinical radiotherapy practice today, with the addition of a fifth aspect: intrinsic radiosensitivity [2]. The contribution of the normal tissue and tumour microenvironments, as well as angiogenesis, to the effects of radiation is increasingly understood and exploited therapeutically.

The probability of associated normal tissue complications limits the dose of radiation that can be safely delivered to a tumour. Radiobiological principles can be used to achieve an increase in treatment efficacy without an increase in total radiation dose, for example, through alternative fractionation schedules. Our increased understanding of cell biology has assisted the deconvolution of the complex molecular interactions that arise in response to radiotherapy. This enhanced knowledge has also helped to develop rational combined modality treatments such as the addition of cytotoxic chemotherapy, molecular targeted therapies and hyperthermia to radiotherapy.

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3.2 Mechanisms of Radiation Injury

3.2.1 Single and Double-Strand DNA Breaks and Mitotic Cell Death

In the simplest terms, ionising radiation (IR) incident on a water molecule in a cell can dissociate the latter into reactive components known as free radicals, which are capable of inducing DNA damage by ionisation (ejecting an electron) if the radiation path crosses a cell nucleus. If a free radical interacts with DNA, it may elicit a range of damaging effects. Alternatively, if IR crosses the nucleus, it may directly damage DNA. A single base may be damaged or displaced from the DNA strand, or the latter may be severed, known as a single-strand break (SSB). More extensive damage is a double-strand break (DSB), which represents a greater challenge for the cell's DNA repair mechanisms. Cross-linking between the two DNA strands and to adjacent proteins may also result. Finally, chromosomes may be fragmented or may undergo translocations which may lead to cell death following attempted cell division.

Curative (or radical) radiotherapy is usually prescribed in multiple small daily doses or fractions. A typical fraction size is 2 Gray (Gy), and it has been observed that 1–2 Gy induce one lethal event per cell, killing approximately 63 % of targeted cells and leaving 37 % viable. In excess of 1,000 bases may be damaged, and 1,000 SSB and 40 DSB may ensue. It is believed that intercellular signalling precipitates rapid calcium fluxes, which produce reactive oxygen species and may achieve cell death in the bystander cells [3].

In normal tissues, DNA damage causes the cell cycle to arrest, whilst the DNA damage is repaired, then the cell cycle resumes. If the damage is too great, permanent cell cycle arrest (senescence) or cell death may result. Nonlethal DNA alterations (mutations) occur most frequently in regions of lower radiation dose, for example, where the dose falls off at the edge of the radiation field. If the cell cycle is able to replicate aberrant cells successfully, this may give rise to a radiation-induced malignancy. Through mutation or deletion, cancer cells frequently lose the protective mechanisms that guard against the replication of damaged DNA and promote cell death through apoptosis. Thus, tumour cells with mutated DNA may continue to proliferate.

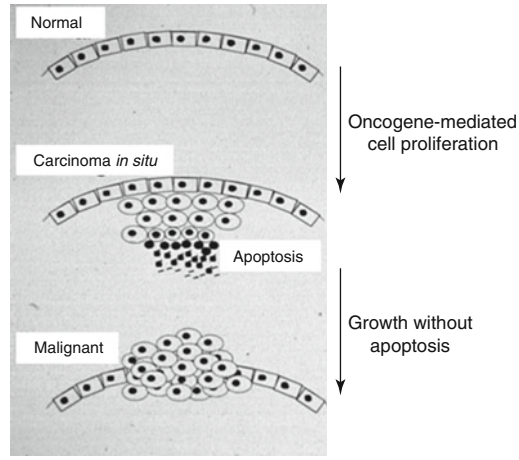

Fig. 3.1 The loss of homeostatic apoptotic mechanisms promote neoplastic epithelial cell proliferation

3.2.2 Apoptosis

Apoptosis, or programmed cell death, is an essential part of normal tissue homeostasis that becomes deregulated in carcinogenesis. Epithelial tissues are constantly proliferating according to the hierarchical model, that is to say pluripotential stem cells self-renew in the basal compartment and terminally differentiate and migrate into the epithelial layers to replenish shed cells [4]. Apoptosis, via the intrinsic (p53 dependent) or extrinsic (p53-independent) pathways, eliminates nonviable cells to prevent damaged DNA being passed to daughter cells and to balance the rate of cell proliferation with cell loss [5].

Following pro-proliferative stimuli, for example through the activation of oncogenes which may inhibit apoptotic signalling pathways, cell division exceeds cell loss which results in tumour formation (Fig. 3.1). Loss of normal apoptotic signalling is a very common abnormality in

cancer, whereby cells with DNA damage are able to replicate. A feature of cancer cells without functional apoptotic mechanisms is intrinsic resistance to anticancer therapies, including radiation [6]. The clinical targeting of apoptotic pathways is a promising emerging strategy in the management of cancer, especially melanoma, as discussed in Sect. 3.5.

3.3 Dose and Treatment Time

Skin cancer was the context for some of the earliest observations of clinically relevant radiobiology concepts. In 1936, Holthusen observed a sigmoidal-shaped distribution of the incidence of late normal tissue effects such as telangiectasia with increasing doses of radiation. A similar curve for skin cancer was derived and, thus, the idea of an optimal radiation dose for cure without complications [7], better known as the 'therapeutic window' (Fig. 3.2). In 1944, Strandqvist studied a single-centre series of patients irradiated for basal cell and squamous cell cancers of the skin and lip and became the first to establish a mathematical relationship between overall treatment time and response to ionising radiation [8].

3.4 The 5 Rs of Radiobiology

3.4.1 Repair

Multiple effective mechanisms have evolved to repair DNA damage and preserve genomic stability. After ionising radiation, DSBs may be repaired through homologous repair (HR), non-homologous end joining (NHEJ) or, less commonly, by base excision repair (BER). 50 years ago, Strandqvist also observed that if radiotherapy was fractionated over several days, a greater total dose was required to be equivalent to a lower dose given in a single treatment. Part of this is due to the ability of tumour cells to repair damage between fractions, which reduces the efficacy of treatment. DNA repair is a double-edged sword however, as it also enhances normal tissue tolerance.

3.4.2 Repopulation and Fractionation

Tumour cell death is the desired outcome of radiotherapy; however, a margin of 5–10 mm of normal skin is added to the visible extent of, for

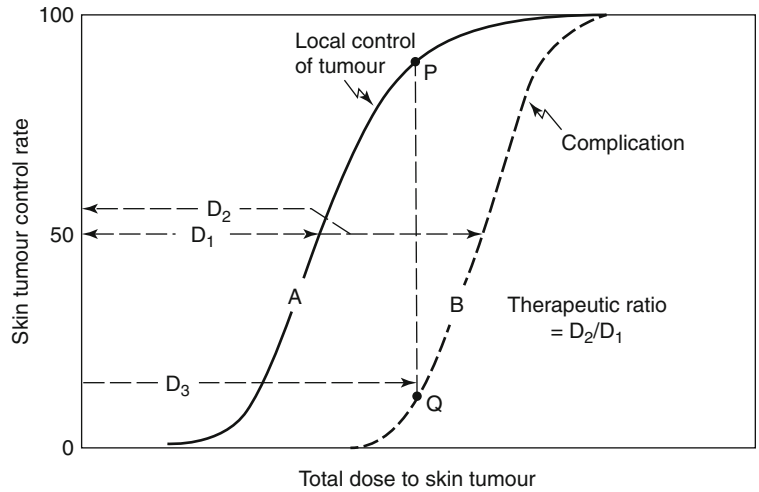

Fig. 3.2 The 'therapeutic ratio' or 'window' describes the separation between the probability of tumour control (*solid line*) and normal tissue complications (*dashed line*). In this theoretical example, the dose of irradiation required to achieve 50 % tumour control (D_1) is less than that which will cause complications in 50 % of patients (D_2). The addition of a radiosensitiser aims to reduce the dose of radiation necessary to achieve the same probability of tumour control and thus further reduce the probability of normal tissue damage and widen the therapeutic window (D_1/D_2)

example, a basal cell or squamous cell skin cancer, both laterally and at depth, to cover the spread of any microscopic tumour cells that may cause a tumour recurrence. This margin should receive 90–95 % of the prescribed dose, and adjacent normal epithelial cells will therefore receive a cytotoxic and genotoxic dose of ionising radiation. Cell proliferation is a normal response to epithelial damage, and stem cells divide and differentiate to replenish the epithelium. Dry desquamation is a sign of increased cell loss, but when moist desquamation occurs, the rate of repopulation of the epithelium from stem cells in the basal layer is being exceeded [9, 10]. Tumour cell repopulation will also occur during a course of fractionated radiotherapy. Even more unfortunate is that radiation can activate cell signalling networks that promote accelerated repopulation. This is especially true for squamous carcinomas. Tumour cell repopulation is an important mechanism of treatment failure and inhibitory strategies are evolving [11].

As epithelial tissues proliferate rapidly, there is no latency in the development of acute effects. Human skin has a high repair capacity and early skin radiation reactions display a half-time to recovery of only 1 hour [12]. Skin thus has a high fractionation sensitivity and is attributed a high α/β ratio, a radiobiology concept to describe a tissue's response to radiation based on the linear quadratic equation [13]. Acute reacting tissues, such as skin and gastrointestinal epithelia, have a high α/β ratio (approximately 10) [14]. In contrast, late responding tissues such as the spinal cord, where DNA damage is only displayed at infrequent cell divisions, have a low α/β ratio (approximately 2). Radiosensitive non-melanoma skin cancer has an α/β ratio of 6–10, whilst melanoma cells typically have a lower α/β ratio, in the order of 3. These α/β ratios can be exploited when choosing the optimal fractionation schedule.

3.4.3 Reassortment

Normal cells divide by progressing through the cell cycle. Quiescent cells (G0) may be recruited into the cell cycle in response to proliferative signals. The cyclin/cyclin-dependent kinases (CDKs) form complexes that act at each phase of the cell cycle to promote entry into the subsequent phase, but natural CDK inhibitors regulate this. The G1 and G2 checkpoints provide an opportunity for the normal cell to audit the integrity of the DNA before further synthesis and cell division, respectively. The tumour suppressor gene p53 is requisite for G1 arrest [15]. As loss of p53 is the most common genetic aberration in cancer, tumours frequently have deregulated cell cycle control and are able to bypass these checkpoints and proliferate unchecked.

Reassortment is the normal redistribution of cells through the cell cycle. As cells move through the cell cycle, it is plausible that cells that were in the relatively radioresistant S phase of the cell cycle during a fraction of radiotherapy will have moved into G2 and M phases and be more sensitive to radiation for subsequent fractions [16].

3.4.4 Reoxygenation

A tumour consists not only of tumour cells but also a stromal matrix that includes, perhaps most significantly, endothelial cells. The ability of a tumour to establish its own vasculature is prerequisite for its survival beyond a cluster of cells greater than 100 μm in diameter [17, 18]. To achieve this, tumours increase secretion of pro-angiogenic proteins such as vascular growth factors (VEGFs) relative to the production of anti-angiogenic factors, including angiostatin, endostatin and thrombospondin-1.

Endothelial cells express high levels of the family of vascular endothelial growth factor receptors (VEGFRs). In endothelial cells in vitro, ionising radiation has been shown to activate VEGFR directly, and consequently AKT, resulting in a possible pro-angiogenic and pro-survival effect. VEGF-mediated radioresistance [19], through the upregulation of the anti-apoptotic protein bcl-2, is a significant clinical problem but one that can be inhibited with targeted agents.

Rapidly proliferating squamous cell carcinomas of the skin are liable to outgrow their blood supply and become necrotic and hypoxic in the

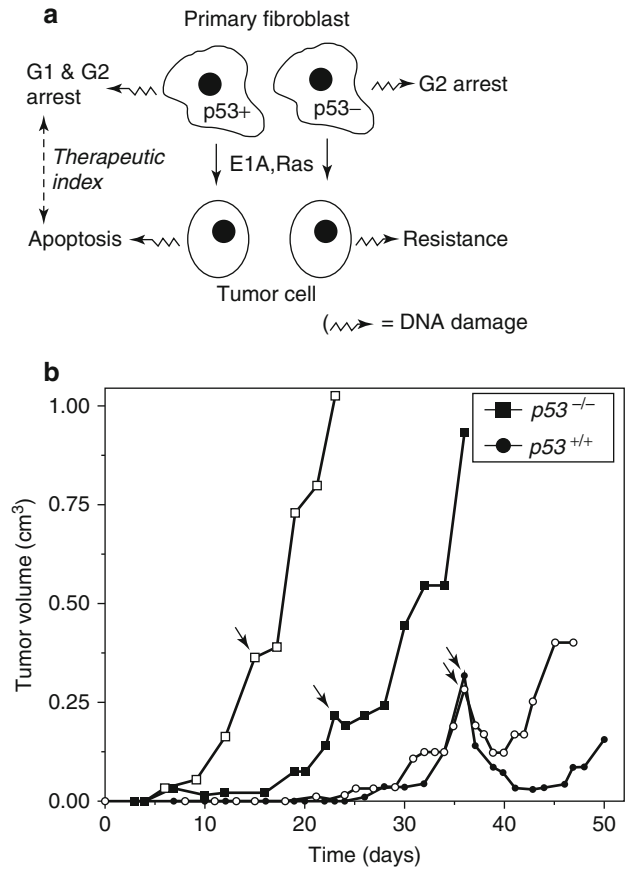

Fig. 3.3 p53 is a key mediator of intrinsic radiosensitivity. (**a**) In this in vitro example using primary fibroblasts, *p53*-deficient cells subsequently underwent oncogenic transformation, for example, by *Ras* mutation. In contrast to the p53 wild-type cells, the p53-deficient cells become resistant to DNA damage by irradiation. (**b**) In vivo, p53 wild-type xenografts from the oncogenically transformed fibroblasts displayed enhanced radiosensitivity following irradiation with 7 Gy relative to p53 mutants. The white and black shading represents different clones

centre. Following a fraction of radiotherapy, the oxygenated cells will be killed and there will be a higher percentage of hypoxic cells. Following mechanisms that include the opening of temporarily closed vessels, reduced respiration in damaged cells and mitotic death, the hypoxic fraction will return to pre-radiation levels which is termed re-oxygenation [20].

3.4.5 Intrinsic Radiosensitivity

Cutaneous malignancies display a particularly wide spectrum of intrinsic sensitivity. The main reason appears to be the extent and facility of tumour cell apoptosis, as deregulation of this cell death pathway renders tumour cells resistant to conventional therapy. It has been demonstrated that tumours grown in p53-deficient mice display a lower proportion of apoptotic cells and fail to regress in response to chemotherapy or gamma irradiation, as compared with those with functional p53 [21] (Fig. 3.3). p53 is one of several compelling targets in cancer therapy, especially in relatively resistant tumours such as melanoma.

Patients diagnosed with the recessive condition ataxia telangiectasia have mutated ATM/ATR genes and may show exquisite sensitivity to radiotherapy. Where ataxia telangiectasia was unsuspected, excessive normal tissue toxicity has resulted from standard radiotherapy schedules. A reduction in both DNA repair fidelity and G1 delay may underlie this sensitivity, and impaired DSB repair has also been implicated. Patients with breast cancer found to have ATM gene mutations did not display increased radiation-induced skin toxicity, however [22]. In the-

ory, assessing the intrinsic sensitivity of a patient's tumour or fibroblasts may enable personalisation of the radiotherapy dose prescription. However, a study in breast cancer has suggested that beam energy and treated volume may impact more on late effects than the intrinsic radiosensitivity of fibroblasts [23].

3.5 Clinical Applications

Lymphoma and melanoma are classic examples of the potential extremes of the spectrum of tumour intrinsic radiosensitivity. Basal cell and squamous cell carcinomas lie towards the more sensitive end of the range. The marked difference in clinical response to radiotherapy has caused contrasting radiotherapy schedules to evolve for the three classes of skin tumour, to best exploit the underlying differences in radiobiology.

3.5.1 Radiosensitive Tumours

3.5.1.1 Lymphoma

The tendency of lymphoma cells to undergo apoptosis readily means that radiotherapy is a very effective treatment for cutaneous T- and B-cell lymphomas. It is unnecessary to exploit particular radiobiological features with the exception of intrinsic sensitivity, which allows a marked dose reduction. Even very low-dose radiotherapy (4 Gy in two 2 Gy fractions) can achieve complete remission of a low-grade small cutaneous lesion [24]. Across the various types of lymphoma, prognosis is generally good and a lower dose of radiation will be associated with a lower risk of radiation-induced second malignancy. The consequent normal tissue sparing is also important in a disease where chemotherapy may play an important role and toxicities of treatment may overlap.

3.5.1.2 Basal and Squamous Cell Carcinoma

As discussed, squamous cell skin cancers in particular can repair DNA and repopulate during a 6-week course of radiotherapy. Reducing overall treatment time (by increasing fraction size, treating 6 days a week or compensating for any missed fractions) is therefore very useful to counteract accelerated repopulation [25]. As an early reacting tissue, the late effects of radiation on the skin (fibrosis, atrophy and telangiectasia) vary less as a function of fraction size than late reacting tissues. For a squamous cell carcinoma of less than 5 cm diameter, a typical curative radiation prescription of 66 Gy in 33 fractions at 2 Gy per fraction over 6 1/2 weeks may by accelerated to 55 Gy in 20 fractions over 4 weeks or 45 Gy in 10 fractions over 2 weeks with equivalent efficacy and no significant increase in long-term complications [26].

Normal cells repopulate an area of irradiated skin from the periphery, thus the diameter of the radiation field and consequently the 3-D volume are important to consider when planning radiotherapy and counselling the patient about anticipated side effects. The prescribed dose is also a significant factor as the higher the dose, the slower the normal tissue recovery due to the greater stem cell depletion.

3.5.2 Radioresistant Tumours

Within skin tumours, malignant melanoma is generally considered to display the greatest relative intrinsic radioresistance. Consequently, surgery is established as the current most effective clinical treatment modality for primary tumours. The range of radiation sensitivity observed in human tumour xenografts following single-dose irradiation may be very variable, however [27], reinforcing radiotherapy as a useful treatment modality. In metastatic melanoma, palliative hypofractionated radiotherapy may be offered using a large dose per fraction (20 Gy in 5 fractions over 1 week or 36 Gy in 6 fractions weekly for 6 weeks). Given the frequently poor response of melanoma even to hypofractionated radiotherapy, efforts have been made to exploit the tumour radiobiology to improve patient outcome through the administration of radiosensitis-

ers. The ideal radiosensitiser increases tumour cell kill without adding to normal tissue toxicity at the same dose of radiation, thus it widens the therapeutic window.

3.5.3 Strategies to Overcome Intrinsic and Acquired Radioresistance

Whilst melanoma may demonstrate intrinsic radioresistance, recurrent previously treated squamous cell carcinoma of the skin is often more resistant to therapy than at first presentation. This is usually due to the survival of the most resistant cells, which then proliferate to cause a recurrence. Such refractory cells often have clonogenic, stem cell-like properties which may also contribute to accelerated repopulation [28], and current research efforts are directed at identifying and eradicating these. With time, surviving tumour cells may acquire further genetic mutations that increase radioresistance.

3.5.3.1 Chemotherapy

The addition of cytotoxic chemotherapy agents to radiation can induce apotosis if the tumour remains 'prone' with acceptable normal tissue toxicity. This is standard practice in other moderately sensitive epithelial cancers such as cervix, anal/colorectal and squamous cell head and neck cancers, for example. Standard chemotherapy has not proven to be an effective radiosensitiser in melanoma, however.

3.5.3.2 Molecular Targeted Therapy

Molecular targeted agents are a more novel class of radiosensitiser. The most successful example is a monoclonal antibody to the epidermal growth factor receptor (EGFR). Cetuximab is now frequently prescribed as a radiosensitiser where patients with squamous cell carcinoma of the head and neck (SCCHN) are unsuitable for the standard chemotherapy drug. Radiation can activate EGFR directly, as well as increasing the release of cognate ligands and reducing inhibitory phosphatase activity, as a response to the cellular stress. EGFR signalling drives cells through the cell cycle and reduces apoptosis, thus contributing to accelerated repopulation. The role of EGFR inhibition in the therapy of melanoma is under evaluation [29].

3.5.3.3 Promotion of Apoptosis

Due to the low intrinsic propensity for apoptosis in melanoma, the combination of p53 inhibitors with radiation is, perhaps, a more compelling strategy. Ionising radiation may trigger signalling through p53 to Mdm2 which precipitates the degradation of p53 and reduces apoptosis. The nutlins are a family of molecules that can prevent the interaction of p53 with Mdm2 and thus preserve p53 function, and these are starting to be combined with radiation [30]. E2F1 is a transcription factor that can induce apoptosis independent of functional p53, which is an interesting target as p53 is often deleted or mutated in cancer [31]. Recently, knockdown of E2F1 gene expression was demonstrated to reduce EGFR expression and reduced the invasive, but not proliferative, capacity of melanoma cells [32]. However, the Mdm2 and E2F1 pathways form part of a signalling network and thus inhibition of both in combination with radiotherapy has proven more effective in experiments on prostate cancer cell lines [33]. This rationale should hold true for melanoma.

Furthermore, there is clinical evidence of the feasibility of using recombinant proapoptotic ligands to drive receptors capable of activating p53-independent apoptosis, such as rhApo2L/TRAIL. Monoclonal antibodies to the death receptors DR4 and DR5 on the extrinsic pathway have reached phase II clinical trials, and TRAIL receptor antibodies are being tested in combination with radiotherapy [34]. Preclinical data support the rationale for inhibiting the intrinsic apoptitic pathway by demonstrating radiosensitisation from concomitant bcl-2 oligonucleotides in head and neck cancer models [35]. Another target in the intrinsic pathway is the 'inhibitor of apoptosis' proteins (IAPs) such as XIAP, a component of the final common pathway that inhibits caspases and suppresses

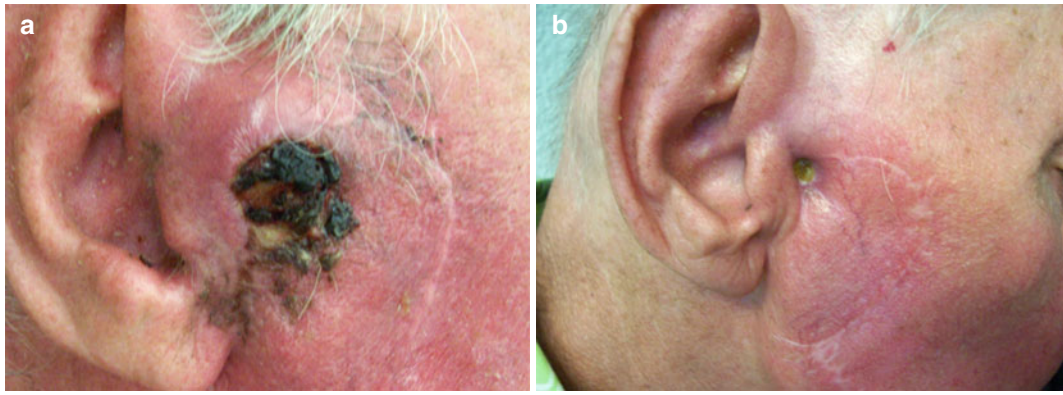

Fig. 3.4 The combination of hyperthermia with radiation is an effective approach for refractory skin tumours. (**a**) This patient had a locally recurrent pre-auricular squamous cell carcinoma, shown in close up before therapy. (**b**) A complete clinical response was achieved

apoptosis. Again radiosensitisation of tumour cells to radiotherapy and cytotoxic chemotherapy has been demonstrated in vitro, with evidence of chemosensitisation in vivo [36]. The more cells that undergo apoptosis, the less DNA repair, cell repopulation and hypoxia will be present in the tumour.

3.5.3.4 Anti-angiogenic and Anti-vascular Strategies

Targeted inhibition of the VEGF tyrosine kinase receptors (TKRs) has been developed clinically and shown to potentiate the effects of radiotherapy alone [19]. A theoretical concern regarding the combination of anti-angiogenic and anti-vascular strategies with radiotherapy is an increase in hypoxia, which is associated with resistance to radiotherapy. It has been suggested, however, that under certain in vitro conditions, anti-angiogenic agents may have the positive effect of 'vascular normalisation' [37], and these combined modality approaches continue to be pursued. Melanoma expresses the family of vascular endothelial growth factor receptors (VEGF-R). The tyrosine kinase inhibitor such as vatalanib (PTK787), which has shown efficacy in combination with radiation other tumour types [38]. Promisingly, a VEGFR-2 inhibitor was able to induce a more radiation-sensitive phenotype in a melanoma animal model [39]. Also in the preclinical setting in melanoma, bevacizumab (Avastin), the monoclonal antibody to VEGF, has demonstrated synergy in combination with an EGFR inhibitor [40].

3.5.3.5 DNA Repair

It is controversial whether improved DNA repair underlies melanoma's relative radioresistance. Inhibiting key DNA repair enzymes such as poly (ADP) ribopolymerase-1 may lead to effective radiosensitisation. To date it has been suggested that levels of PARP-1 expression may correlate with disease in malignant melanoma, and inhibition may provide a means of chemosensitisation, with evidence of sensitisation to temozolamide [41]. Small molecule inhibitors of other proteins involved in DNA repair (DNA-PK, ATM and Chk1) are also in clinical development as radiosensitisers. A specific DNA-PK inhibitor (NU7441) has provided proof of principle in vitro and in vivo of chemo- and radiosensitisation [42].

3.5.3.6 Hyperthermia

With the advent of more modern technology, revisiting hyperthermia is a promising approach for melanoma and treatment-refractory non-melanoma skin cancer (Fig. 3.4). Synergistic effects of simultaneous hyperthermia and radiation on tumour growth delay have been observed in vivo, but the exact mechanisms remain to be elucidated. There is no differential effect on normal and tumour cells, and thus, the tumour must be heated to a higher temperature than the normal tissues to achieve a therapeutic window.

A second clinical benefit of hyperthermia is that heating a tumour to 41–43 °C has a direct cytotoxic effect. The increased acidity in solid tumours relative to normal tissues enhances the

cell kill, probably by enhancing cytoplasmic and membrane damage. Hyperthermia transiently induces resistance to radiotherapy; however, weekly, rather than daily treatments tend to be delivered to achieve a predominantly cytotoxic effect. In a clinical trial where hyperthermia was administered following each 8 Gy fraction with treatment three times a week, local control rates of 46 % at 2 years were achieved in patients with melanoma, as compared with 28 % following radiation alone [43]. Vessel dilation should reduce hypoxia, but at present, the tumour blood flow response to hyperthermia appears to be variable and uneven. As with all radiation therapy, normal tissue tolerance may limit the delivery of hyperthermia: It has been estimated that, assuming an α/β of 10 for normal tissue, 3 Gy of radiation delivered during an hour of hyperthermia at 43.5 °C achieves radiation-induced damage equivalent to 15 Gy as a single fraction [44]. The integration of hyperthermia into routine radiotherapy as a concurrent radiosensitiser will require the workflow to be streamlined using state-of-the-art engineering and information technologies.

3.5.3.7 Proton Therapy

A further attempt to exploit the radiobiology of melanoma is the exploration of particle beam radiation, rather than photons. One of the appeals of particle beams for radiation refractory tumours is that they may have a greater effect per unit dose compared with photons (relative biological effectiveness or RBE). Also, particles have a higher linear energy transfer (LET) than photons, which means that they deposit their energy more densely, resulting in more DNA damage. Other radiobiological advantages are that higher LET particles are less sensitive to hypoxia and to the phase of the cell cycle. Finally, charged particles such as protons have a shorter path length than photons. Unlike photons, protons do not exit the body beyond the tumour, which may reduce additional side effects. For these reasons, treating ocular melanoma with protons has been highly successful for at least the past 30 years [45, 46] and may become more common for cutaneous melanoma as the availability of proton centres for research and therapy increases.

3.6 Dose-Limiting Normal Tissues

The major factor that limits the ability of radiation to cure cancer is normal tissue toxicity. As outlined above, if the ability of the epithelial stem cells to replenish the epithelium is exceeded, then moist desquamation and even necrosis can result as side effects of radiotherapy. The possibility of late side effects arising from dermal irradiation (telangiectasia and fibrosis) must also be considered as cosmetic outcome may be important to the patient. Permanent hair loss, or alopecia, may also represent a late side effect that can negatively impact on quality of life. A dose-dependent reduction in human hair diameter of 2–7 % per Gy has been observed [47]. Doses as low as 0.2 Gy can cause apoptosis, which increases in a dose-dependent manner. A single 2 Gy fraction of radiotherapy can arrest the production of hair and permanent hair loss occurs once the stem cells in the hair follicles are destroyed [48]. There is a dose-response relationship between radiation and hair loss, and whilst 33 Gy is associated with minimal permanent alopecia, 45–46 Gy causes moderate permanent hair loss [49]. Higher-energy photon beams have a hair-sparing effect that can be explained by the relationship between the depth-dose profile of megavoltage photons and the location of the majority of hair follicles at approximately 4 mm under the skin surface. 16 Gray is believed to be the lethal dose to hair follicles and therefore, to maximize hair sparing, it is recommended that the skin dose to a depth of 5 mm should be kept below this dose level if possible [50]. This is impossible in the treatment of epidermal skin cancers, but, fortunately, hair loss on skin other than the scalp does not usually represent a significant adverse late side effect.

Conclusions

The management of the different types of dermatological cancers varies according to their underlying radiobiology, which can be exploited to enhance therapeutic outcome. A consideration of DNA repair, repopulation, reoxygenation, reassortment and intrinsic radiosensitivity will guide the selection of the most effective radiotherapy schedule, in

particular the total dose, dose per fraction and overall treatment time. Modern radiobiology includes the combination of radiation with other sensitising modalities such as molecular inhibitors (e.g. anti-EGFR or pro-apoptosis) or hyperthermia to enhance the efficacy of therapy without an unacceptable increase in normal tissue toxicity. In the future, we should aim to further exploit the principles of radiobiology to improve the outcome of patients with malignant melanoma in particular.

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Radiation Therapy of Nonmalignant Skin Disorders

4

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4.1 Introduction

While the modern use and indication for radiotherapy (RT) of *malignant skin disorders* is a well-established strategy which includes the treatment of basal cell and squamous cell carcinoma, melanoma, Merkel cell tumors, and cutaneous lymphomas (all, see previous chapters of this book), the use of ionizing radiation *for nonmalignant or benign skin disorders* is less recognized, is not represented in actual interdisciplinary treatment guidelines, and has clearly decreased as many new and better systemic and local noninvasive and invasive treatment options have become available in the past two decades. Moreover, in many dermatological departments throughout the world, the actual training and knowledge of medical specialists about the possible implementation of ionizing radiation to treat nonmalignant skin disorders has slowly faded away and is dismissed in modern dermatology textbooks. Local surgical methods and/or systemic medication options dominate the actually recommended treatment strategies for most nonmalignant skin disorders.

Nevertheless, for several skin disorders, radiation therapy (RT) using low-voltage photons or X-rays (50–250 kV) of low-energy X-ray units or low-energy (3–6 MV) electrons of linear accelerators or local brachytherapy can be still regarded as a useful therapeutic alternative for selected disorders such as lymphocytoma cutis or hypertrophic scars/keloids. In some other benign skin disorders, e.g., chronic eczema, the use of RT is only applied as a last resort approach after failing all other therapeutic methods or when no other treatment option is available for the well-being and quality of life of the affected patient. About 20 years ago a survey among dermatologic specialists indicated that the eczematous and hyperproliferative skin disorders constituted the most frequent indications for benign skin disorders especially in older or senescent patients with contraindications to the use of systemic or continued permanent use of topical steroids [1]. Interestingly this situation has not much changed over the past two decades.

Regarding possible drawbacks and risks of ionizing radiation, modern X-ray techniques, much more accurate dosimetric planning and dose calculation, and strict adherence to some clearly defined safety rules have contributed to reduce the formerly reported radiogenic acute and chronic cutaneous and noncutaneous chronic side effects to a minimum [2–6]. Nevertheless, worldwide the standards of care differ widely, partially depending on the lack of equipment or lack of knowledge and training and partially depending on different legal professional allowances in the different countries with variable cultural and medical background.

For example, the use of X-rays for treatment of benign diseases in all medical specialties in the United States has been evaluated by the National Academy of Sciences, and their recommendations are endorsed by the Food and Drug Administration (FDA) (Table 4.1). In contrast, in

Table 4.1 FDA recommendations on ionizing radiation therapy of benign diseases

1. The potential risk of treatment with any form of radiation of a benign, nonlife-threatening disease must be recognized. Ionizing radiation therapy may be considered if other safer methods have not succeeded in alleviation of the condition and if the consequences of no further treatment are unacceptable
2. It must remain the prerogative of the physician to have available for use any form of therapy – radiation, drugs, or others – in which the benefits accruing to the patient from its use are considered to outweigh the risks inherent in its use
3. Infants/children should be treated with ionizing radiation only in exceptional cases
4. Direct irradiation of the skin areas overlying organs that are particularly prone to late effects, e.g., thyroid, eye, gonads, bone marrow, and breast, should be avoided
5. Medical practitioners using ionizing radiation should be adequately trained in both the practical and theoretical aspects of radiation therapy and protection
6. Meticulous radiation protection techniques should be used in all instances
7. The less penetrating X-ray qualities, e.g., Grenz rays, offer a wider margin of safety
8. Laboratory and epidemiologic studies should be initiated and/or continued to fill the gaps in our knowledge of the effects of ionizing radiation at the doses used in the past and currently

most other countries no specific regulations exist with regard to the use of ionizing radiation for benign conditions. In contrast, published guidelines for the use of RT for nonmalignant conditions exist in Germany [7, 8].

Even nowadays the use of RT for nonmalignant skin disorders can and should be based on the assumption that the FDA criteria have been fulfilled, other standard therapies for these conditions have been proven either ineffective or less effective than RT, special target cells and mechanisms are known, possible contraindications to the use of RT do not exist, the RT equipment and machines are well surveyed and calibrated regularly, and internationally accepted standards and appropriate RT guidelines and protection measures are applied on a routine base [9].

4.2 Use of Appropriate RT Techniques

The specific details of RT physics and technical aspects for the treatment of benign skin disorders are described in more details in another chapter of this book (Chap. 2, this book). In general for all the different skin disorders addressed in this chapter, specific anatomical considerations are most relevant for the targeting of the relevant cells and tissues, as the optimal choice of the appropriate RT technique will warrant achieving sufficient surface coverage and penetration depth. These anatomical aspects are summarized in Table 4.2.

Figure 4.1 illustrates the typical composition of the skin and subcutaneous tissue and the different depths of target cells within the skin amenable to ionizing radiation.

4.2.1 RT-Dose Planning

Instead of using the former dosimetric concept of surface dose (SD) and half-value-layer (HVL), i.e., the depth at which the radiation dose reaches 50 % (D½), nowadays the total superficial spread and full depth of the treated lesion, i.e., the true dimensions of the *target volume*, is defined as the "target volume," and then the dose is calculated to reach at least 90 % at the deepest portion of the lesion or of the defined target volume. However, this requires a "translation" of the former dose concepts into the newer ICRU 50/62 concepts using the reference point or isodose concept with specification of the minimum and maximum and the reference dose within the target volume. Thus, the extension of disease process determines the size of the target volume to be treated (planning target volume = PTV/clinical target volume = CTV) and the optimum type and energy of the radiation to be chosen (either being X-rays/linac electrons or brachytherapy). Depending on the dimensions of the target volume and the normal tissue at risk that have to be protected, different radiation energy techniques have to be applied [10].

4.2.2 Grenz Ray Treatment (GRT) (5–20 kV)

This very superficial application of ionizing radiation is the preferred RT technique for the treatment of the most superficial skin regions and benign skin conditions and considered as a first RT option in the most superficial cutaneous disorders like psoriasis or eczema. A specific chapter in this book has been dedicated to this technique (Chap. 5, this book).

Table 4.2 Anatomical extension and target depth for benign skin conditions normal skin (mm) nonmalignant cutaneous

Type of normal skin layer	Depth (mm)	Nonmalignant condition (examples)	Extension (mm)
Epidermis	0.02–0.25	Dermatitis/eczema	0.8–2.1
Epidermis	0.04–0.5	Psoriasis vulgaris	0.7–3.2
Epidermis	0.25–1.0	Chronic lichen simplex	1.1–4.4
Hair follicle	0.5–3.5	Folliculitis, acne	3.0–5.0
Sweat glands	1.0–3.0	Benign skin tumors	10.0
Deep fascia/structures	2.0–10.0	Hypertrophic scars or keloids, Dupuytren's disease (hand palm), Ledderhose disease (foot sole)	1.0–30.0

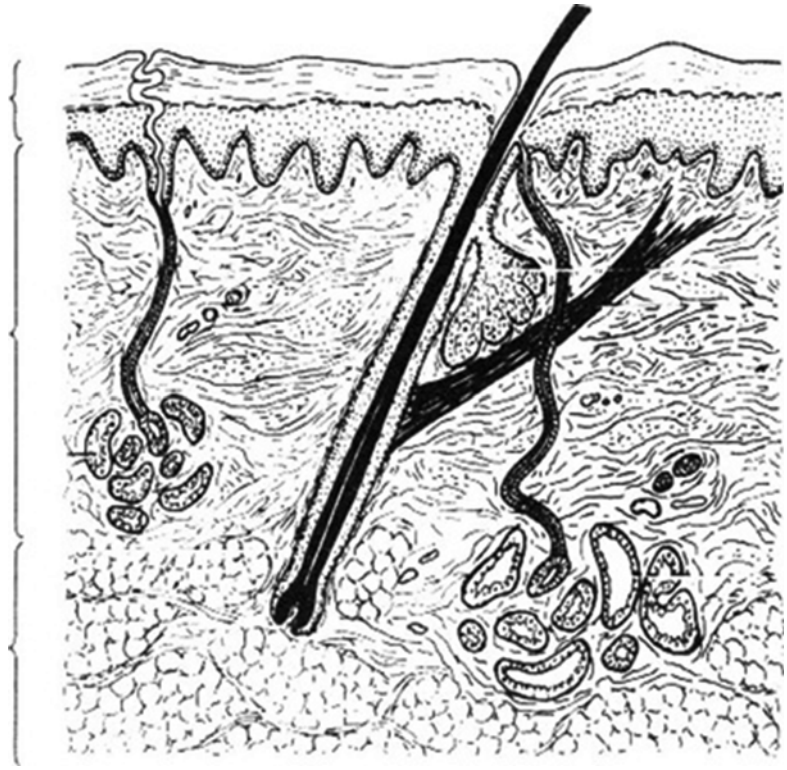

Fig. 4.1 Composition of skin and target cells for radiotherapy

4.2.3 Soft and Superficial X-Rays (SXR) (>20–100 kV)

The slightly deeper penetrating X-rays with energies between 20 and 100 kV are more suitable for disorders with skin involvement extending at least to the subcutaneous tissue layer, especially in the regions of the hand, palms, or foot soles. This X-ray quality is often applied for treatment of lymphocytoma cutis or recalcitrant keratotic eczematous disorders or other resistant or recurrent thicker dermatoses. GRT would not be sufficient in these clinical situations.

4.2.4 Deep X-Rays (DXR) (>100–300 kV)

The deep penetrating X-rays applied either by orthovoltage machines or by *low-energy electrons* (3–6 MeV) from modern linear accelerators are implemented for lesions which arise from the skin or subcutaneous tissue and are able to penetrate into the deeper tissue structures neighboring the skin layer or arise from the deeper tissue structures and extend into the skin surface layers. Most of these conditions address the hyperproliferative disorders like keloids or palmar and plantar fibromatosis or rarely the warts on extremities. SXR or even GRT would be insufficient RT techniques for these disorders.

4.2.5 Dose Limitation and Possible Cancer Induction

To avoid late effects of the skin and subcutaneous tissue including severe fibrosis or secondary tumor induction, it has been generally recommended to limit the total lifetime radiation dose for soft X-rays to 12 Gy and the total dose of Grenz rays to 50 Gy/per field and/or anatomic region. However, so far only very few case reports exist which have linked the application of dermatologic radiotherapy with the increased incidence of skin cancer, even if the radiation dose is given in the early childhood (examples: 11–13).

One of the best examined groups worldwide addressing the question of carcinogenesis after X-ray exposure derives from Scandinavia [11]: a large-scale study investigated the potential side-effects after exposure to GRT on 14,140 individuals who were treated with radiotherapy for eczema, psoriasis, and warts. After a minimum follow-up of 15 years, only in 58 patients (0.4 %) a malignant skin tumor was diagnosed, the earliest more than 5 years after GRT: 19 patients had developed malignant melanomas and 39 other malignant skin tumors. However, in the same period the expected number of incidental melanomas was 17.8 patients and that of other malignant skin tumors 26.9 patients. None of the patients with melanomas and only eight of the patients with other malignant skin tumors had received GRT at the site of the tumor, and six of these eight patients had also been exposed to other known carcinogens, like psoralen ultraviolet applications. Thus, the authors concluded that the available clinical data suggested that even doses up to 100 Gy per field and lifetime are not associated with any significant increase in side effects or tumor induction.

Similarly, it has been concluded, that in most cases of localized radiation exposure for therapeutic reasons, the cancer risks estimated by the effective-dose method may well overestimate the true risks by about one order of magnitude, yet in other cases even may underestimate it. The authors proposed a method using the organ-specific risk factors which is more suitable for the individual radiation treatment planning [12]. In addition Janssen et al. have proposed a method to calculate the risk of cancer induction in various realistic nonmalignant conditions including Dupuytren's disease [13].

4.3 General Rules for Application of Radiotherapy

The use of RT for benign skin disorders is a safe form of therapy provided that appropriate safety guidelines are adhered to and that the prescribing physician has received adequate training and preserves clinic skills to recognize the various diseases and knows specific treatment options and undergoes continuous special training [14].

In addition to the general recommendations of the FDA (see Table 4.1), the following *practice rules for the irradiation of benign skin diseases* are emphasized [6, 15, 16]. Specific guidelines have also been published by the German Cooperative Group for Radiotherapy of Benign Disorders (GCG-BD) (Table 4.3).

As the overall implementation of RT for nonmalignant skin disorders has decreased in the past decades, the order of its use has also changed. In earlier surveys, some disorders like acne, warts, and hidradenitis were much more often irradiated than eczematous conditions. In contrast, the emphasis in recent years has been on the use of superficial X-rays for difficult to treat clinical situations and for chronic eczemas [17, 18] and the use of RT for hyperproliferative disorders

Table 4.3 General practice rules for the application of radiotherapy

1. Diagnosis of the disorder must be clearly established (if possible by biopsy)
2. There should be an established mechanism of action or defined target cells on which ionizing radiation interacts to expect an improved outcome
3. Radiation treatment should be started at the appropriate clinical situation of the specific disease, especially after failing previous treatments (e.g., after surgery for keloids or topical medical treatment for eczema)
4. Patients have to provide a clear record about possible previous RT treatments and received RT doses per body site should be precisely known if appropriate
5. Certain defined RT dose limits are not to be exceeded per RT field and lifetime
6. Use of additional topical treatments prior to and parallel to RT can induce irritating effects and/or reduce the intended X-ray effect
7. Known radiosensitive organs (e.g., eyes, thyroids, breasts, gonads) should be carefully protected by means of absorbing materials (e.g., lead foils) or adequate RT techniques (such as beam direction etc.)
8. Use of RT in children and young adults for benign skin disorders is very rare

such as keloids [19] and palmar or plantar fibromatosis [20].

The following clinical sections discuss the various specific benign skin conditions in which radiation therapy may still be helpful, starting with those dermatoses in which Grenz ray treatment is likely to suffice and ending with the hyperproliferative disorders which need RT techniques with deeper penetration, such as DRT and low-energy electrons.

4.4 Radiotherapy for Eczema and Eczematous Dermatitis

4.4.1 General Aspects

Eczematous dermatitis is a common condition that may negatively interfere with professional and leisure activities, the social function, recreation, and sleep activities of afflicted persons. Its long-term persistence and especially the accompanying pruritus may be very stressful and frustrating. The attempts to relieve the itch by scratching simply worsen the rash, thereby creating a vicious circle and secondary problems. Clinically various types of eczemas have to be differentiated. The most common and best characterized type of eczema, the atopic dermatitis, appears to be increasing in incidence over the past decades. Other more common eczematous dermatoses must be accurately diagnosed, particularly the allergic dermatitis and irritant contact dermatitis, as possible improvement and even complete resolution strictly rely on the appropriate diagnosis and avoidance of pertinent triggering factors.

The therapy should be directed at limiting the itching and allowing the long-term repair of the damaged skin and decreasing the surrounding inflammation when necessary. Thus, the principles of treatment include careful general skin care (including appropriate skin cleaning and moisturizing), patient's education about prophylaxis and strict avoidance of specific irritants, use of different methods of skin hydration and lubrication, and when necessary the temporary and adequate use of topical corticosteroids. The recommended systemic medication includes antihistamines and corticosteroids for certain clinical situations, but is not generally advocated for therapy of chronic eczematous dermatitis. If the pruritus does not respond to local or systemic measures as described above, other diagnoses, such as bacterial overgrowth or viral infections, should be excluded.

Radiotherapy as a treatment option is available for the refractory recurrent chronic eczemas, but should be reserved for more unique situations and always requires an interdisciplinary consultation between medical specialists including allergist, dermatologist, and radiation therapist/oncologist. Radiation treatment should be performed by the radiation therapist and evaluation again by the interdisciplinary team.

4.4.2 Rationale and Technique of Radiotherapy

In general, very low-energy X-rays are sufficient to reach the sensitive cells which create the eczematous lesions. Thus, in most cases Grenz rays with 10–20 kV are a suitable technique. However, in some chronic, long-standing eczematous conditions, especially palms and soles, more penetrating radiation qualities of 20–50 or even 100 kV, are much more effective because of better penetration depth [16, 17]. If Grenz rays are not available, linear accelerator-based therapy with electrons of the lowest available energy (e.g., 3–5 MeV) plus 5 mm bolus would be the preferred technique. The main rationale of using radiotherapy as treatment is the known positive effects of low radiation doses on the inflammatory process and the affecting enzymes, cytokines, and peripheral mononuclear blood (PMNB) cells, especially the lymphocytes which are the cellular component of the inflammatory process [21–25].

The effects of X-rays on the eczematous lesions are probably mediated by a decrease of epidermal Langerhans' cells after irradiation [26]. Different RT concepts for soft X-rays in eczemas have been studied by Goldschmidt [27]; they could demonstrate that single doses of 0.4 Gy and lower are less effective and repeated fractions are required to compensate for the reduced effect of

lower doses; however, no further improvement was achieved with higher single doses of 0.6–1 Gy. The typical RT dose recommendations are summarized in Table 4.4. In general, a typical radiation course consists of 6–12 fractions of 2 Gy Grenz rays (with 20 kV energy) or 1 Gy soft X-ray (up to 100 kV) two or three times per week.

Two typical clinical cases with eczematous skin condition before and after treatment with low-dose radiotherapy are illustrated in Fig. 4.2 (hand eczema) and Fig. 4.3 (lower foot).

Table 4.4 Dose recommendations for chronic eczemas

D½	1–3.0 mm
Energy (kV)	10 or more
Filter	None or 0.4 mm Al
HVL	0.1 or 0.2 mm Al
Single dose	0.5–2 Gy
Total dose	3–12 Gy
Interfraction interval	3–6 days
Fractionation	1–3×/week for 2–4 weeks

4.4.3 Clinical Experience and Results

The early clinical studies reported favorable response rates for hyperkeratotic eczemas and chronic lichenified eczemas. In these studies usually single radiation doses of 0.75–1.0 Gy were administrated at weekly intervals over a period of 3–4 weeks up to a total radiation dose of 4–6 Gy [3]. Few other clinical studies suggested the application of lower single doses in the range of 0.5–0.75 Gy once per week or more protracted in intervals of every 2 weeks for a limited number of two to three exposures and a total radiation dose of 1–3 Gy [28]. With regard to randomized studies and the comparison with a placebo control, the following clinical investigations are important: in one investigation, 24 patients with chronic symmetrical constitutional eczema of the hands were treated with superficial X-ray therapy applying three fractions of 1 Gy in intervals of 21 days (total dose 3 Gy) to one hand,

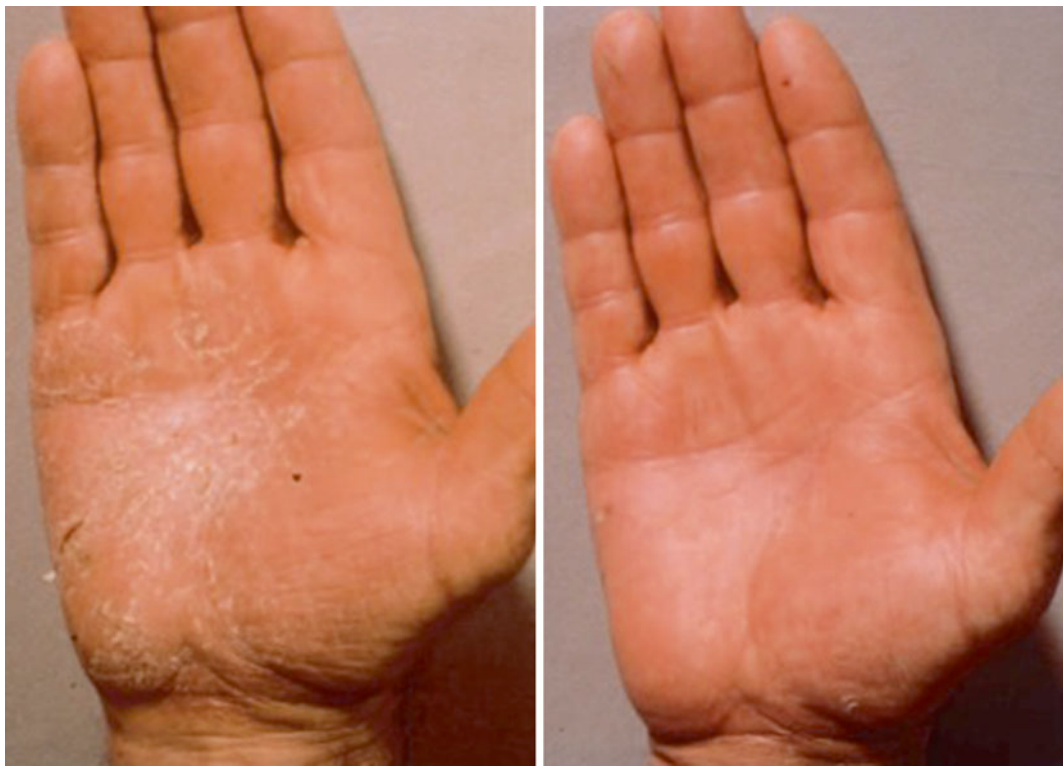

Fig. 4.2 Chronic hand eczema

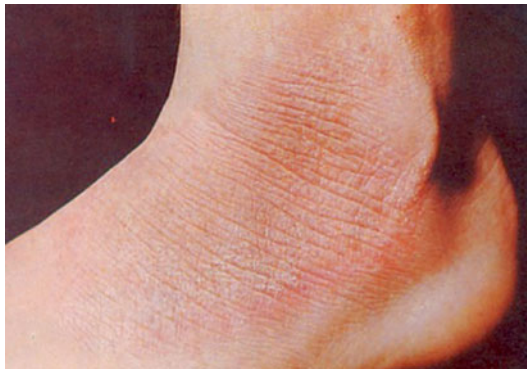

Fig. 4.3 Chronic foot eczema

while the other hand received a placebo treatment. A significantly better therapeutic result was recorded on the hand that received X-ray treatment [16]. The same group explored in a double-blind clinical study the difference between the use of superficial X-ray therapy (>20–100 kV) and Grenz ray therapy (10–20 Gy). As to be expected, they found that using conventional superficial X-rays (up to 100 kV) and total dose of 3 Gy applied in three fractions of 1 Gy was superior to Grenz rays (20 kV) and a total dose of 9 Gy applied in three fractions of 3 Gy with fractions spaced 21 days apart [17].

Recently a few case studies and one clinical series have been published which support the successful concept of superficial low-dose radiotherapy when using the megavoltage equipment: Stambaugh and coworkers [29] reported a patient who was refractory to multiple forms of topical and systemic agents, but achieved complete resolution of severe dyshidrosis within 1 month following low-dose radiation therapy; the durable response even allowed withdrawal of oral steroids after 6 weeks without flare of disease and with the patient remaining free of medication at the 6-month interval. Walling and coworkers [30] published a case study of a 48-year-old dermatologic surgeon with frictional hyperkeratotic hand dermatitis (FHHD) – an unusual form of chronic eczema related to repeated frictional trauma. The sudden eruption of these lesions was completely resistant to all topical and protective treatment modalities, but finally the lesion responded to a total of six sessions of 1 Gy Grenz ray treatment (total dose 6 Gy). Despite continuous work, no relapse occurred for over 4 years since completion of therapy.

The latest published clinical series from a Swiss group [31] reported long-term outcome of 22 patients suffering from therapy-refractory eczema and six patients with psoriatic lesions of the palms and/or soles. Lesions received twice weekly either a single dose of 1 Gy up to a median total dose of 12 Gy or 0.5 Gy up to a median total dose of 5 Gy. A total of 88 regions were treated, 49 with 1 Gy and 39 with 0.5 Gy single dose. Eight symptoms were scored from zero (absent) to three (severe), resulting in a possible sum score of 24 points. Patients' rating was also recorded (worse/stable/better/complete remission). After a median follow-up of 20 months, the sum score had decreased from 15 [6–20, 32–34] before RT to 2 (0–16) at the end of RT and to 1 (0–21) at last follow-up, respectively. The improvement was highly significant in both treatment regimens. Good remission was also stated by the patients in 83 of 88 localizations. From these data the group recommended a single dose of 0.5 Gy twice weekly up to a total dose of 4–5 Gy.

In summary, the major limitation of RT for eczematous lesions is that it may be repeated only for a few times until reaching the still very cautiously defined lifetime dose limit. Thus, it is important to note that ionizing radiation is rarely advisable for the chronic atopic (constitutional) eczema because of the high tendency to local recurrence. The lichen simplex chronicus often responds quickly to radiation exposure; the antipruritic effect of ionizing radiation in this dermatosis and in other skin diseases is quite striking.

4.5 Radiotherapy for Psoriasis and Psoriatic Conditions

4.5.1 General Aspects

Psoriasis is a noncontagious chronic inflammatory disease of the skin caused by an accelerated growth cycle of skin cells and is mediated by the immune system. The severity varies from small

localized patches to the complete body coverage. Clinically two major groups, the *nonpustular type* and the *pustular type psoriasis*, can be distinguished.

The *nonpustular psoriasis* is differentiated into the *plaque-like psoriasis* (chronic stationary form) which is the most common form and affects 80–90 % of all patients; in the plaque-type psoriasis, the skin rapidly accumulates and thickens at distinct locations providing a silvery-white appearance. The plaques commonly occur on the elbows and knees but may also affect any other area of the body. Another nonpustular type is the *erythrodermic psoriasis* characterized by a widespread inflammatory and exfoliative skin pattern which can be accompanied by severe symptoms like swelling, itching, and pain and severe complications due to the loss of the skin barrier function and thermoregulation.

The *pustular psoriasis* is characterized by raised skin bumps filled with noninfectious pus; the surrounding skin is red and tender. This type of psoriasis commonly is localized and affects the hand and feet (i.e., palmoplantar psoriatic pustulosis), but can be also more generalized (i.e., palmoplantar pustular psoriasis) and may develop different other types like *annular pustular psoriasis*, *acrodermatitis continua*, and *impetigo herpetiformis* (see Fig. 4.4).

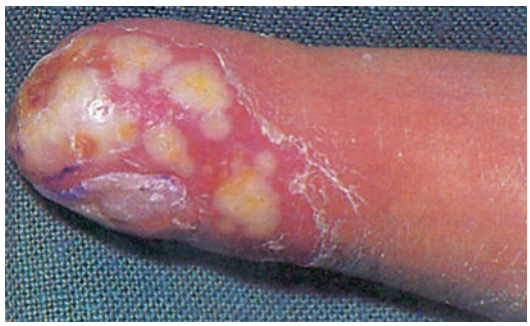

Fig. 4.4 Pustulous finger psoriasis

One type of psoriasis is the *inverse psoriasis* which typically affects the skin folds particularly between the thigh and the groin, the armpits, and underneath the breasts, the panniculus, or other skin folds; it is aggravated by skin friction, sweat, or liquids and may be prone to fungal infections. Another type is the *guttate psoriasis* which shows numerous small scaly, red to pink drop-like lesions; these psoriatic spots may cover large parts of the body, primarily the trunk and less often the extremities and the scalp; it may be preceded by a streptococcal infection mostly originating from the pharynx.

A special type of psoriasis which is relevant for radiotherapy indications affects the nails of fingers and toes (*nail psoriasis*): it produces a variety of characteristic changes including the discoloring underneath the nail plate, the pitting of the nails, the appearance of lines passing across the nails, the loosening and crumbling of the nail (onycholysis), and the thickening of the skin underneath the nail (see Figs. 4.5 and 4.6).

In summary, there are five different patterns of psoriasis appearance: the most common is the plaque type; the other types are the guttate, inverse, pustular, and erythrodermic type.

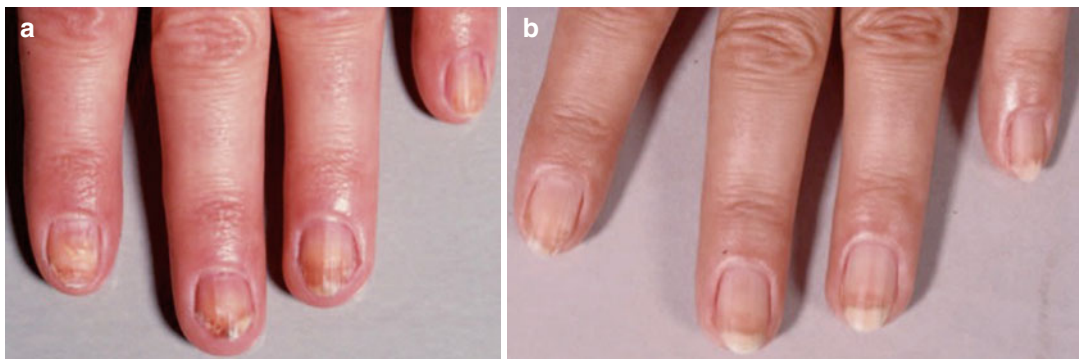

Fig. 4.5 Psoriasis of fingernails in a 46-year-old women (**a**) before and (**b**) 8 months after treatment, 12 Gy total dose with 12 kV

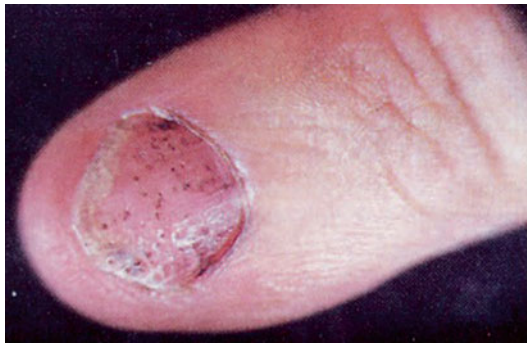

Fig. 4.6 Subungual finger psoriasis

In 10–40 % of all affected patients, an inflammation of various joints can occur which is known as psoriatic arthritis. The specific cause of psoriasis is not well understood, but a genetic component, a local injury, and environmental factors have been suggested which can aggravate psoriatic affections including stress factors or withdrawal of steroids. Despite the various treatment options available, none is really suitable to provide lifelong relief. Treatment of psoriasis remains a general and individual challenge. In the acute situation, most often topical ointments are applied containing corticosteroids. Radiotherapy is limited to refractory cases in specific anatomical locations.

4.5.2 Rationale and Technique of Radiotherapy

Several decades ago Grenz ray treatment (GRT) was widely used to treat psoriatic lesions, but nowadays – with many options of local and systemic medications available – X-ray therapy currently is used only as a last resort in difficult-to-treat-situations like recalcitrant localized lesions in psoriasis of the *scalp* or psoriasis of the *nails*. Moreover, in view of the tendency of psoriasis to recur, the current opinion is to limit X-ray therapy only to very severe and refractory cases. In contrast to other psoriatic lesions, the palmoplantar pustular psoriasis is not considered a valid indication for the use of radiotherapy [35].

In former clinical studies it has been shown that RT technique is of some importance. While one group found no difference between conventional superficial X-ray therapy and Grenz rays in over 70 % of the patients [36], other groups have observed a superior and longer-lasting effect of deeper penetrating superficial X-rays as compared to Grenz rays; however, the beneficial effect is mostly dependent on the complete physical coverage of the treated lesion. If properly applied radiation therapy is not associated with any major side effects and it remains still to be seen whether the local application of antimetabolites or long-range psoralen-ultraviolet A (PUVA) treatments will develop fewer sequelae than judiciously used X-ray therapy. Today previously accepted X-ray treatments are nowadays considered a contraindication to PUVA therapy in view of the potential inherent increase in the frequency of treatment-related skin cancers by PUVA itself.

Regarding the use of an appropriate RT technique, it is important to estimate the nail thickness and to know the specific transmission of the chosen X-rays through normal and diseased nails before irradiating any psoriatic nails. Although low-energy Grenz rays (with up to 20 kV energy) may be tried in psoriatic nails of normal thickness [37], it has been shown that they are much less effective in the thickened diseased finger or toe nails [38]. Since most psoriatic nails are relatively thick, higher energy X-rays (up to 100 kV) should be preferred. If only electrons from linear accelerators are available, the lowest possible energy (3–5 MeV) and adaptive bolus material with 5–10 mm thickness should be chosen to limit the penetration depth to 5–10 mm. Dose recommendations for psoriasis of the nails are summarized in Table 4.5.

4.5.3 Clinical Experience and Results

Good clinical responses were reported in over 50 % of irradiated patients, when treated with three fractions of 1–1.5 Gy at weekly intervals;

Table 4.5 Dose recommendations for psoriasis of the nails or scalp

D½	1–5 mm
kV	10 or more
Filter	none or 0.4 mm Al
HVL	0.1 or 0.2 mm Al
Single dose	0.5–2 Gy
Total dose	3–12 Gy
Fractionation	1–3×/week for 2–4 weeks

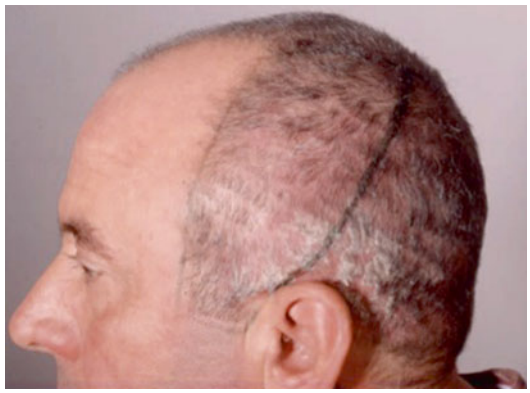

Fig. 4.7 Psoriasis of the scalp

the fingernails, nail matrix, and the periungual areas should be always included in the irradiated fields [39]. Finnerty described three patients treated with six to eight doses of 0.5–0.75 Gy with a total dose of approximately 4–6 Gy; all treated nails were cleared after several months [40]. Kouskoukis and colleagues suggested a single dose 1 Gy at weekly intervals up to a total dose of 4–5 Gy with which they achieved clinical remissions lasting for several months up to many years [41]. In accordance with other reports in the literature, the recommended dose schedule is summarized in Table 4.5, i.e., 6–12 fractions of 2 Gy soft X-ray two times a week or 1 Gy three times a week. Dose recommendations for psoriasis of the scalp are the same as for the nails.

Two typical clinical cases with initial conditions and outcome after use of low-dose radiotherapy are illustrated in Fig. 4.5 (nail psoriasis) and Fig. 4.7 (scalp psoriasis).

4.6 Lymphocytoma Cutis (Pseudolymphoma)

4.6.1 General Aspects

Lymphocytoma cutis is a rare type of pseudolymphoma that is also defined as "cutaneous lymphoid hyperplasia" or "lymphadenosis benigna cutis." Early lesions mostly start in the third to fourth decade, with a male to female ratio of 3 to 1 and a white to black race ratio of 9 to 1.

Clinically the disorder can occur in a more circumscribed or localized or a widespread or disseminated form. It appears to be a reactive process of "blood cell cancer" developing in the skin; however, it behaves more as a benign tumor in a rather harmless manner [42, 43].

Commonly no cause can be attributed to the disease itself, but some may act as trigger process which include contact with foreign agents (proteins) like reaction to tattoo dyes, reactions after exposure to insect bites, stings of mosquitoes and spiders, vaccination agents, desensitization injections, or acupuncture procedures; some other skin trauma like piercing or infection with Borrelia burgdorferi (Lyme disease), varicella zoster (chickenpox), and human immunodeficiency virus (AIDS virus) are also considered as trigger factors.

Clinically the lesions present either as nonitching soft and doughy or more firm nodules of red to brown or red to purple color and occasionally with a scaly or crusty surface. About two thirds of the lesions develop on the face and another third on the chest and upper extremities. Over 70 % appear as single nodules or local group of small lesions, while numerous or disseminated lesions are rather uncommon.

Skin biopsy reveals a local inflammatory process with mixed B and T lymphocytes and benign immunohistochemistry. Typical features of malignant lymphomas are absent, e.g., tingible bodies, higher proliferation rate, positive gene rearrangement, and cells that stain with CD10+ and Bcl6+ outside follicles and Bcl2+ within

Table 4.6 Classification and subtypes of lymphocytoma cutis/pseudolymphomas

B-cell lymphocytoma cutis
Primary or Idiopathic cutaneous B-cell pseudolymphoma
Borrelial lymphocytoma cutis
Tattoo-induced lymphocytoma cutis
Post-zoster scar lymphocytoma cutis
Persistent nodular arthropod-bite reactions
Lymphocytoma cutis caused by antigen injections/acupuncture
Lymphomatoid drug eruptions
Acral pseudolymphomatous angiokeratoma
T-cell lymphocytoma cutis
Primary or idiopathic cutaneous T-cell pseudolymphoma
Lymphomatoid drug reactions
Lymphomatoid contact dermatitis
Actinic reticuloid (chronic actinic dermatosis)
Anticonvulsant-induced pseudolymphoma
Persistent nodular arthropod-bite and scabies reaction
Acral pseudolymphomatous angiokeratoma

follicles; lesions can mimic B-cell lymphomas such as follicle center lymphoma, marginal zone B-cell lymphoma, or large B-cell lymphoma. Classification into B-cell or T-cell and by its cause, if any is identified, has been proposed. Often times the more general term of "pseudolymphoma" is used. Table 4.6 summarizes the two classes and subtypes.

Other than distinguishing this condition from cutaneous lymphoma, it is also important to consider other alternative diagnoses like Jessner lymphocytic infiltrate, cutaneous lupus erythematosus, and plaque type of polymorphous light eruption. Specific features seen in the biopsy specimen may be the only way to determine the correct diagnosis in some cases.

4.6.2 Rationale and Technique of Radiotherapy

Radiotherapy is only one of many options to treat lymphocytoma cutis. The first approach is the detection and removal of any potential cause or offending agent. Watchful waiting can be accepted to await spontaneous regression unless the patient develops symptoms or is disturbed by the esthetic appearance. Small series have been successful with the following agents: topical steroids or intralesional steroid injections, topical tacrolimus or hydroxychloroquine, or surgical methods such as local excision or cryotherapy. The use of RT with small doses of superficial X-rays has been shown to be effective especially for localized and circumscribed lesions which do not respond to primary treatments, however, with early lesions being far more radiosensitive and responsive to RT than older lesions. The recommended RT schedule is presented in Table 4.7.

Table 4.7 Dose recommendations for lymphocytoma cutis/pseudolymphoma

D½	1–15 mm
kV	50–100 or more
Filter	0.4–2.0 mm Al
HVL	0.2–1.6 mm Al
MeV	3–5
Bolus	5–8 mm
Single dose	1–2 Gy
Total dose	2–12 Gy
Fractionation	2–4×/week

4.6.3 Clinical Experience and Results

Benign lymphocytomas respond to very small RT doses of 0.75–1 Gy in two fractions within 1 week up to a total dose of 1.5–2 Gy or a single treatment with 1.5–2 Gy or single doses of 3 Gy at 3–4-week intervals up to 12 Gy total dose [28, 44]. Goldschmidt and Sherwin reported successful treatments with single doses of 1.5–2.5 Gy at 1–3-week intervals in one to three sessions [3]. Some other groups have suggested higher single doses of 5 Gy up to a total dose of 25 Gy. In one other series, multiple lesions on the face were treated with 15 Gy in five fractions of 3 Gy over a period of 5–7 days with excellent cosmetic results [45].

4.7 Radiotherapy for Keloids and Hypertrophic Scars

4.7.1 General Aspects

Keloids or "keloid scars" represent overgrowth of granulation tissue at the site of a healed skin injury where collagen type 3 is replaced by collagen type 1; they form as a result of an aberrative physiologic wound healing process after insult to the deep dermis. Depending on its maturity keloids are composed of either type III ("early type") or type I ("late type") collagen; they should not be confused with hypertrophic scars, which also raise above skin level but do not show lateral growth beyond the boundaries of the original wound.

Keloids do affect both sexes equally, although the incidence in younger females has been reported to be higher than in the younger male, which is probably reflecting the higher frequency of earlobe piercing and other piercings among women. Interestingly, there is a significantly higher frequency of occurrence in highly pigmented populations; especially Africans and Afro-Americans are at increased risk of keloid formation.

Keloids present as "benign tumor-like lesions" which are firm, rubbery lesions or fibrous nodes that vary in color from pink to flesh-like or red to dark brown. Histologically they are characterized by atypical fibroblasts with excessive deposition of extracellular matrix components, especially collagen, fibronectin, elastin, and proteoglycans; they usually contain relatively acellular centers and thick, abundant collagen bundles that form nodules in the deep dermal portion of the lesion.

By causing pain, local inflammation, pruritus, and contractures, the excessive scarring can significantly affect the patient's quality of life, both physically and psychologically. Severe cases may interfere with the movement of the skin and even joints can be affected. Local infection(s) and/or bleeding are complications which require additional surgery. In visible areas (e.g., face, ear, breast etc.) the personal esthetic is heavily disturbed and may lead to severe personal stigmatization, isolation, discrimination, and restricted lifestyle of the patient which can severely affect the overall quality of life.

So far no universally accepted treatment protocol has been established. Some modalities have been introduced several decades ago; others have been introduced more recently. Surgery is the treatment of choice, but also compromised by high relapse rate of 50–80 % if used as single modality. Additional therapies were introduced as preventive strategies after local surgery including radiation therapy, pressure therapy, cryotherapy, intralesional injections of corticosteroids, interferon, fluorouracil, topical silicone, and pulsed-dye laser treatment. Thereby the recurrence rate of 50–80 % after surgery was reduced to 50 % with intralesional steroid therapy, while external RT reduced the recurrence rate to 12–28 %.

4.7.2 Rationale and Technique of Radiotherapy

The use of RT belongs to the long-term established treatments despite lack of randomized studies but owing to large patient populations treated and a convincing radiobiological rationale as several radiosensitive target cells and biological mechanisms available which support the therapeutic rationale and are summarized in Table 4.8

Different RT techniques have been reported and applied in the past: low-energy orthovolt radiotherapy, high-energy external beam electrons from linear accelerators, and remote-control afterloading brachytherapy through implanted catheters. There has been a long debate about the optimal timing and RT dose concept.

RT is rarely considered as primary treatment for keloids, but very effective when combined with surgery [28]. Clinical response improves if keloids are treated *at the earliest time*, *generally considered to be within 72 h of excision*. A study showed that RT is less effective in keloids older than 6 months. In contrast, Enhamre and Hammar et al. found no correlation between therapeutic

Table 4.8 Radiosensitive targets and mechanisms for hyperproliferative disorders

1. Proliferating mitogenic fibroblasts/myofibroblasts are radiosensitive cells [46, 47]
2. Induced free radicals impair proliferative activity of fibroblasts [48]
3. *Interference with growth factors*, especially PDGF and TGF-beta [49]
4. *Reduction of activated monocytes and macrophages* interacting with the inflammatory process and myofibroblast proliferation [50]
5. *Similar radiosensitive target cells/mechanisms* found for prophylactic RT:
In intravascular hyperproliferation after arterial stenting [51, 52]
In keloid relapses after surgical excision [53]
In relapses of recurrent pterygium [54]

results and time interval between excision and irradiation, reporting 88 and 99 % good results, respectively [55].

Different fractionations, single and total doses, have been applied ranging from 2 to 20 Gy, administered over a period of 1 day to 2 weeks [56–61]. A minimum isoeffect time-dose line for postoperative keloid control was seen with total doses of 9–10 Gy delivered over 1 week or 15 Gy delivered over 2 weeks. Higher total doses or high single doses of 10 Gy are prone to late effects like teleangiectasias [62].

Two meta-analyses have examined RT dose requirements. Kal and Veen [63] found a dose relationship with decreasing relapse rate as a function of the bioequivalent dose (BED): BED dose above 30 Gy resulted in a relapse rate below 10 % and no differences within high stretch tension sites. Recommended RT doses fulfilling this concept were 1×13 Gy and 2×8 Gy external beam RT or 27 Gy LDR brachytherapy [63, 64] undertook a radiobiological analysis of postoperative keloid RT. A 95 % long-term local control was achieved with three fractions of electron beam RT up to 18.3–19.2 Gy (for the earlobe) or 23.4–24.8 Gy (for other sites) total RT dose. Single fraction equivalent doses were 11.4 Gy (earlobe) and 14.5 Gy (other sites) [64]. The actual dose recommendations for keloids are listed in Table 4.9.

Table 4.9 Dose recommendations for keloids

D½	1–15 mm
kV	50–125 or more
Filter (with kV technique)	0.4–2.0 mm Al
HVL	0.2–1.6 mm Al
MeV	3–5
Bolus (with MeV technique)	5–8 mm
Single dose	2–8 Gy
Total dose	12–30 Gy
Fractionation	1–2×/day (brachytherapy) 4–5×/week (external RT)

4.7.3 Clinical Experience and Results

Postoperative RT achieves a success rate of 75–90 % if surgical excision is followed immediately by local RT. The most established RT concepts apply three to five times 3–4 Gy per fraction, which is somewhat lower than the calculated BED doses of [63] with cumulative doses of over 30 Gy (which represents 1×13 Gy, 2×8 Gy, or 3×6 Gy; in case of recurrence or high risk areas (e.g., high-tension areas), these escalated doses should be primarily considered.

So far there are only very few controlled clinical studies available. In a randomized study local steroid injection was compared to local RT with 12 Gy in a total of 31 keloids which resulted in a recurrence rate of 2 of 16 (13 %) after RT as compared to 4 of 12 (33 %) after steroids, which was no statistical different, but the study was too small and likely to be underpowered.

Two Dutch single institution data were published recently with contradictory results. In Utrecht, 35 patients with 54 keloids (23 earlobe/auricle; 17 sternum $n=17$, 14 others) were treated with HDR BT and different dose concepts. The first RT dose was applied 6 h after surgery followed by two additional doses on the next day separated by 6 h. After a mean of 19 months, the outcome showed 45 % relapses after HDR 1×4 Gy and 2×6 Gy, only 3 % recurrence after HDR with 1×6 Gy and 2×8 Gy, and even no recurrence after a dose of 3×6 Gy. The functional and cosmetic outcome was also better with HDR 3×6 Gy and 18 Gy total dose. The author

concluded a dose-response relationship favoring higher RT single and total doses [65]. The opposite and much better results were reported from Amsterdam [66].

A prospective study with long-term outcome was reported from Washington University [58]. Postoperative RT treated 75 patients with 113 keloids and followed them for almost 10 years. Seventy-four percent involved the earlobe and 60 % had no prior treatment. Superficial X-ray techniques were used in most cases (89 %), usually a total dose of 12 Gy in three fractions of 4 Gy over 3 days were applied. Long-term local control rate was 73 % and the local failure rate was 19 % if no prior treatment was applied in comparison to 42 % for recurrent lesions. The only treatment-related toxicity was mild hyperpigmentation in 5 %. Carcinogenesis was not observed. Prognostic evaluation found a significantly higher relapse rate for males, lesions larger than 2 cm and after previous therapy. No advantage or disadvantage was found with regard to starting treatment within 24 h versus more than 1 day (range 4–21 days). Mean time to recurrence 12.8 months.

In Germany a large national patterns of care study (PCS) was performed during the period of 1997 through 2000 [19]. A total of 101 institutions participated and recruited a total of 1,672 patients which received all postoperative RT with treatment follow-up of over 35 years. Treatment concepts included total doses ranging from 10 to 20 Gy and single doses from 2 to 3 Gy and number of fractions from three to five times per week. A total of 880 patients were followed for at least 2 years and in long-term follow-up. The total relapse rate was 101 of 880 (11.4 %); most relapses occurred within 2 years. Cosmetic and functional outcome was good to excellent in over 80 % and the rate of acute or chronic side effects was low. No secondary malignancies were seen during the long observation period.

With regard to toxicity only very few data exist regarding late radiogenic effects such as local fibrosis and teleangiectasias. Overall, the patient's satisfaction with the cosmetic and functional outcome after RT appears to be generally very good. Only one case of carcinogenesis was reported by Bootwood [67] related to a female who had accidental severe chest burns at the age of 20 and consecutively developed severe keloids. External beam RT was applied in five fractions up to a total dose of 13 Gy to the bilateral chest wall. At the age of 57 years, she developed an invasive lymph node negative breast cancer on the left side and at the age of 59 years an invasive multifocal breast cancer on the right side. A causal relationship appears strong in this case, as no other predisposing factors could be found [67].

In summary postoperative radiotherapy for keloids is a very effective and successful treatment which should be used after previous failures following surgery.

4.8 Radiotherapy for Palmar and Plantar Fibromatosis

4.8.1 General Aspects

Palmar and plantar fibromatosis, also called Dupuytren's disease (DD) and Ledderhose disease (LD), are proliferative disorders of the connective tissue which involve the palmar fascia of the hand and plantar fascia of the foot, but may also involve the subcutaneous fat layer and the skin itself. The typical digito-palmar and digito-plantar changes are part of a systemic connective tissue disorder which is confirmed by subtle biochemical changes and obvious ectopic fibrous deposits, which may be located above the dorsal proximal interphalangeal joints (=knuckle pads), on the auricular helix, the hand wrist, the elbow, and the penis (=Morbus Peyronie) in males. All tissue changes are histologically identical, but efforts to identify a single cause of this generalized disorder have failed so far. Numerous hypotheses exist about the disease onset and progression, but a simple and straightforward explanation is still missing.

Often the palpable and later clearly visible subcutaneous nodules are fixed to the overlying skin thereby distorting the skin folds and surface creating unusual "bumps" and "pit holes"; later longitudinal cords develop and predominate the

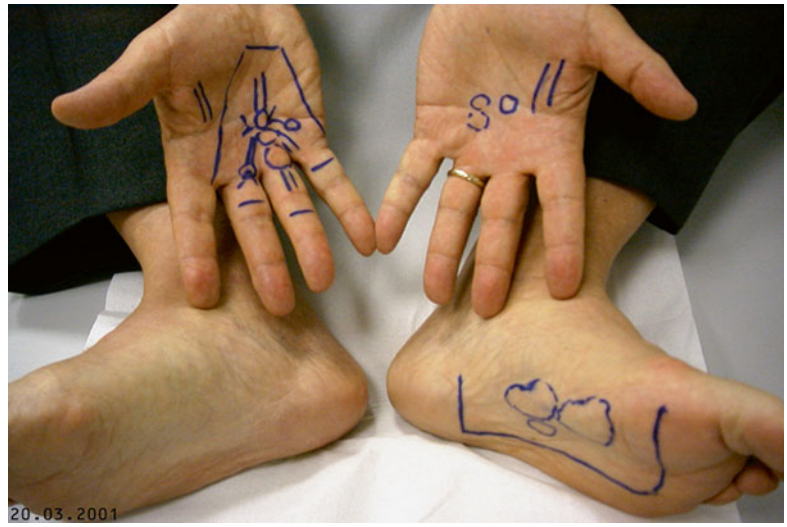

Fig. 4.8 Shows a 46-year-old male with positive family history and bilateral involvement of DD and unilateral involvement of the left foot

later phase of DD and LD; finally the cords reach the periostium of the hand or foot bones and lead to functional impairment and contraction of the fingers and palm and the medial arch of the foot, respectively. In DD, this creates the flexion deformity or lack of full finger extension, while in LD the functional deficit may be accompanied by pain and gait disturbance up to full loss of walking ability.

The clinical course comprises (a) the *proliferative phase* (with increased number of fibroblasts, nodules, and early cord formation); (b) the *involutional phase* (with increased number of myofibroblasts in diseased fiber bundles leading to cords and contractures); and (c) the *residual phase* (with collagenous fibers dominate the connective tissue). Unlike desmoids, no invasion of voluntary muscles occurs. DD and LD may slowly progress and stabilize for years, but rarely regress spontaneously. Without any therapy the average progression rate of patients is about 50 % within a period of 5 years. In LD, the slowly growing nodules and cords are rarely detected in the early phase, until the functional impairment (walking difficulties, pain, tension, or pressure sensation) alert the patient and lead to a first medical exam. Concomitant knuckle pads and Morbus Peyronie in males support the diagnosis.

The clinical course of DD and LD is dependent on the individual disposition [68]. Spontaneous regression or slow progression may be interrupted by phases of stagnation; other cases rapidly progress within a very short time causing contracture-induced dislocation of digital joints in DD and walking difficulties in LD. Special subtypes are differentiated according to their characteristic clinical course: (a) the particularly "mild DD variant" in patients with diabetes mellitus and (b) the "aggressive DD variant" in younger people with a disease onset at about 30–40 years expanding rapidly and bilaterally on the ulnar and radial side of palm. Figure 4.8 shows a 46-year-old male with positive family history and bilateral involvement of DD and unilateral involvement of the left foot.

The clinical staging of DD is based on the functional loss of finger movement [69] (Table 4.10), while in LD the extension and number of nodules and the extension to skin or deeper structures determine the stage (Table 4.11).

4.8.2 Rationale and Technique of Radiotherapy

Despite decades of research, nowadays, no curative treatment is available for DD and LD. All efforts including local injection of enzymes, systemic medication, radiotherapy of involved areas minimal invasive, or radical open surgery aim to prevent progression or to improve the impaired functional status. While surgery is justified with

Table 4.10 Classification of Dupuytren's disease (DD)

Stage	D1 (thumb)	D2–D5 (other fingers)	Points
0	Neither nodule nor loss of abduction	No extension deficit	=0
		No nodular or cord lesion	
N	Nodule without loss of abduction	Nodule without flexion contracture	=0.5
I	Abduction angle range 45–30°	Extension deficit of all finger joints is equivalent or less than 45°	=1
II	Abduction angle range 29–15°	Extension deficit of all finger joints reaches 46–90°	=2
III	Abduction angle range 14–0°	Extension deficit of all finger joints reaches 91–135°	=3
IV	Not defined	Extension deficit of all finger joints reaches more than 135°	=4
Tubiana score	Maximum : 3 points	Maximum : 5×4 points	=23

Table 4.11 Classification of Ledderhose disease (LD)

Stage	Short form	Definition
I	Unifocal disease	One nodule/cord or one well-circumscribed region involved without adherence to skin or extension to the flexor sheath (plantar fascia)
II	Multifocal disease	Several nodules/cords or several regions involved without adherence to skin or extension to flexor sheath (plantar fascia)
III	Stage II plus deep extension into one direction	Several nodules/cords or several regions involved; with deep extension to either skin (=III A) or flexor sheath (plantar fascia) (=III B)
IV[a]	Stage II plus deep extension into both directions	Several nodules/cords or several regions involved; with deep extension to skin (III A) and flexor sheath (plantar fascia) (III B), i.e., stage III C
R	Recurrent stage	Any status progression after previous surgical therapy
Others	Specific disease parameters	Nodules (N), cords (C), pain symptoms (P), other symptoms (S), walking disorder (W)

[a]The two stages III and IV can be combined and then specified into three categories III A, B, C

functional deficit, radiotherapy aims for prevention of progression, but requires radiosensitive target cells or biological mechanism within the disease process for a successful interaction.

The gold standard for *advanced DD and LD stages* is surgery, if symptoms are increasing and function is impaired with progressive contracture. Typical interventions are transection of cords (fasciotomy) or excision of diseased fascial bands (fasciectomy) with or without excision of the overlying skin. Sometimes more radical procedures are required such as total fasciectomy with overlying skin (dermatofasciectomy). The main goals of surgery are to reverse digital contractures and to restore hand or foot function.

In *early DD and LD stages,* a wait and see policy is advised, as no conservative treatment has been firmly established. Glucocorticoid injections may lead to regression but can also induce severe complications like atrophy at the injection site or rupture of tendons and have no long-term impact on disease progression. Without therapy progression of DD is observed in about 50 % of patients after 6 years. Radiotherapy is effective for prevention of disease progression in early stages of DD [70–74] with mild acute or late side effects.

There is a good radiobiological rationale available for the efficacy of ionizing radiation: proliferating fibroblasts and myofibroblasts are radiosensitive cells; ionizing radiation effectively impairs their proliferative activity by induction of free radicals which leads to a reduced cell density [48]; this can result in stabilization of disease as long as proliferation dominates in early DD/LD stages N and I; however, in later disease stages characterized by repair and contraction of fibrous tissue, ionizing radiation is ineffective. Thus, the

rationale is to use radiotherapy only in early sensitive stages to avoid a further disease progression and later dysfunction or even necessity of surgical procedures.

Different dose concepts have been applied in the past with single RT doses ranging from 2 to 10 Gy, fraction numbers from four to ten sessions, and treatment time from 2 weeks up to a several weeks and months. So far, single fractions of 3 Gy and total doses above 20 Gy appear to be the most successful concepts, but only a few groups have compared different RT concepts within a controlled trial. Recently, Seegenschmiedt and coworkers presented a randomized trial comparing no treatment versus 21 Gy and 30 Gy applied in 3 Gy single fractions over 2 weeks (7×3 Gy) versus 3 months (2 times 5×3 Gy). Both RT schemes were significantly superior to no therapy regarding disease progression and avoidance of later surgery (further details below, [75]).

Careful planning precedes RT of DD/LD; this involves clinical target volume (CTV) outline on the skin surface including all nodules and cords plus "safety zone" of at least 1 cm in the lateral and 2 cm in the proximal and distal extension. RT is applied by direct palmar or plantar en face portal with low-energy electrons (5 MV) from linear accelerators with 5–10 mm bolus or low-energy photons (100–125 Kilovolt = kV) from orthovoltage units without bolus due to rapid dose falloff at low energies. Reference dose is calculated at a depth of 0–10 mm depending on skin thickness and lesion extension into deep structures of the hand or foot. The calculated doses should account for energy differences, tube size, target depth, and reduction of portal size due to shielding. Target volumes can be shaped with lead cutouts (for electrons) or lead rubber plates (for low-energy photons) depending upon the RT technique.

4.8.3 Clinical Experience and Results

External beam RT has been shown to prevent DD/LD progression in many retrospective studies, but most results are based on short follow-up, using different indications and patient selection criteria, stages of disease, RT treatment concepts, outcome evaluation, or follow-up periods which allow no direct comparison between these studies. Only a few studies qualify for substantial conclusions.

One German retrospective study from Erlangen [76] reported long-term outcome after a median follow-up of 13 years for a total of 135 patients (208 hands). They used orthovoltage RT applied in two courses of 5×3 Gy up to 30 Gy total dose separated by 6–8 week interval. One hundred and twenty-three (59 %) cases remained stable, 20 (10 %) improved, and 65 (31 %) progressed after RT. In stage N 87 % and stage N/l 70 % remained stable or regressed, while advanced stages progressed in 62 % (stage I) and 86 % (stage II). 66 % achieved long-term symptom relief. 31 % progressed either in-field only (14 %), out-field only (3 %), or in- and out-field (14 %), respectively. RT did not enhance complications after surgery in case of disease progression. In 32 % of patients minor late effects (skin atrophy, dry desquamation) were observed. No secondary malignancy was observed.

Another German group from Essen performed a controlled clinical study to define the most effective RT dose [77]. 489 patients and (due to bilateral affliction) 718 hands were analyzed after at least 5 (mean 8.5) years. Patients could choose between observation only (83 patients, 122 hands) or RT (406 patients, 596 hands); the RT group was randomized into one group (207 patients, 303 affected hands) receiving 10×3 Gy (total 30 Gy) in two series of 5×3 Gy separated by 12 weeks and another group (199 patients, 297 hands) receiving 7×3 Gy (total 21 Gy) in one series in 2 weeks orthovolt RT (120 kV) photons with individual shielding of uninvolved areas of the palm. Relevant patient and disease parameters were equally distributed between control and both RT groups. Evaluation was performed at 3 and 12 months after RT and last follow-up in 12/2010. Radiogenic toxicity was low (26.5 % CTC grade 1, 2.5 % CTC grade 2; 14 % LENT grade 1) and no secondary cancer was observed in the long-term follow-up. 119 (16.5 %) hands had remission of nodules, cords,

or DD stage; 383 (53 %) remained stable; and 206 (29 %) progressed and of those 97 (13.5 %) had surgery. Progression in the control group (any progression 62 %, surgery 30 %) was significantly higher as compared to RT groups (21 Gy: 24 %/surgery 12 %; 30 Gy: 19.5 %/surgery 8 %) ($p<0.0001$). 50 (8 %) relapses occurred inside and 114 (19 %) outside the RT field in the RT group; salvage surgery was possible without problems. Uni- and multivariate prognostic factors for disease progression were smoking habit (trend), symptom duration prior to RT over 24 months, Dupuytren stage, extension deficit, and digital involvement (all $p<0.05$). The most important independent prognostic factor was implementation of RT as compared to the control without RT. In summary, both RT schedules were highly superior to observation, but only minor differences were observed between the two RT schedules. Acute toxicity was slightly more enhanced in the 7×3 Gy group and long-term outcome slightly better in the 10×3 Gy group with over 90 % no progression of disease in the early DD stages N and N/I. RT did not increase the complication rate in cases when surgery was necessary [77].

Long-term data are important, as hand surgeons themselves provide often outcome data with less than 5-year follow-up, but are critical to RT for possible long-term inefficacy, complicated surgery after performance of RT, and potential late effects like radionecrosis or carcinogenesis [78–80]. None of these criticisms have been confirmed by a controlled clinical study. There is no single case in the literature reported about the development of a malignant tumor after RT for DD.

With regard to RT for LD, few clinical studies have been published. A series from Essen [77] summarized long-term outcome of 91 patients with 136 affected feet receiving RT; all had progressive nodules or cords, 88 (97 %) had symptoms (numbness, pain, other symptoms), and 86 (95 %) had walking problems due to pain. Thirty-five feet had recurrent or progressive LD after surgery. Sixty-seven patients (with 134 unaffected feet) served as control without RT. Orthovoltage RT (125–150 kV) was applied with 5×3 Gy repeated after 12 weeks up to 30 Gy total dose. Six patients (11 ft) progressed and of those five (7 ft) had salvage surgery, one with a longer healing period. 60 ft (44 %) remained stable and 65 (48 %) regressed with regard to nodules, cords, or symptoms, and of those, 35 ft had complete remission with freedom of all nodules, cords, and symptoms. Previous symptoms and dysfunction improved in up to 90 % and patients' satisfaction improved in 81 (89 %). Acute side effects (CTC 1° or 2°) occurred in 29 (21 %) or 7 (5 %) feet. Late sequelae (LENT 1°: dryness or fibrosis of skin) occurred in 22 (16 %) feet. Grade 3 acute or late side effects were not observed. Patients without RT had significantly higher progression and surgical intervention rates. In multivariate analysis recurrent LD after surgery, advanced disease and symptoms, and nicotine intake were indicators of worse prognosis.

Another retrospective study confirmed the excellent remission and local control rate of RT for LD with pain remission and improved gait [73]. The study compared two schemes (10×3 Gy or 8×4 Gy) and megavoltage electron or orthovolt RT techniques, but found no difference in treatment outcome. After a median follow-up of 2 years, none of the cases had progressive nodules, cords, or increase of symptoms. Complete remission was achieved in 33 % (11 sites), partial remission (reduced number and size) was achieved in 55 % (18 sites), and 12 % (4 sites) remained unchanged, but had no surgery in follow-up. Pain was relieved in 63 % and gait improved in 73 %; 92 % of the patients were satisfied with the outcome.

The use of RT after surgery may improve short- and long-term outcome, but available data are limited. In one retrospective study the relapse rate of LD after plantar fasciectomy with or without postoperative RT was evaluated over three decades [81]: 27 patients with 33 affected feet (6 bilateral LD) underwent 40 surgical procedures and had a relapse rate of 60 %; radical surgery (total plantar fasciectomy) for primary LD achieved the lowest relapse rate (25 %), while limited local resection without RT resulted in the highest relapse rate (100 %); the existence of multiple versus single nodule(s) was also associ-

ated with a higher relapse rate. The relapse rate for primary LD after fasciectomy was reduced with postoperative RT. Total plantar fasciectomy alone was most successful particularly for primary LD, but still compromised by a 25 % relapse rate. Thus, RT may be a useful additive treatment for more complicated cases of LD treated with limited surgery.

In summary, the use of RT for early stage DD and LD is a very effective treatment with acceptable acute and late toxicity in long-term follow-up. The reported results from a limited number of studies are far better than any reported surgical series. These findings should promote further recruitment of patients into prospective RT protocols and eventually a long-term evaluation and comparison with established surgical techniques. Moreover, the exposure to 30 Gy RT dose does not increase the surgical complication rate when surgery becomes necessary. Thus, our recommendation is to apply RT for early stage DD and LD as the first noninvasive therapeutic approach within the first 1–2 years after diagnosis when clinical progression has been confirmed after an observation period of at least 6–12 months.

4.9 Radiotherapy for Other Rare Nonmalignant Skin Disorders

4.9.1 Lichen Planus (LP)

Lichen planus (LP) is a papular disease which occurs mostly in the middle-aged adults and displays pruritic violaceous papules most commonly on the extremities. The oral and genital mucous membrane may also be involved. The clinical course is generally self-limited for a few months to years, but may be lasting lifelong. Many similar entities have been described, ranging from lichenoid drug eruptions to association with other diseases like diabetes mellitus, autoimmune disorders, and the graft-versus-host reaction. Several clinical variants of LP have been differentiated according to their clinical aspect including (a) annular LP, (b) linear LP, (c) hypertrophic LP, (d) verrucous LP, (e) atrophic LP, (f) vesiculobullous LP, (g) erosive LP, (h) lichen planopilaris, (i) lichen planus pigmentosus, and (k) lichen planus actinicus 84). Multiple therapeutic options exist including corticosteroids, retinoids, griseofulvin, PUVA, and cyclosporine.

Nevertheless, severely pruritic and refractory cases of the verrucous type of LP, particularly on the legs or the nails, may be considered for external beam radiotherapy [5, 28, 82]. A sufficiently deep half-value depth must be selected, and one must be aware of temporary, occasionally long-lasting, hyperpigmentation. Along with most other authors, the same total and single RT dosages are suggested for the treatment of psoriatic lesions which are summarized in Table 4.5.

4.9.2 Cutaneous and Associated Hemangiomas

Cutaneous hemangiomas are benign vascular tumor-like lesions mostly occurring in the early childhood. They are characterized by a typical evolution consisting of rapid proliferation phase during the first years of life and slow involution phase that usually is completed at the age by 5–10 years. While in most cases, no treatment is necessary, some lesions are located in areas at risk for functional complications or are of considerable size or repeatedly undergo bleeding, ulceration, or superinfection, which requires a prompt and adequate treatment.

In the first half of the last century, the cutaneous hemangiomas of neonates or young children within their first 2 years of life had been irradiated often to control the growth of these benign vascular lesions and achieve better cosmetic outcome. However, in recent decades the conviction has grown that nearly all strawberry angiomas disappear spontaneously during the first years of life, without any type of treatment. If treatment is required nowadays, first-line approaches include topical, intralesional, and systemic corticosteroids. Second-line options include interferon alfa-2a and alfa-2b, laser therapy, and surgical therapy. Third-line approaches may include use

of cytotoxins, embolization, and angiogenesis inhibitors. Other therapies and procedural approaches including intermittent pneumatic and continuous compression; cryosurgery; radiotherapy; implantation of copper needles; sclerotherapy; electrocautery; electroacupuncture; imiquimod cream 5 %; and other prospective agents, such as OXi4503 (diphosphate prodrug of combretastatin A1), cidofovir, and beta blockers are discussed.

Nevertheless, for exceptionally large hemangiomas or those involving locations close to vital organs or associated with rapid growth or thrombocytopenia (so-called Kasabach-Merritt syndrome) and for other types of hemangiomas not responding to oral corticosteroids, interferons, beta blockers, or other treatment options, small total doses of 6–10 Gy delivered in 1 Gy fractions within 1–2 weeks may be very helpful to overcome the refractory and sometimes life-threatening situation [28].

Kasabach-Merritt syndrome (KMS) is a rare thrombocytopenic consumption coagulopathy which is associated with an enlarging tufted angioma or Kaposi-like hemangioendothelioma [83]. In a Japanese study seven neonates aging from 1 day to 5 months with KMS received RT [84]. The hemangiomas were situated mostly in the extremities with lesion size ranging from 70 cm to more than 150 cm in greatest diameter; initial platelet counts were all less than 40,000/mm^3 except for one. The total RT dose applied to the hemangioma was 8–10 Gy, with a daily dose of 1 Gy five times a week. Four sites responded dramatically with a concomitant rise of platelet count parallel to the RT series. The remaining three hemangiomas, all of which were ill circumscribed by widespread overlying shiny, dusky purple skin, became less tense during RT. Disseminated intravascular coagulopathy was not improved, but they have responded favorably to two or three courses of RT with an extended field by 1.5 years of age. All seven patients survived with no evidence of hemangioma or hematological abnormalities, but growth delay and shortening of the extremity was observed in three patients who received multiple courses of RT.

In general for neonates and children an absolute contraindication for RT prevails, especially in locations over radiosensitive tissues; thus, RT should be limited to life-threatening cases only. There have been also a few case reports which have described the potential initiation of cutaneous angiosarcomas derived from sites with formerly irradiated congenital hemangiomas [85, 86]. One third of all angiosarcomas arise in the skin. They often show one of three clinical patterns: (a) most common is the occurrence as a bruise-like lesion on the scalp or the face of mostly elderly people, (b) second in frequency is the Stewart-Treves syndrome, and (c) the least common is the angiosarcoma developing as a sequela of previous RT; however, the prognosis in general is poor, with a mean survival length of 24 months and 5-year survival rate of 10 %. Thus, effective treatment relies on early diagnosis and wide-margin surgical excision. Another risk is the development of secondary skin cancer after radiation exposure in early childhood in long-term observation. There are case reports of basal cell carcinoma and other skin cancers which could be well induced by previous irradiation; however, other types of additional risks like excessive sunlight exposure are often not taken into account [87].

4.9.3 Hidradenitis Suppurativa (HS)

Hidradenitis suppurativa (HS) or Verneuil's disease is a chronic inflammatory disorder of the apocrine gland-bearing skin which is clinically hallmarked by multiple abscesses and sinus tracts distributed in areas densely populated with apocrine glands. It is associated with alterations in innate immunity and frequent bacterial infections. Three disease stages have to be differentiated: (a) *stage I HS* is characterized by the presence of abscesses without scarring or sinus tracts, (b) in *stage II HS* additional scarring and sinus tract formation develop, and (c) in *stage III HS* patients have multiple interconnected sinus tracts in multiple regions. The disease displays a significant chronic morbidity and emphasizes the need for effective treatment strategies [88].

The therapeutic management of this devastating disease comprises medical, surgical, and procedural therapies. Medication can be successful in controlling mild diseases, but local relapses are frequent. Surgical and procedural treatments can be more successful than medical treatments, especially for patients with severe disease. Surgery is considered the only curative therapy for HS. Nevertheless, the chronic type of hidradenitis suppurativa is most difficult to treat. In selected cases, the addition of radiation therapy (0.75–1 Gy administered for four to six doses at weekly intervals or 1 Gy three times at 3 week intervals) to other treatment modalities is possible and often very effective [5, 81].

A large retrospective study summarized outcome of 231 patients undergoing RT for hidradenitis suppurativa [82, 89]. All patients received orthovoltage RT with 175 kV energy and 0.5 mm copper-filtering. Single doses of 0.5–1.5 Gy up to total RT doses of 3–8 Gy were applied in one series with daily fractionation. In chronic recurrent disease two or more series with a total dose of more than 10.0 Gy were applied in a hypofractionated regimen. After RT completion 89 patients (38 %) experienced complete relief of symptoms and in 92 patients (40 %) a clear improvement of symptoms was noted by the patients and confirmed by the physician. There were only two patients who did not respond to RT, and no radiogenic side effects were observed.

It is important to note that the *acute painful* HS and the *chronic* HS require different RT techniques and individual doses. While the acute painful type often responds well to very low total and single doses, e.g., 1–2 Gy applied in 0.2 Gy fractions administered daily, the chronic type requires higher total and single doses, e.g., 3–12 Gy applied in 0.5–1.0 Gy fractions every other day (two to three times per week). Technical details of RT are summarized in Tables 4.12 and 4.13.

Table 4.12 Dose recommendations for hidradenitis suppurativa and chronic paronychia

D½	1–20 mm
kV	50–100
Filter	>0.4 mm Al
HVL	>0.2 mm Al
MeV	3–5
Bolus	5 mm
Single dose	0.5 or 1 Gy
Total dose	2–12 Gy
Fractionation	Every 1–2 days 3–5×/week

Table 4.13 Dose recommendations for vasculitic ulcers, acute hidradenitis, or acute paronychia

D½	1–10 mm
kV	50–100
Filter	>0.4 mm Al
HVL	>0.2 mm Al
MeV	3–5
Bolus	5 mm
Single dose	0.1–0.2 Gy
Total dose	1–2 Gy
Fractionation	5–10×/week

4.9.4 Paronychia and Panaritium

Paronychia is a fairly common inflammatory disorder of the nail bed. It is usually caused by local injury, e.g., from biting off or picking a hangnail or from trimming or pushing back the cuticle. The complications occur by bacterial, candidal (yeast), or fungal infection. *Fungal paronychia* may be seen in persons with a fungal nail infection. It is also common among persons with diabetes and those who have their hands in water for long periods of time. The key symptom is a painful, red, swollen area around the fingernail, often at the cuticle or at the site of a hangnail or other injury. There may be also pus-filled blisters, especially with a bacterial infection which causes the condition to occur suddenly. A sole fungal infection tends to occur more slowly. In chronic cases typical nail changes may occur, such as detachment, abnormal shape, or unusual nail bed color.

As in hidradenitis suppurativa, one must distinguish more acute from chronic types of paronychia. Irradiation is indicated only in exceptional cases, usually in combination with antibiotics and other treatment modalities. Chronic paronychia is often multifactorial and even with appropriate local treatment, this disease may be resistant and cause considerable tenderness and discomfort.

A large retrospective study summarized outcome data from 252 patients undergoing radiotherapy for either panaritium ($n=202$) and/or paronychia ($n=50$) [82, 89]. While the patients presenting with panaritium were usually in their 60s, those with paronychia were mostly in their 40s; both genders were equally distributed. All had undergone unsuccessful treatments with antibiotics and/or by surgery. The key symptom was pain, second was osseous involvement, and third was suppuration. Orthovoltage RT with 175 kV energy and 0.5 mm copper-filtering and single doses of 0.5–1.5 Gy up to total RT doses of 3–8 Gy were applied in one series with daily fractionation. In chronic recurrent disease two or more series with a total dose of more than 10.0 Gy were applied in a hypofractionated regimen. After RT completion 89 patients (36 %) were free of symptoms (panaritium 34 %; paronychia 42 %); moreover, 114 patients (45 %) noticed a clear improvement of symptoms (panaritium 48 %; paronychia 36 %). Surgical incision due to abscess formation was required in 27 patients. Paronychia on the fingers responded better than on the toes. Best results were achieved when the beginning of RT was not too much delayed, i.e., beyond 1 month after the beginning of the disease. A few older clinical series which are not discussed herein indicate similar outcome data.

Thus, in summary, when the disease is resistant to more standard therapies and radiation therapy is prescribed, the dose schedules are similar to those used for hidradenitis suppurativa which are summarized in Tables 4.12 and 4.13 [3, 4, 28]. For painful acute lesions, smaller single doses and daily fractionation are usually sufficient to relieve the symptoms quickly [44]; for more chronic inflammatory types of paronychia, single doses of 0.5–1 Gy twice weekly are recommended.

4.9.5 Chronic Vasculitic Ulcers (CVU) of the Lower Extremity

Vasculitis is an inflammation with subsequent destruction of the vascular wall of blood vessels. The *cutaneous vasculitis* is s specific type of limited or *focal vasculitis* which implies that the process is confined to the skin and subcutaneous tissue only as opposed to the *systemic vasculitis* indicating an additional involvement of other organs. The clinical presentation can range from reticulated erythema to widespread purpura finally leading to necrosis and patchy to confluent skin ulceration.

Chronic leg ulcers mostly derive from chronic venous insufficiency (CVI; about 70 %), while about 10 % arise from occlusive disease of major arteries and another 10 % have a mixed etiology; among them there are about 5 % with *vasculitic ulcers*, a diagnosis which nowadays is still beset with controversies about their pathogenesis and hence the appropriate therapeutic management [90, 91]. Although vasculitic leg ulcers present a very small proportion of all leg ulcers of specialized wound centers, they pose a difficult challenge in terms of diagnosis and treatment. The cutaneous vasculitis may be associated with a systemic involvement and occur as a result of *hypersensitivity reaction* with formation of immune complexes. Possible causes of this hypersensitivity reaction are listed in Table 4.14. Only by obtaining a deep biopsy from the margin of the ulcer will help to affirm a definitive diagnosis of a vasculitic leg ulcer. The essential elements of treatment of vasculitic leg ulcers include treatment of the primary cause, providing moist occlusive dressings, protection from further trauma, and, most importantly, relieving pain.

Careful examination and thorough history may provide important clues to the causative agent of the CVU (see Table 4.14); besides exposure to infectious agents and prescribed drugs, the analysis of food intake is of equal importance to find potential allergic agents and components. However, a triggering factor can only be found in about 50 %, and NSAID and antibiotics are the most common culprits [92].

So far there are no randomized clinical studies to indicate the optimal therapeutic management for chronic vasculitic ulcers. Most of the information in the literature comes from case reports and uncontrolled trials. Nevertheless, the general guidelines are detect and treat the primary cause, support local healing, protect from further

Table 4.14 Causes of vasculitic leg ulcers

Infectious agents	Skin rash Fevers	Bacteria (meningococcus, Mycobacterium leprae) Rickettsia (various spotted fevers) Spirochetes (e.g., syphilis, leprosy) Fungi (e.g., aspergillosis, mucormycosis) Viruses (e.g., varicella-zoster virus, childhood virus infections
Immune reactions	Immune Complex Formation Antibody Reaction	Exogenous agents (infection or drug-related reactions) Endogenous agents (rheumatoid arthritis, systemic lupus erythematosus, and other connective tissue disorders), cryoglobulinemia Kawasaki disease, Goodpasture syndrome Drug-induced (NSAID, antibiotics) Inflammatory bowel disease and malignancies
Unknown causes		Giant cell arteritis, Takayasu arteritis, polyarteritis nodosa

trauma, prevent secondary contamination of the wound, and relieve the very painful and recalcitrant condition.

In more severe cases of hypersensitivity vasculitis or ones that do not show signs of healing, a mild immunosuppressive treatment with prednisolone may be indicated. In this clinical context also very low doses of X-rays, e.g., 0.2 Gy on a daily basis, are frequently well appreciated by patients since the pain relief occurs rapid and is often much more effective than any analgesic medication [13, 44, 45]. The RT dose concept for CVU is summarized in Table 4.13.

A typical clinical example of a large CVU responding to RT is presented in Fig. 4.9. Much active research is being done in attempts to discover new therapeutic options. Various topical growth factors look promising, including platelet-derived growth factor, epidermal growth factor, and nerve growth factor (NGF). It is believed that NGF works by promoting keratinocyte proliferation and vascular neoangiogenesis.

4.9.6 Verrucae

Warts are small benign lumps on the hands and feet which can have different appearances depending on the body site. They are caused by the infection with human papilloma virus (HPV), which causes an overproduction of keratin, a hard protein in the epidermis, and creates the rough, hard texture. There are several types which are usually differentiated as common warts, plantar warts (verrucas), plane warts, filiform warts, periungual warts, and mosaic warts. The appearance of warts depends on several factors such as the body location, the type of HPV, and the immune status. An increased risk appears in the early childhood and in the adults with weakened immune system, e.g., following organ transplant, cancer treatment, or acquired immune deficiency syndrome (AIDS).

About 65–80 % of warts will disappear within 2 years without specific treatment. Treatment is recommended when warts are causing local pain, infection, or distress and there are risk factors, such as a weakened immune system. Several treatment options are available to help treat warts and verrucas which may cause side effects such as pain, blistering, and skin irritation around the wart. The aim of all types of treatment is to remove the wart without relapse or local scarring and improve long-lasting immunity to HPV, which causes warts.

As there is no single treatment fully effective for the warts in different locations, so far several treatment options have to be applied in a stepwise approach including (1) local treatment with salicylic acid (applied as creams, gels, paints, and medicated plasters); (2) local cryotherapy (i.e., surgical removal via liquid nitrogen sprayed onto the wart to freeze and destroy the cells); (3) local duct tape (stepwise removal of wart); (4) chemical treatments using different agents such as formaldehyde, glutaraldehyde, or podophyllin; and (5) local excision by surgery to remove all traces of the warts.

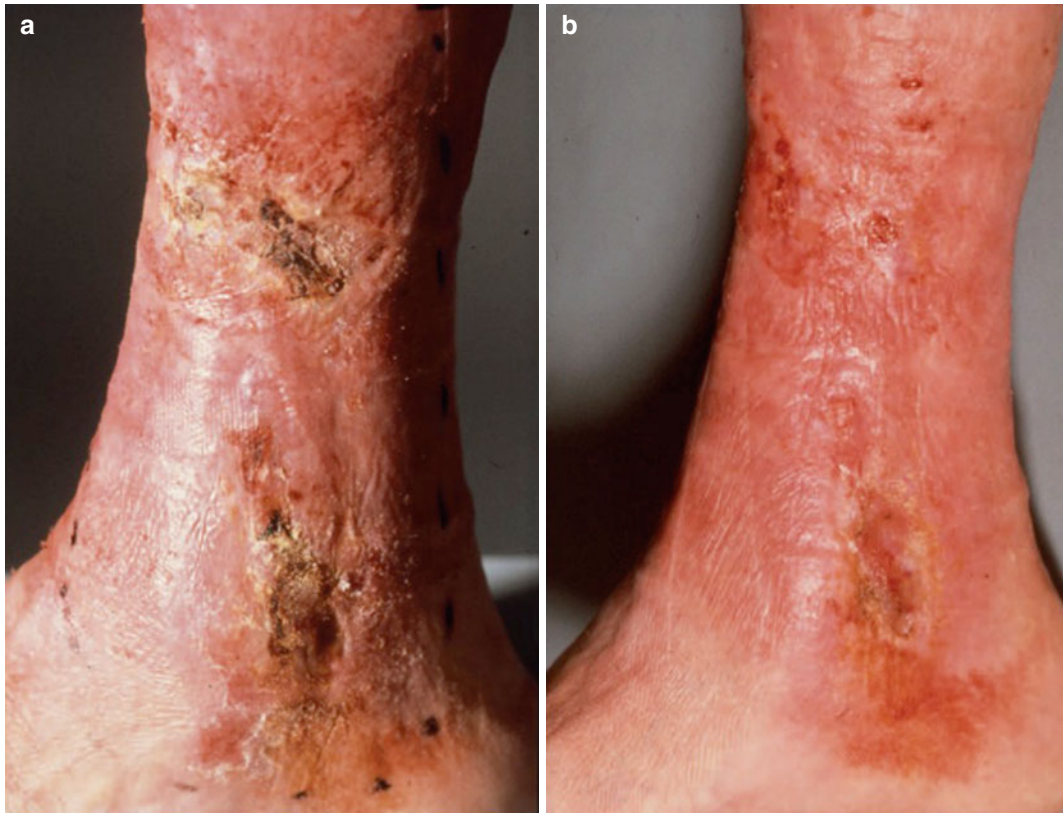

Fig. 4.9 Painful chronic ulcer of lower leg in a 73-year-old women (**a**) before and (**b**) 3 weeks after treatment, 1.6 Gy total dose with 40 kV

The aim of any surgical treatment is to remove all traces of the warts. The techniques that are used to remove warts surgically are (1) cryotherapy (as mentioned above); (2) curettage, where tissue is removed by scraping; and (3) cautery, where tissue is destroyed by burning using an instrument or an electric current; recently "radiosurgery" was introduced which applies radiofrequency to ablate the warts. Surgical approaches are usually carried out under local anesthesia as all these procedures can be quite painful.

The use of radiotherapy with orthovoltage was well accepted up to the 1970s of the last century, especially for plantar warts, when other methods had failed and normal function was disabled such as gait or other leisure activities. However, over time this method was more or less abandoned when more effective local treatments became available [93–96]. From these former quite favorable clinical experiences, the application of radiotherapy may be justified nowadays only in those rare stubborn, painful warts especially located on the plantar region, which do not respond to other treatments. However, instead of applying "ablative doses" of 1 × 10 Gy, we would recommend to apply radiation dose concepts similar to the use of prophylactic radiotherapy for the prevention of keloid recurrence, which is four times 3 Gy within 1 week (Table 4.15). With this

Table 4.15 Dose recommendations for plantar warts

D½	1–10 mm
kV	50–100
Filter	>0.4 mm Al
HVL	>0.2 mm Al
MeV	3–5
Bolus	5 mm
Single dose	3.0–4.0 Gy
Total dose	12 Gy
Fractionation	3–4×/week

concept 60–80 % of plantar warts may respond over a very long time with a low chance for local relapses.

In a recent systematic review of the Cochrane Database, the use of local radiotherapy is not mentioned probably due to lack of recent publications; however, the authors concluded for all other methods that there is a considerable lack of evidence on which to base the rational use of the local treatments for common warts. The reviewed trials are highly variable in method and quality. Cure rates with placebo preparations are variable but nevertheless considerable. There is certainly evidence that simple topical treatments containing salicylic acid have a therapeutic effect. There is less evidence for the efficacy of cryotherapy and some evidence that it is only of equivalent efficacy to simpler, safer treatments. Dinitrochlorobenzene appears to be effective, but there were no statistically significant differences when compared with the safer, simpler, and cheaper topical treatments containing salicylic acid. The benefits and risks of 5-fluorouracil, bleomycin, interferons, and photodynamic therapy remain to be determined. In summary, radiotherapy will be available, but needs to be well justified in exceptional cases where no other method is available or not effective.

4.10 Summary and Future Directions

Using radiation therapy for nonmalignant skin condition appears to be a rare but still meaningful indication in several clinical situations, where primary surgical or medical treatment fails or may not provide a satisfactory outcome for the affected individual. Always the indication should be based on an interdisciplinary assessment. Well-defined outcome parameters should allow a prospective long-term evaluation. Controlled clinical trials for most clinical applications are still required in the future to better establish the role of radiotherapy and increase the level of evidence (LOE). Possible late effects including the rare incidence of secondary tumors should be well respected, but not overestimated, as long as a meaningful gain in function or quality of life can be achieved for the individual patient. Our future initiatives should specifically focus on the preservation and availability of the relevant RT techniques in major dermatological and/or radiotherapeutic departments; this is especially important in academic institutions. The setup of a continuous medical education and quality assurance program should parallel the initiation and quality control in prospective clinical trials. Besides interdisciplinary collaboration, translational research can enhance our knowledge about the different pathomechanisms of the skin disorders and the relevant mode of action with which ionizing radiation interferes with inflammatory or hyperproliferative or other pathomechanisms of the different diseases.

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Grenz Ray and Ultrasoft X-Ray Therapy

5

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Contents

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5.1 Introduction

Grenz rays are part of the electromagnetic spectrum. In 1923, Gustav Bucky developed a hot cathode vacuum tube with a lithium borate glass window capable of delivering low-energy X-rays which he labelled grenz rays (grenz = border in German) as he believed that the biological effects resembled ultraviolet light in some ways and traditional X-rays in other ways.

5.2 Physics

Grenz rays form that part of ultrasoft X-rays (kVp <30, HVL <0.2 mm Al.) with HVL less than 0.035 mm Al (upper limit of grenz ray set at a meeting of the Council for the study of grenz ray therapy March 17, 1950) [14].

Occasionally grenz ray will be referred to as soft (HVL <0.02 mm Al), medium (HVL 0.023–0.29 mm Al) and hard (HVL 0.030–0.036 mm Al).

In addition to the factors which affect the penetrating power of X-rays such as kilovoltage, milliamperes and added filtration, grenz rays are so soft that they are absorbed to a significant extent in air and therefore target skin distance also affects the quality of the beam. As a result, the machine must be calibrated specifically for each distance at which the tube is to be used.

The inverse square law which states that the intensity of the beam, or dose rate, varies

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inversely with the square of the distance from the point source does not apply to grenz rays (although conventional X-rays follow it).

Grenz rays are absorbed predominantly by the photoelectric effect. The path of the photoelectron is short 0.05–0.1 μm and therefore backscatter is not a concern [15].

Calibration of machines designed to produce ultrasoft X-rays can be problematic as the thimble chambers designed to calibrate conventional X-rays walls can absorb ultrasoft X-rays excessively [15]. Free-air chambers such as the Lamperti (10–20 kV) free-air ionisation chamber, Ritz (down to 20 kV) free-air ionisation chamber [21] or specialised grenz ray film-type chambers can be used [50]. Calibration of the author's machines (Gulmay D3100 producing HVL 0.033 and 0.047 mm Al and Philips RT100 producing HVL 0.047 mm Al) is done by ARPANSA, Australia's radiation reference laboratory, while the superficial X-ray is calibrated by a local hospital physicist.

5.3 Biology

Grenz rays have a half-value depth dose of approximately 0.5 mm, 75 % absorption in under 1 mm and for practical purposes completely absorbed within the first 2 mm of skin [35]. See Fig. 5.1.

It appears that the biological effect of grenz ray is localised to the absorbed area – clinical benefits in treating dermatoses are limited strictly to the irradiated area.

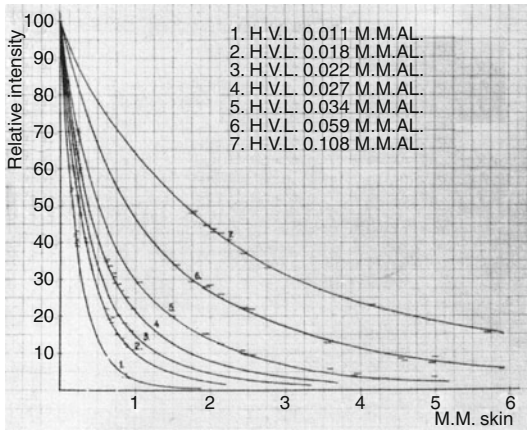

Fig. 5.1 Absorption curves (From Ebbehoj)

The exact mechanism of action of grenz rays is unknown.

It appears to exert its effect by affecting the afferent arm of the immune response.

5.3.1 Effects on Langerhans Cells

There have been a number of studies showing effects on Langerhans cells in the epidermis [1, 30]. Following 4 G 10 kV grenz ray, Langerhans cells were reduced significantly at 1 and 3 weeks after irradiation. Comparing 3 × 4 G grenz ray weekly to 3 × 30 J/cm^2 UVA (suberythemal) weekly, there was a marked decrease in epidermal Langerhans cells in grenz ray-treated sites and those that remained showed little change (fewer Langerhans cell granules) – keratinocytes and intercellular spaces were unaffected. No Langerhans cells were found in the dermis in grenz ray-treated nor control skin. By contrast low-dose UVA did not show reductions in Langerhans cells in the epidermis (high-dose UVA, low-dose UVB and PUVA do). The Langerhans cells showed an increase in Langerhans cell granules, mitochondria and enlarged Golgi apparatus. A few sunburn cells were seen but keratinocytes in general appeared unaffected by low-dose UVA.

The fate of the Langerhans cells removed from the epidermis has not been determined. As the Langerhans cells return, it is speculated that the Langerhans cells probably migrate to the draining lymph nodes as part of the afferent arm of the local immune response.

5.3.2 Effects on Dermatitis

By pretreating nickel allergic patients with grenz rays (3 × 3 G weekly) then applying nickel patch tests on treated and untreated skin, it is has been shown possible to significantly reduce allergic contact dermatitis reaction. This reduction lasts 3 weeks and correlates with reduction in the epidermal Langerhans cell population.

There was a tendency towards weaker irritant reactions with sodium lauryl sulphate pretreating

patients with grenz ray although this was not statistically significant [29]. Grenz rays reduced itch but not flare following intradermal injection of histamine, but this was not statistically different from placebo [8]. Grenz rays can decrease histamine levels and mast cells in rat skin (although control animals also showed similar changes) [3]. Grenz ray can stimulate amino acid production in the epidermis similar to tape stripping.

5.3.3 Factors Affecting Grenz Ray Erythema

Grenz ray erythema can be inhibited by a single application of hydrocortisone ointment applied 6 h prior and washed off 1 h before irradiation [19], but concomitant therapy with grenz ray and topical corticosteroids for psoriasis did show an additive effect in scalp psoriasis [28].

Bergamot oil application can encourage development of erythema in grenz ray fields [36].

5.3.4 Regional Skin Sensitivity Variability

Kalz [18] has described a number of observations of grenz ray:

I. Thickness of epidermis particularly the stratum corneum affects the reaction:

A dose producing no visible reaction in a thick well-pigmented epidermis may result in marked erythema in a thin-skinned person.

Body areas arranged in order of decreasing sensitivity are

1. Eyelids
2. Neck, popliteal and antecubital fossae, female breasts
3. Flexor thighs, arms, chest and abdomen
4. Dorsal fingers, hands, toes, feet
5. Face (unless pigmented)
6. Back, extensor extremities
7. Nape of neck
8. Palms
9. Soles
10. Scalp (sensitivity depends on the amount of hair)

5.3.5 High-Dose (>10 Gy) Effects

Kalz [18] describes a triphasic erythema response with doses greater than 10 Gy hvl 0.02 mm Al:

1. Early erythema appears within a few hours, increases for 24 h and fades quickly.
2. Second wave reaching peak within 10–14 days and persists for 3–4 days.
3. A third and more intense erythema (main erythema) occurs between 24th and 34th day lasting 5–7 days – occasionally the erythema waves may coalesce or second wave may not appear at all. If a main erythema develops, then erythema may recur with heat suggesting vascular damage. If the dose is fractionated, then main erythema can be avoided and clinical experience indicates that late sequelae will not appear.

5.3.6 Effect on Pigmentation

Pigmentation: the relationship between dosage and pigmentation is less definite – but usually disappears spontaneously within 4–12 weeks. Lentigo like spotty pigmentation can be seen with overdosage.

5.3.7 Nail Transmission

Gammeltoft and Wolf who have examined transmission of 12 kV grenz rays through normal and diseased nails found that normal nails transmitted about 30 % [11].

5.3.8 Effect on Psoriasis

The mechanism of benefit for psoriasis is unknown but it is speculated that it may be similar to the anti-inflammatory mechanisms demonstrated for low-dose radiation (<1 Gy): modulation of cytokine and adhesion molecule expression on activated endothelial cells and leukocytes and of nitric oxide production and oxidative burst in activated macrophages and granulocytes [40].

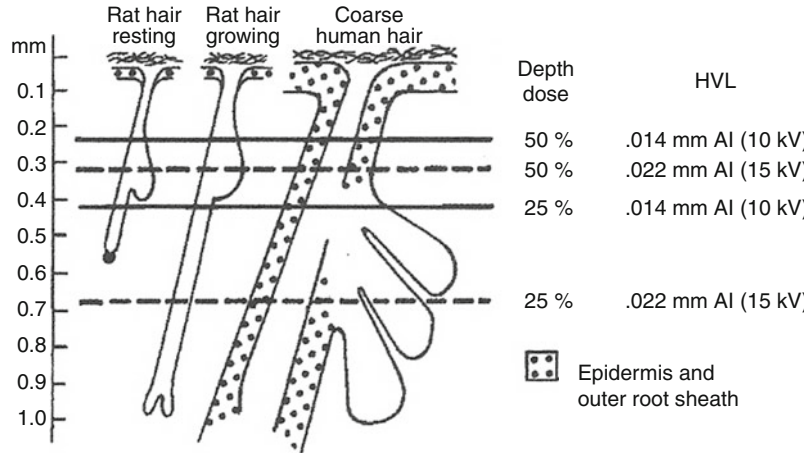

Fig. 5.2 Depth dose of Grenz ray

5.3.9 Cancer Production

Cutaneous neoplasms in rats have been produced with grenz rays: effective single doses ranged from 50 to 90 Gy; effective weekly (3–6 Gy) schedules totalled 78–264 Gy. The amount of grenz ray was greater (possibly five times) than that required by 80 kV X-ray [55]. In mice, squamous cell carcinoma was induced by grenz ray 0.5 G daily 5 days per week to total of 300 Gy [44].

Many authors have discussed the different penetration of grenz ray in animals compared to human skin [44]. See Fig. 5.2.

5.3.10 Effect on Melanocytes

Nakatani and Beitner [34] studied melanocytes after irradiating with 4 G grenz ray weekly for 3 weeks compared with UV-A 30 j/cm^2: ultrastructural changes were an increase in the number of premature and mature melanosomes, elongation and protrusion of cytoplasm and sometimes indented nuclei – the qualitative changes were similar to UVA.

5.3.11 Overdose

Telangiectasia, atrophy and hyperpigmentation have occurred with single dose of 37.2 Gy [43]. One-hundred Gy in one session can produce epidermal necrosis [23] p. 176].

5.4 Equipment

1. Progressus Medica AB makes new grenz ray machines. The tube has a beryllium window 0.65 mm thick. Although the tube is rated for 50 kV, it operates at 9.95 kV. The unit has six cones 1–12 cm diameter, operates at a focal skin distance 17 cm, has a computer controlled timer and produces audible signal when X-rays are produced. www.progressus-medica.se
2. Xstrahl make Xstrahl 100 unit which can provide superficial X-ray and grenz ray therapy (formerly Gulmay D3100). The unit can be configured to provide a number of X-ray qualities. The author uses this machine configured to deliver HVL 0.033, 0.047, 0.7, 1 and 2 mm Al. It comes with a set of standard cones (now advertised to give range of 1–15 cm field size diameter), but we have a custom cone 18.7 cm diameter (to simulate the 20 cm diameter square cone available with the Philips RT100 machine which allows treatment of whole palm and sole) (Fig. 5.3).
3. Old units: Philips RT100 (capable of delivering HVL 0.047 mm Al) and other old units may be able to be obtained from oncology

centres or by word of mouth from members of the International Dermatologic Radiotherapy Society.

5.5 Safety Requirements

Grenz rays as a form of ionising radiation may have acute effects on skin generally mild with normal treatments (erythema, burning sensations, tanning and blistering) and more severe in overdosage, (atrophy, telangiectasia, crusting, erosions) [22] and potential long-term effects of carcinogenesis (to be discussed later). However, if guidelines are followed, then grenz ray can be given safely. Warner and Cruz [52] have proposed the following recommendations for safe and effective administration of grenz ray (based on their review of the literature) which I will add to:

1. There should be an established diagnosis.
2. Grenz rays should only be used in refractory cases when treatment failure consequences are unacceptable or alternatives not accepted by or tolerated by patients.
3. Grenz rays should only be used when there is a reasonable expectation that treatment will be helpful (inflammatory conditions where pathology is within the absorption range or previous literature reports of effectiveness).
4. Grenz rays should not be used in children (I would add not in pregnant patients – primarily for medicolegal reasons).
5. Grenz rays should only be given by trained personnel.
6. Meticulous radiation protection should be used: operators should stand no closer than 4 m when grenz rays are delivered – ideally the machine should be in a proper shielded treatment room with operating controls outside the room and with interlock doors – this requirement will probably be mandated by governing bodies. Cones should be used (if they cannot, then protective measures as for superficial radiotherapy should be used. The use of cutouts may produce well-defined field edges which may exaggerate the appearance of pigmentary changes).
7. Patients should be questioned re previous radiation exposure and exposure to other potential carcinogens.
8. No topical agents should be applied to the treatment areas on the treatment day prior to irradiation to avoid irritation or reduced efficacy.
9. Radiation dose should be adjusted for the treatment site's sensitivity to grenz ray. Palms, soles and scalp can tolerate 2–4 Gy per treatment, other sites generally 2 Gy and anogenital area 0.5–2 Gy. Adjustment of dosage due to the presence of hair which absorbs grenz ray has been recommended by Wulf et al. [54] by multiplying dose by 1.5–3 times based on the assessment of thin or thick hair layer – this advice I believe should be taken cautiously – I would not give more than 4 Gy per treatment.
10. While the US literature recommends 50 Gy lifetime cumulative dose per treatment area, Lindelöf [25] (one of the authors of the only large-scale study of carcinogenic effects of grenz ray [27]) believes higher doses can be tolerated: he recommends 100 Gy maximum cumulative dose; although if higher doses are required, patients should be monitored closely, dose should be fractionated four to six treatments once per week with 6 months rest between courses and the palms, soles and scalp can safely tolerate more than 100 Gy per lifetime. I believe that areas that are not routinely exposed to other carcinogens (especially UV light) such as the palms and soles are at less risk of subsequent cancer and that although lifetime doses should be kept under 100 Gy, higher doses on the palms and soles can be considered provided that Lindelhof's suggestions are followed. Although scalp tolerates grenz ray well, I hesitate to consider exceeding 100 Gy lifetime dose in view of the potential for this area to be exposed to UV (especially in patients with alopecia).

5.6 Practical Aspects

At the Skin and Cancer Foundation, Victoria, we have two X-ray machines capable of providing ultrasoft X-rays: our original machine is a Philips RT 100 which has a 20 cm square cone suitable for treating soles in one field and a Gulmay D3100 (now renamed as Xstrahl 100) with standard cone sizes and custom cone 18.7 cm diameter. The former machine is calibrated to give hVL 0.047 mm Al, the latter hVL 0.047 and 0.033 mm Al. We use hVL 0.047 mm Al routinely. We use a treatment schedule similar to that of the Karolinska Institute: four to six weekly treatments of 3 or 4 Gy for palms and soles, 1–2 Gy for other areas.

5.7 Clinical Aspects

Grenz ray is indicated for treatment of a variety of inflammatory skin disorders: eczema, psoriasis, palmoplantar pustulosis, neurodermatitis and, pruritus ani, et vulvae. It has also been reported for lichen planus, Grover's disease, Darier's disease and histiocytosis X [35]. It was used in the pre-antiviral era for herpes simplex [35] I have used grenz ray for Shamberg's disease and erythema elevatum diutinum. Grenz ray has been reported to soften skin in generalised morphea [33] and to decrease lesions and itch in pruritic disseminated superficial actinic porokeratosis [39].

Grenz ray treatment of acne vulgaris [41] has been superseded by other therapies and is not recommended.

Grenz ray has been used for treatment of actinic keratoses and Bowen's disease.

Some of these indications will be discussed in more detail.

5.7.1 Hand Eczema/Dermatitis

There is no generally accepted classification of hand eczema and a paucity of controlled trials of any treatment for this common skin disease [49].

A double-blind study of grenz ray in chronic eczema of the hands [31] showed a significantly better response to active treatment 5 and 10 weeks after commencement of treatment compared with untreated control utilising treatment schedule at the Karolinska Institute.

Lewis reports using 2 Gy dorsum of hands and 3 Gy palms weekly two to three doses for resistant adult atopic chronic hand eczema [23].

Cartwright and Rowell found that treatment of chronic hand eczema with grenz 3 Gy every 3 weeks for a total 9 Gy was no better than placebo (this treatment schedule is not usual) [4].

Fairris compared superficial X-ray to grenz ray therapy: 1 Gy superficial compared with 3 Gy grenz given three times at 3-week intervals and found that both produced clinical improvement although superficial X-rays were more efficacious [6].

Schalock et al. reported their patient's perception of treatment of recalcitrant dermatoses with grenz ray – 29 % had dermatitis – 65 % of these had treatment of the hands with 66 % reporting decreased severity or resolution [42].

Walling et al. has reported complete remission and no recurrence for 48 months of frictional hyperkeratotic hand dermatitis in a dermatologic surgeon [51].

A quality assurance analysis of ultrasoft X-ray (hvl 0.047 mm Al) treatment at the Skin and Cancer Foundation, Victoria [53], for treatments given from 2003 to 2009 was conducted, and patient's perception of treatment was recorded by standardised telephone questionnaire. One-hundred fifty patient responses were obtained (total number of treated patients was 259) for a total of 628 fields treated. Dermatitis was the diagnosis in 42.3 % patients who responded.

Two-hundred forty-five dermatitis fields were treated with 137 clearing, and 71 much improved (206/245 fields were hands). One-hundred thirty-eight fields could be evaluated for duration of response: 10 had never recurred, 69 within 6 months, 17 6–12 months and 42 after 12 months.

Hanfling and Distelheim performed a comparative study comparing grenz ray with superficial X-ray in 24 patients with various forms of dermatitis and showed 21/28 had similar response and 6/7 had better response to grenz ray [12].

King and Chalmers showed statistically significant improvement in chronic hand dermatitis with superficial X-ray at 1 month after treatment [20], but this difference was not present at 6 months, and Duff et al. showed benefit with megavoltage therapy for chronic vesicular dermatitis with 47 % complete resolution, 53 % decreased severity [5].

Sheehan-Dare et al. compared topical photochemotherapy (PUVA) given three times per week for 6 weeks to superficial radiotherapy 0.9 Gy 50 kV 1 mm Al added filter given three times at 3 week intervals [45]. The mean clinical severity scores showed significant improvement over pretreatment scores for both treatments – radiotherapy significantly better than topical PUVA at 6 weeks but not at 9 and 18 week assessments. The symptom severity scores were lower for superficial X-ray treated compared to topical PUVA at 9 and 18 weeks.

Sumilia et al. reported 22 patients with therapy-resistant eczema and six with psoriasis treated with 43 kV or 50 kV radiation for a total of 88 fields which showed reduction [45] or complete remission [40] in symptoms in 83/88 fields treated with 62/88 maintaining benefit at last follow-up (median 20 months – range 4–76 months) – 32 with complete remission [48]. There was no difference between single doses of 0.5 Gy (median total dose of 5 Gy) and 1 Gy (median total dose of 12 Gy).

In summary, although it is difficult to compare these different studies, there is evidence that:

1. Grenz ray given in treatment schedules as performed at the Karolinska Institute is helpful for refractory hand dermatitis.
2. Superficial X-ray radiation and megavoltage radiation are also helpful and may be more effective than grenz ray because of greater penetration. Grenz ray has the advantage of greater safety (less risk of carcinogenesis and late radiation changes) and can be repeated.
3. Ultrasoft X-ray is at least as helpful as grenz ray given in treatment schedules as performed at the Karolinska Institute and may be more so (although this remains to be proven) (Figs. 5.4, 5.5, 5.6, 5.7, 5.8, 5.9 and 5.10).

5.7.2 Psoriasis

Johannesson and Lindelöf performed a double-blind trial of grenz ray in the treatment of psoriasis of the scalp – in 14/16 patients there was complete healing on the grenz ray-treated side after 6 weeks of treatment; nine patients were still free of lesions of the scalp 3 months after the start of the grenz ray therapy [16]. Johannesson and Lindelöf showed in a double-blind trial that topical steroids added to grenz ray treatment had faster clearing and longer remission time in treating scalp psoriasis [17]. Lindelöf and Johannesson

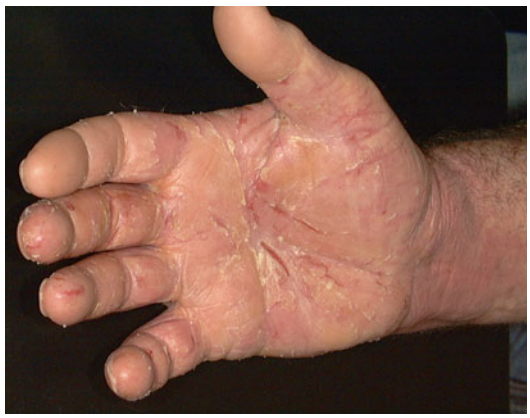

Fig. 5.3 Right hand dermatitis pretreatment

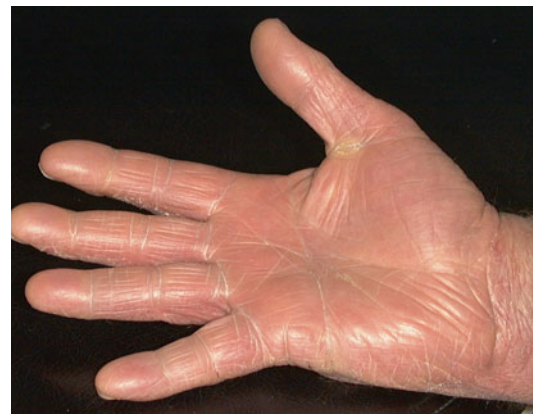

Fig. 5.4 Right-hand dermatitis posttreatment

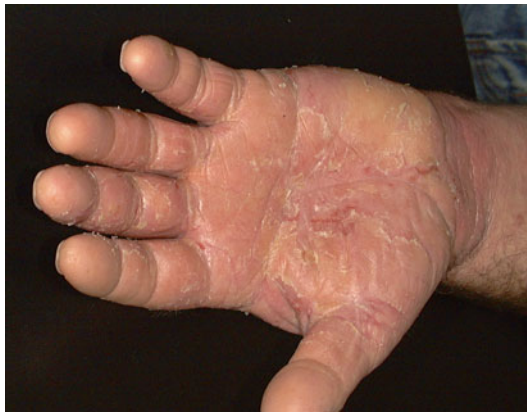

Fig. 5.5 Left-hand dermatitis pretreatment

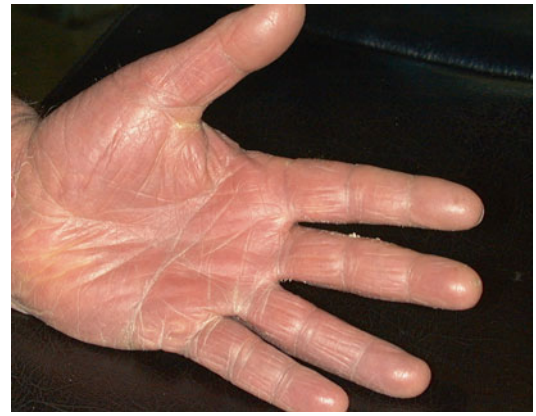

Fig. 5.6 Left-hand dermatitis posttreatment

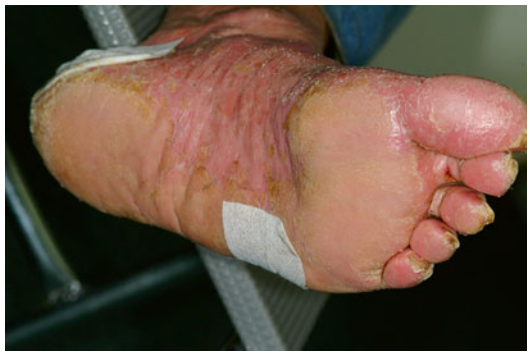

Fig. 5.7 Left-foot dermatitis pretreatment

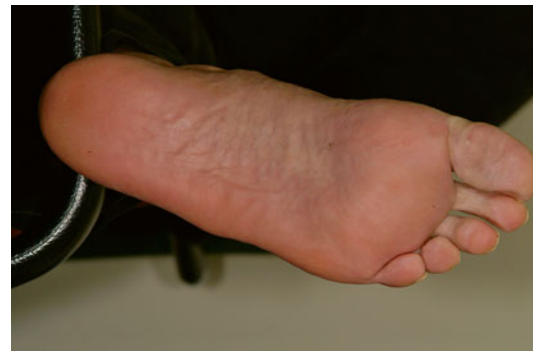

Fig. 5.8 Left-foot dermatitis posttreatment

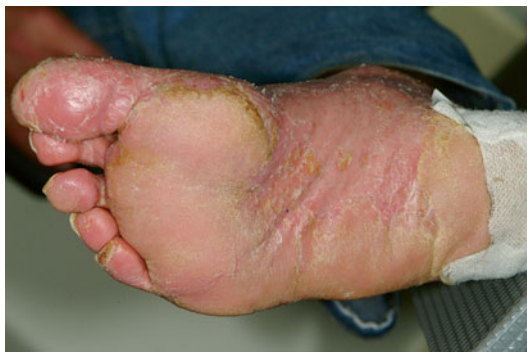

Fig. 5.9 Right-foot dermatitis pretreatment

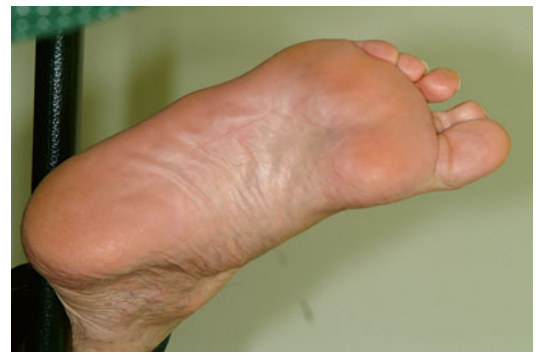

Fig. 5.10 Right-foot dermatitis posttreatment

performed a comparative randomised trial of grenz ray or topical corticosteroid and grenz ray therapy for treatment of scalp psoriasis – 84 % of grenz ray group and 72 % patients in the combination group healed – remission time did not vary between the groups and 5/16 patients in grenz ray only and 4/13 combination group remained healed at 6 months [28].

Frain-Bell and Bettley showed grenz ray (6–12 Gy) cleared psoriasis in 33 % patients after 4 weeks, but after 3 months only 18 % remain improved [9].

A quality assurance analysis of the grenz ray clinic at the Skin and Cancer Foundation, Victoria, 2003–2009 [53], with 150 patient responses (259 patients total) revealed 55 % patients had a recorded diagnosis of psoriasis. Three-hundred twenty-three fields were treated with ultrasoft X-rays with 137 cleared, 71 much improved, 23 slightly improved, 11 no improvement and 2 worse. 181/323 fields were evaluable for duration of response: 64 fields had not recurred, 12 had recurred after 12 months, 28 recurred within 6–12 months and 77 had recurred within 6 months. Areas treated were palms and palmar fingers 145, dorsum hand 47, soles 97 and dorsum of feet 34 (Tables 5.1, 5.2 and 5.3) These results are particularly encouraging considering all treated patients had failed topical treatment and most had failed UVB, PUVA and systemic therapies or combinations of these.

Table 5.1 Region of treatment by disease category

Diagnosis	Palm and fingers	Hand	Sole	Foot	Other	Not recorded	Total
Psoriasis	145	47	97	34			323
Dermatitis	127	79	32	6		1	245
Actinic keratosis					5		5
Lichen planus	2						2
Lichen simplex					1		1
Pompholyx	3						3
Not recorded	16	7	18	3	1	4	49
Total	293	133	147	43	7	5	628

Table 5.2 Patient's assessment of treatment by disease category

Diagnosis	Excellent	Very good	Good	Neutral	Bad	Very bad	No response	Total
Psoriasis	175	65	40	34	4	5	-	323
Dermatitis	85	62	66	24	6	–	2	245
Actinic keratosis	4	–	–	–	–	–	1	5
Lichen planus	–	–	–	2	–	–	–	2
Lichen simplex	–	–	–	1	–	–	–	1
Pompholyx	1	–	2	–	–	–	–	3
Not recorded	27	7	9	6	–	–	–	49
Total	292	134	117	67	10	5	3	628

Table 5.3 Response to treatment

Diagnosis	Cleared	Much improved	Slight improvement	No improvement	Got worse	Cannot remember or don't know	No response	Total
Psoriasis	178	101	20	23	0	1	0	323
Dermatitis	137	71	23	11	2	0	1	245
Actinic keratosis	0	4	0	0	0	1	0	5
Lichen planus	0	0	0	2	0	0	0	2
Lichen simplex	0	0	0	1	0	0	0	1
Pompholyx	3	0	0	0	0	0	0	3
Not recorded	28	16	3	2	0	0	0	49
Total	346	192	46	39	2	2	1	628

In summary there is evidence of benefit for grenz ray therapy for psoriasis on scalp, hands and feet. There are no comparative trials of grenz ray therapy with any therapy for psoriasis involving hands and feet.

Grenz ray has been shown to be helpful for nail psoriasis in a double-blind trial but only if nail thickness is normal and the benefit was modest [24] (Figs. 5.11, 5.12, 5.13, 5.14, 5.15, 5.16 and 5.17).

5.7.3 Palmoplantar Pustulosis

Lindelof and Beitner have demonstrated benefit of grenz rays for this condition in a double-bind

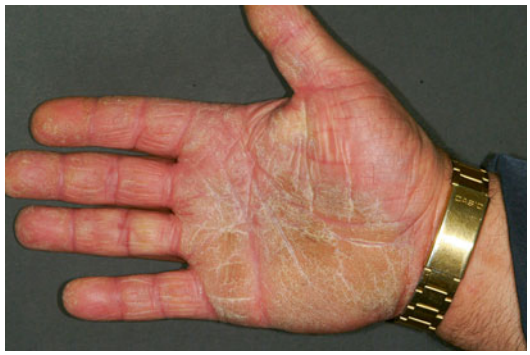

Fig. 5.11 Hand dermatitis pretreatment

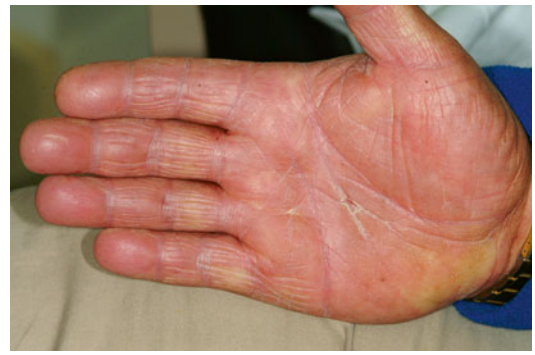

Fig. 5.12 Hand dermatitis posttreatment

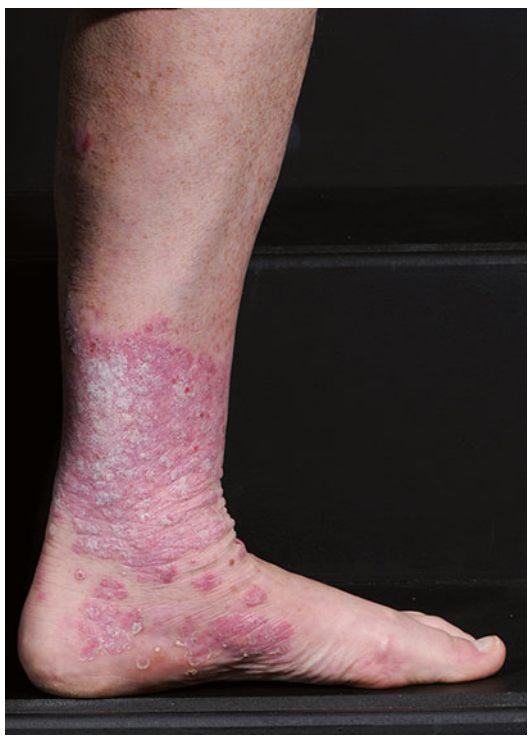

Fig. 5.13 Left leg psoriasis pretreatment

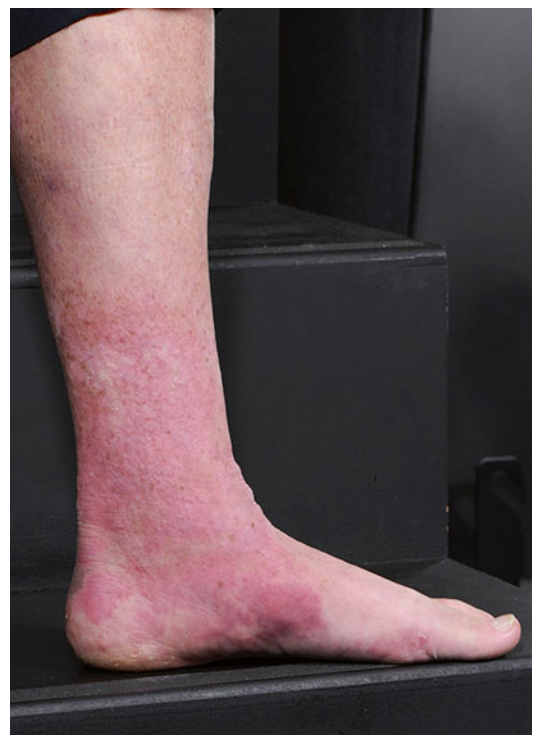

Fig. 5.14 Left leg psoriasis posttreatment

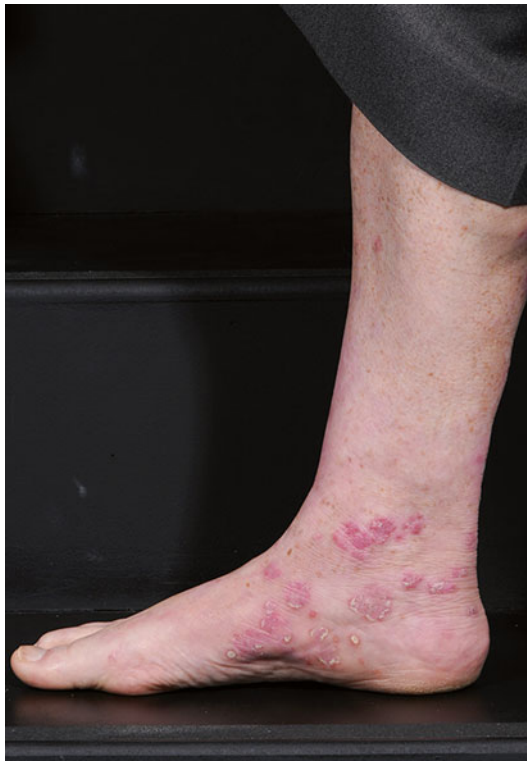

Fig. 5.15 Right leg psoriasis pretreatment

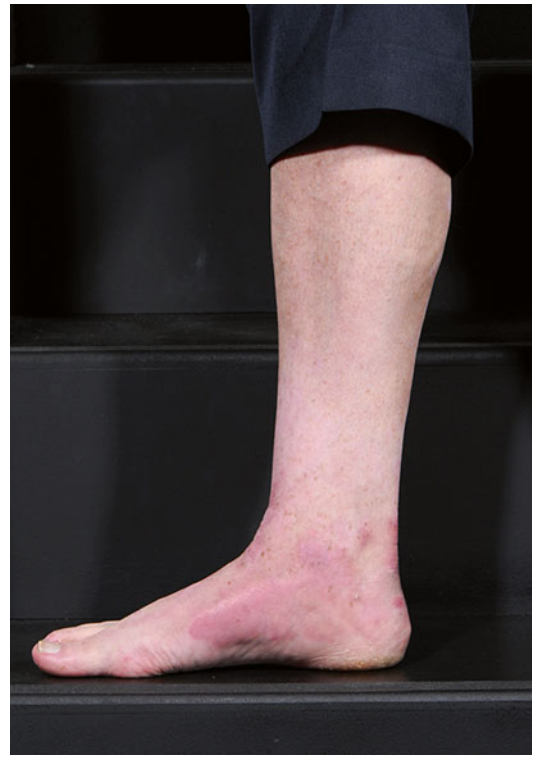

Fig. 5.16 Right leg psoriasis posttreatment

trial with weekly treatment for 6 weeks compared to placebo [26]. They concluded that grenz ray could be used as an adjunct. A Cochrane Skin Group Review concluded that grenz ray therapy may be useful for chronic palmoplantar pustulosis [32]. In my experience it responds to ultrasoft X-ray but recurrence is usual.

5.7.4 Actinic Keratoses and Bowen's Disease

Lewis describes his experience at the Denver Skin Clinic of more than 40,000 grenz ray treatments for actinic keratoses [23]. He used 15 Gy in a single exposure for the face with hand and forearm lesions having 15–20 Gy in a single treatment. He describes an erythematous reaction (similar to 5 fluorouracil but with less discomfort) starting at 7th–11th posttreatment day peaking at day 17–22 and generally fading by day 50. He states a recurrence rate of 5 % at 3 years. He states that he has not seen evidence of radiodermatitis in patients he has treated (up to 22 years following treatment) despite ongoing sunlight exposure – he does not mention malignant transformation. Beneficial response can be seen with lower doses 6×4 Gy weekly (personal experience) and 4×6 Gy weekly (as recommended by Panizzon, personal communication). There appears to be no advantage to high-dose single therapy compared with fractionated therapy – no comparative trials have been reported.

The author advises caution in using grenz ray for actinic keratoses – particularly for face – as there are a number of reports of radiation induced thyroid cancer, salivary gland cancer and multiple skin cancer following radiation for benign facial and scalp skin conditions [37, 46].

There is a limited role for grenz ray treatment for persistent actinic keratoses when alternative therapies are ineffective. The author has used ultrasoft X-rays for treatment of extensive actinic

Fig. 5.17 Robyn, technician treating patient at Skin and Cancer Foundation Victoria

keratoses and Bowen's disease on legs and scalp when all other alternatives have failed with benefit.

Stevens et al. reported on treatment of Bowen's disease: 19 patients were treated with grenz ray – total dose 50 Gy given 5 Gy fractions two to three times per week. Two had recurrences average follow-up 51/2 years (11/2–121/2 years). Twelve were reported as excellent cosmetic outcome, four good and one fair. Recurrence rate of 10.5 % compared well with 20 % reported for excision – most lesions were treated with curettage and electrodesiccation with 9.6 % recurrence rate [47]. The authors felt that the recurrences with grenz were due to its limited penetration and suggested that biopsies be taken to assess the thickness of the atypical epidermal hyperplasia and treatment adjusted for this. Stratum corneum can be removed to enhance grenz ray penetration. The authors suggest that grenz ray be considered for lesions located on cosmetically or functionally important areas, such as nose, eyelid or fingers where surgery might give less acceptable results; large lesions; anticoagulated patients or patients who refuse surgery. Ultrasoft X-rays with higher penetration may be more suitable. Superficial radiotherapy may give more consistent results because of its even greater penetration but is inadvisable on the lower legs (delayed or poor healing) or upper eyelids (possible keratosis of palpebral conjunctiva).

Bodner reported on the use of the photon radiosurgery system (PRS) for treatment of non-melanoma skin cancers [2]. The PRS is a portable device which produces low-energy X-rays from the tip of a needlelike probe at a high-dose rate. The 50 % depth dose of this system is 1.5 mm. They found an overall response rate at 12 months of 100 % for basal cell carcinomas, 83 % for squamous cell carcinomas and 95 % for Kaposi's sarcoma. This modality needs further investigation.

5.7.5 Lentigo Maligna

Hedblad and Mallbris have reported on treatment of lentigo maligna and early lentigo maligna melanoma with high-dose grenz ray [13]. Farshad et al. reported on a retrospective study of 150 patients with lentigo maligna and lentigo maligna melanoma using grenz or soft X-rays [7].

5.8 Side Effects and Carcinogenesis

The primary side effects are erythema and hyperpigmentation and are usually temporary particularly with low fractions. Hyperpigmentation is most commonly obvious where shielding produces a sharp demarcation between the treated and untreated skin.

The carcinogenic potential of grenz ray has been demonstrated in experimental animals.

Kalz in 1959 was the first to report squamous cell carcinoma on a finger of a dermatologist who carelessly exposed his hand to grenz ray [18].

Frentz, in 1989, reported grenz ray-induced nonmelanoma skin cancer: a literature review showed 13 reported cases and 28 cases were reported. Most patients had been exposed to other carcinogens (UV tar thorium radium arsenic sunlight) and with a few exceptions most had more than 100 Gy [10].

Lindelöf and Eklund conducted a study of patients treated at the Karolinska institute from 1949 to 1975. A total of 14,237 patients received grenz ray; 14,140 patient records were evaluable [27]. Average follow-up time was 15 years. The Swedish Cancer Registry was searched for malignant skin tumours (basal cell carcinomas are *not* recorded). Expected number of malignancies was calculated on the basis of age and sex standardised incidence data from the Swedish Cancer Registry. In 58 patients a skin malignancy was diagnosed 5 years or more after grenz ray therapy: 19 melanomas (expected 17.8) and 39 other (expected 26.9) (SCC32, basosquamous 5, 2 Kaposi's sarcoma). None of the patients with melanomas and only eight of the patients with other skin malignancies had grenz ray at the site of the tumour – most of these were on the lower limbs and 6/8 had been exposed to other carcinogens, and three of the patients had two additional known carcinogens to the tumour site. All patients had less than 100 Gy grenz ray total dose. Furthermore 481 patients had more than 100 Gy with only one patient having a skin cancer in a nonirradiated site. The risk for SCC was reported as 0.2 per 10,000 persons/Gy.

It has been suggested that grenz ray exposure to an area should be limited to 100 Gy lifetime dose [27].

Although a full discussion re radiation carcinogenesis is beyond the scope of this chapter, current theory re radiation-induced tumours is that there is a linear relationship between exposure dose and induction of tumours without threshold. Extrapolation of data obtained from high-dose exposure however may overestimate the risk at low doses suggesting a threshold [38]. It is the author's opinion that, although keeping the total dose of grenz ray less than 100 Gy will tend to reduce the risk of subsequent cancer, it does not ensure it and that essentially all radiation has to be considered carcinogenic. The inherent risk of developing skin cancer for the area being treated and the past actual and future likely exposure to other carcinogens particularly sunlight and UV exposure has to be taken into account when deciding whether to treat a particular area with grenz ray.

Conclusion

Grenz ray and ultrasoft X-rays remain useful for refractory dermatoses and psoriasis and are useful in selected cases of actinic keratoses and Bowen's disease. It can be performed with a minimum of risk provided; guidelines given above are followed. The availability of new equipment now allows this treatment to be performed reliably. The lack of knowledge of the benefits of grenz ray and the limited training opportunities for dermatologists appear to be the biggest hurdle to having greater access to this useful treatment.

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Superficial Radiation Therapy in an Office Setting

6

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Contents

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6.1 Introduction

Ionising radiation was an important part of dermatological therapy for many decades of the twentieth century. Its use in more recent years has diminished but continues to be a useful tool in properly selected cases. Several factors have resulted in this reduced application. The discovery of systemic and topical steroids and the development of new surgical procedures have provided effective alternatives. The negative connotations of Hiroshima, Nagasaki, Three Mile Island and Chernobyl have exaggerated the public's adverse view of radiation, and patients are sometimes wary of selecting radiation as a treatment alternative.

Although federal- and state-mandated protocols and safety measures have reduced the risk of accidental exposures and have promoted proper patient care, most patients are unaware of these safeguards. Moreover, these safeguards have led to added expenses for the treating physician to comply with regulatory guidelines and mandatory site surveys and annual calibrations by qualified physicists. In a New York Times front page

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article dated February 10, 2010, titled *F.D.A. to Increase Oversight of Medical Radiation,* errors in dosage of imaging radiation were outlined. The FDA is proposing that radiation doses be displayed and an alert be issued if doses are exceeded on the equipment panel. The information would then be transmitted to the patients' electronic medical record and to national dose registries. This recommendation for diagnostic equipment will most likely be applied to therapeutic equipment as well as making many of the current machines used in dermatologists offices noncompliant. These changes will likely take a few years to be implemented.

As a result of these changes, most dermatological residency programs in the USA no longer offer specific training in radiation therapy. The number of related questions on the Dermatology Certification Boards has dwindled, and many US dermatologists sadly are unaware of the benefits of radiation therapy or proper patient selection. The American Academy of Dermatology continues to offer a perennially well-attended session on "dermatological radiation therapy" at its annual meeting, and, at the time of writing, approximately 60 US dermatologists are members of the International Dermatologic Radiotherapy Society.

In Australia, currently all dermatologists have received training in *superficial therapy* during their registrar (residency) training and are required to observe the setup of a minimum number of patients (currently set at 5) for treatment of malignant disease (although the apparatus may be restricted to the use of licenced personnel).

The authors believe that with new cost-saving measures being implemented in health care, the economic value of radiation therapy will be realised and dermatological radiotherapy will have a stronger role in patient care. This can be achieved by a modest increase in reimbursements for in-office radiotherapy procedures. Savings over surgical procedures would still be substantial. We also believe that with the right equipment and training, dermatologists are well suited for treating dermatological diseases with radiation.

6.2 Selecting a Unit for Your Personal Office

Sensus Healthcare sells a superficial X-ray unit SRT 100 which can produce superficial X-rays up to 100 kV HVL 2.1 mm Al (it cannot deliver Grenz ray).

www.sensushealthcare.com. Although based in the USA, Sensus does supply to a number of countries.

Xstrahl (formerly Gulmay Medical) manufactures a number of superficial and orthovoltage systems suitable for in-office treatment and offers the benefit of being able to be configured to provide Grenz ray. These machines are available in many countries in Europe, USA and Australia. One of the authors uses a Gulmay D3100.

Another option is offered in the USA by Intraop Medical where a portable electron beam machine Mobetron is brought to the office to provide treatment. This machine is quite large and may not fit in all offices.

Occasionally, used equipment may be available when Oncology Departments upgrade their equipment. Older units may be found by word of mouth from members of the International Dermatological Radiation Therapy Society. Because of their durable construction and simple design, older units are often an attractive alternative, although spare parts and maintenance can sometimes be difficult to obtain.

Proper installation by a qualified installer is required. Radiation physicists, which can be found at hospital radiation therapy centres, can be helpful in contacting these qualified installers. They also can become invaluable colleagues when the newly installed unit requires field survey and calibration.

6.3 Administrative Guidelines

The precise rules that govern the use of superficial X-ray-producing equipment vary from location to location. However, several common principles apply universally. Practitioners need to be able to demonstrate a minimum level of proficiency. The

room in which the X-ray unit is housed must meet specified shielding requirements to protect both medical staff and visitors to the facility. Periodic calibration of the equipment must occur and be documented properly. Appendix 1 details specific examples of these principles for American and Australian facilities.

6.4 Why Perform Superficial Radiotherapy?

In the authors' opinion, dermatological radiotherapy holds its strongest case for the treatment of uncomplicated non-melanoma skin cancer, and we believe that this should be performed by dermatologists.

Superficial radiotherapy, of course, can be used for treatment of cutaneous lymphoma especially nodules and thick plaques, Kaposi's sarcoma, lymphocytoma cutis and keloids.

Grenz ray therapy with its limited penetration is more suitable for treatment of benign dermatoses and premalignant conditions.

Patient satisfaction is high with outpatient dermatological radiotherapy. In a study performed at the Skin and Cancer Foundation Victoria, in Melbourne, on patients undergoing superficial radiotherapy for non-melanoma skin cancer, the patients were asked to rate the outcome of their treatment and also the cosmetic outcome of their treatment. Of the 245 respondents, that is, 71 % of patients (with 341 treatment fields) replied, with outcomes rated as 76 % excellent, 21 % good, 3 % average and one patient reporting a poor result. Cosmetic outcomes rated by the patient were 61 % excellent, 32 % good, 6 % average and 1 % less than average or poor. The maximum follow-up period for the study was 8 years [18].

Caccialanza et al. [3] has also reported on physician-assessed cosmetic results reporting good or acceptable cosmesis in 90 % patients for up to 1-year posttherapy, 80 % 3–5-year posttherapy and 76 % 9–12-year posttherapy with small treatment areas having better cosmesis than larger areas [4].

Superficial X-ray therapy is most suitable for treatment of non-melanoma skin cancers in the head and neck area where:

1. Patient refuses surgery (fear of surgery or needle phobia).
2. Patients who are not medically fit for surgery or who are relatively contraindicated for reconstructive surgery, e.g. patients on anticoagulants, patients who are unfit for general anaesthesia.
3. Where radiotherapy may be a simpler option than extensive reconstruction or prosthesis, especially alar rim and columellar of nose, helix of ear and some inner canthus lesions (Figs. 6.1 and 6.2).
4. Where radiotherapy may give a better (at least in the short term) cosmetic outcome, e.g. philtrum of upper lip and oral commissure (Figs. 6.3 and 6.4).

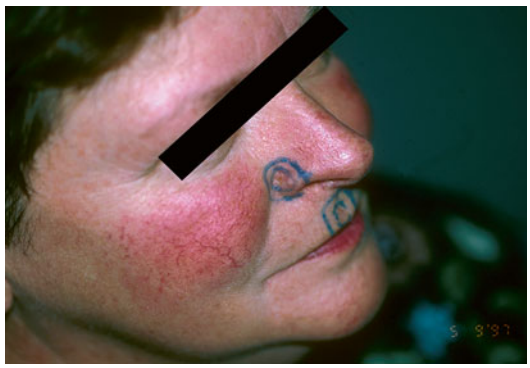

Fig. 6.1 Columella, ala rim and base of nostril SCC presenting a challenge to surgically repair without prosthesis

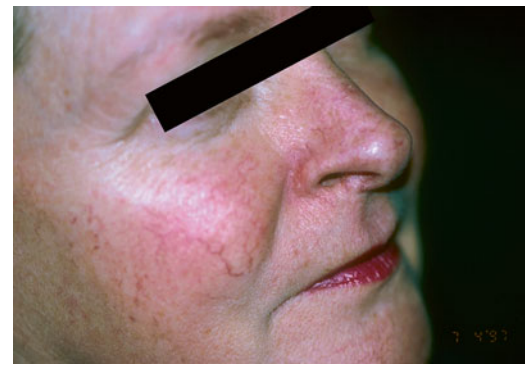

Fig. 6.2 Good cosmetic result 2 years following treatment

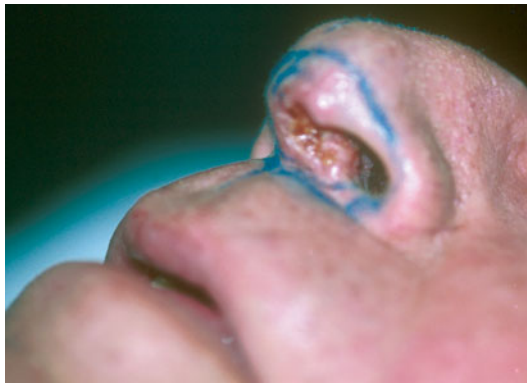

Fig. 6.3 Right ala nasi and philtrum of upper lip BCCs pretreatment

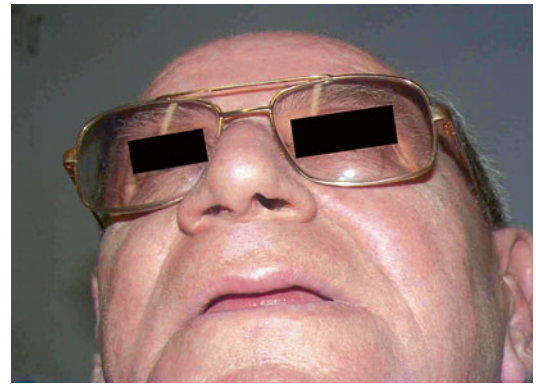

Fig. 6.4 Following completion of treatment, good cosmetic result not obtainable by surgery

5. Where surgery may cause nerve damage or functional impairment, e.g. tumours overlying spinal accessory nerve or marginal mandibular nerve.
6. Patients with deep or lateral marginal involvement following excision of tumours, where further surgery is not feasible, not likely to be tolerated or refused.
7. Patients with high risk of microscopic residual disease, e.g. completely excised tumours with perineural invasion with no clinical signs of perineural invasion, or following curettage of poorly differentiated squamous cell carcinomas.
8. Selected patients with small volume or marginal recurrent disease following surgery (in these cases, the area should include the full length of the surgical scar and a generous margin).

Opinions differ regarding suitability of morpheic BCC for superficial X-ray therapy. Although there may be a higher risk of recurrence with radiotherapy (as there is for all other forms of therapy) and reported cure rates vary [7], we will use radiotherapy for morpheic BCC selecting larger margins and more penetrating qualities.

We avoid treating middle third of the upper eyelid to avoid the risk of keratinisation of the palpebral conjunctiva and also avoid treating scrotal skin.

We generally insist on biopsy confirmation and if there is doubt to the extent of the lesion, then biopsies to assess the extent of tumour are taken.

Debulking tumours will reduce acute reactions and may allow the use of less penetrating X-ray qualities. We generally use the same doses for basal and squamous cell cancers.

Treatment on other areas of the body is usually only considered if surgery or other treatments are not feasible and should be avoided below the knee because of very slow healing times. (Multiple fractions or hyperfractionation should be considered if X-ray is used in poor healing sites.)

Patients should be over 50 years of age, not pregnant, able to give informed consent for treatment (acknowledging the risks of developing a radiation induced scar and the very low risk of future skin cancer development in the site) and be able to attend for fractionated treatment. This latter requirement is often the most difficult treatment-limiting step. They should obviously not have a contraindication to radiation treatment such as idiosyncratic reactions, sister chromatid exchange deficiency syndromes, Gorlin's syndrome, ataxia telangiectasis or previously irradiated tumour.

Very large tumours or tumours with bone involvement, Merkel cell carcinoma, malignant sweat gland tumours and named nerve perineural invasion are all best treated at specialised oncology/radiation treatment centres and are beyond the scope of office radiotherapy [9].

Current opinion in Australia is that melanoma is beyond the scope of superficial X-ray therapy treatment [6] although this view is not universally

held and lentigo maligna is treated successfully with superficial radiotherapy in many parts of the world. (The treatment of lentigo maligna and melanoma will not be discussed further in this chapter.)

6.5 Selecting Radiation Quality

In selecting radiation quality, there must be adequate hardness of the radiation beam to penetrate to kill the deep aspect of the tumour whilst minimising harm to surrounding normal tissues.

The ultimate dose will be determined by the size, depth and anatomical location of the tumour. Thick tumours may be surgically debulked to allow them to be treated by less penetrating qualities of superficial radiation.

There are differing philosophies used at different centres to determine the X-ray quality.

6.5.1 D1/2 Philosophy

Select the radiation quality which will deliver the half-value depth (the distance from the skin surface where the skin surface dose has been reduced to 50 %) at the base of the tumour. The depth of the tumour can be estimated clinically or by histology. This approach generally utilises X-ray qualities less than HVL 1 mm Al. There is a risk of underdosing the deep aspect of the tumour if the depth is underestimated.

6.5.2 Ninety Percent Isodose Philosophy

The entire tumour should be within the 90 % isodose line to ensure homogeneity of dose. This generally utilises more penetrating radiation (or electrons). This approach is often employed by radiation oncologists who have access to more penetrating X-ray equipment and electron beam therapy and decreasing access to dermatological superficial X-ray machines.

6.5.3 An Intermediate Position

Select radiation quality which allows 70–80 % superficial dose at base of tumour. The Australasian College of Dermatologists suggests a modification of this approach where an additional margin of 2.5 mm is added to the estimated thickness of the tumour [6].

The latter two philosophies risk exposing tissues deep to the tumour to radiation [2].

In general, radiation qualities ranging from HVL 0.5 mm Al to HVL 4 mm Al will be adequate to treat skin malignancies likely to be treated by dermatological radiotherapy.

In one of the author's practice, the approach is fairly simple: HVL 1 mm Al for thin Bowen's disease and superficial BCCs and HVL 2 mm Al for SCCs, nodular BCCs and morpheic BCCs.

Despite these varying philosophies, it appears that actual cure rates are comparable:

Silverman et al. published results of treatment of 5,755 basal cell carcinomas treated at the New York University Skin Cancer Unit between 1,955 and 1982 – the 5-year recurrence rates were 13.2 % for curettage and electrodesiccation, 4.8 % for excision and 7.4 % for X-ray therapy [15]. And a further article on X-ray therapy (1,288 cancers) showed essentially no difference in failure rates for recurrent carcinomas versus primary tumours [16].

Caccialanza et al. reported results of 1,188 patients with 2002 primary malignant epithelial neoplasms treated from 1982 to 1995 – complete remission in 98.7 % and 5-year cure rates of 90.73 % [3].

Caccialanza et al. have also reported on recurrent basal and squamous cell carcinomas 45–70 Gy with 5-year cure rate 83.62 %, with acceptable or good cosmesis in 92.62 % of treated lesions in complete remission [4].

There are varying opinions about the suitability of morpheic basal cell carcinomas for radiotherapy –recurrence rates are higher. Bart et al. showed that morpheic basal cell carcinomas are radioresponsive [1], Wilder et al. showed that morphea-form basal cell carcinomas treated with a 1 cm margin were controlled with radiation therapy with no statistically significant difference

versus other histological subtypes (using orthovoltage and electrons) [19], but Pannizon showed 22 % recurrence rate in 36 basal cell carcinomas with sclerosing component [8] utilising D1/2 approach.

It is the authors' opinion that although Moh's micrographic surgery or wide excision is preferable, radiotherapy can be used if larger margins both laterally and deeply are considered (1 cm margin, higher HVL).

6.6 Radiation Dose

6.6.1 Non-melanoma Skin Cancer

The biological effect of radiation is not only dependent on the dose but the time that the dose is delivered over. Neoplasms tend to repair the damage from X-rays slower and less completely than normal tissues, and therefore, if the dose is fractionated sufficiently, then the tumour will have time to accumulate lethal damage whilst allowing normal tissues to recover. In general the more fractions, the less dose per fraction is required, the longer the total treatment time and the more radiation delivered.

Although there are numerous treatment schedules practiced around the world, cure rates are roughly the same [9]. The more fractions given, the better the cosmetic result will be and the less necrosis seen [9]. It also appears that the less dose underlying tissues get, then the better the cosmetic result is likely to be. The cosmetic benefits of more fractions has to be weighed up against the often considerable logistic problems in getting elderly patients to the treatment centre. A 2–3-week course of therapy is probably just as effective as a prolonged course of treatment for small tumours [9].

Single-fraction radiotherapy for small superficial carcinoma of the skin was reported by Chan et al. [5]. For field size less than 3 cm in diameter, 20 Gy HVL 0.45–1 mm Al had less late skin necrosis compared to 22.5 Gy with no significant difference in tumour control, apart from inner canthus lesions. Although follow-up was limited to 18 months, using Kaplan-Meier analysis, the disease-free survival rate and necrosis rate was reported as 90 and 84 %, respectively, at 5 years. In another study by Hliniak et al., 20 of 25 lesions were controlled (3 years or more follow-up) with single-dose radiation (130 kV, HVL 2 mm Al 22–26 Gy). In this study for the 20 tumours in 8–16 square cm field size, the dose for 50 % tumour control was 22 Gy; 50 % necrosis dose was 24.6 Gy [12]. Trott et al. has stated that for small skin cancers less than 1 cm in diameter, single-dose irradiation is as good as any fractionation schedule – 50 % control dose was 18.2 Gy; 10 % necrosis, 20.2 Gy; and 50 % necrosis, 24.5 Gy, but as tumour size is the most important single factor determining cure that for big tumours uncomplicated 80–90 % 3-year local control can only be obtained with high total doses given in a fractionated course with low doses per fraction [17].

It is the author's opinion that single-dose therapy should be reserved for the very infirmed or elderly patient not able to tolerate or consent to definitive surgery with small tumours who cannot attend for fractionated treatment. If possible, tumours should be debulked – one of the authors uses 20 Gy.

The factors that affect the response of tumours to fractionated therapy are multiple, and clinical data relating dose and fractionation to tumour cure and early skin side effects have been compiled into time-dose fractionation (TDF) tables – cure of non-melanoma skin cancers requiring TDF number between 90 and 110 [8, 14]. However, large or recurrent tumours probably do require higher TDF [8]. The volume of tissue irradiated also determines cure rate and side effects with larger volumes generally resulting in lower cure rates [17] and more side effects than smaller volumes unless more fractions (and hence higher total doses) are used. The overall treatment time may also affect cure – in a study by Hlinak [12] in squamous cell carcinomas treated with 60 Gy in 40 fractions, the recurrence rate decreased from 88 to 37 % as overall treatment time decreased from 70 to 45 days (only 2 of 78 tumours were less than 10 cm^2 field size) . Modifications to TDF and linear quadratic equation modelling have been proposed that account for the volume of tissue irradiated [13].

A number of standardised treatment schedules have been developed (see Table 6.1, [9]). The

Table 6.1 Radiation dose schedules for cutaneous neoplasms

Tumour diameter/ type	Dose per fraction (cGy)	No. of fractions	Fractions per week	No. of weeks	Total dose (cGy)	TDF factor
<4 cm	500	8	5	1 3/5	4,000	108
	500	10	5	2	5,000	135
	400	12	5	2 2/5	4,800	115
>4 cm	300	15	5	3	4,500	92
	300	20	5	4	6,000	123
	300	19	3	6	5,400	102
	300	20	3	6 2/5	6,000	111
BCC	680	5	2	2 1/2	3,400	94
SCC	680	8	2	4	5,440	152
<2 cm	800	5	1	5	4,000	109
2–8 cm	400	12	2	6	4,800	96
>8 cm	200	26	2	13	5,200	81
All carcinomas	300	15	5	3	4,500	92
	300	18	5	3 1/5	5,400	111
	300	22	5	4 2/5	6,600	135
	200	30	5	6	6,000	99
	200	34	5	6 1/5	6,800	112
	200	40	5	8	8,000	132

authors use a schedule of 9×4.5 Gy (three times per week for 3 weeks) or 6×6 Gy (two times per week for 3 weeks). If the tumour is larger, 15×3 Gy (five times per week for 3 weeks) or 30×2 Gy (five times per week for 6 weeks) are occasionally used.

6.6.2 Cutaneous Lymphoma

Other chapters in the book specifically outline treatment of cutaneous lymphomas. Many of these lymphomas can successfully be treated in the office with superficial X-ray. The classification of lymphomas is constantly evolving and based upon histological, clinical and immunological criteria. Although there is a spectrum of lymphomas, they are basically divided up into B- and T-cell types.

Mycosis fungoides patients make up the majority of the T-cell lymphoma treatment candidates. A typical patient in an office setting would usually be under treatment with PUVA, narrowband UVB or topical therapy. The development of persistent plaques or small tumours that are unresponsive to therapy would be candidates for in-office radiotherapy. Radiation therapy is given in small doses of 75–250 cGy at weekly to twice weekly intervals until the lesion shows involution. A therapeutic response can be seen after a total dose of only 200–1,000 cGy. A favourable response is often seen within the week of the first treatment. More extensive disease is best treated with electron beam therapy.

Cutaneous B-cell lymphomas such as follicular centre cell lymphoma and marginal zone lymphoma have an indolent behaviour. Low doses of 100–250 cGy given one to two times weekly can result in complete remission with total doses less than 3,000 cGy. Large B-cell lymphoma of the leg has an intermediate prognosis with a 5-year survival rate of 50 %. This usually presents as erythematous nodules on the lower extremities in elderly females. It has a similar response, in localised treatment, to the other cutaneous B-cell lymphoma doses.

6.6.3 Kaposi's Sarcoma

With the development of effective antiviral therapy for HIV, incidence of epidemic Kaposi's sarcoma has dropped considerably; however,

occasional cases are still seen. 300 cGy administered twice weekly for three to six treatments is usually sufficient to achieve complete remission of localised lesions. Classic Kaposi's sarcoma responds well to 200–400 cGy given once weekly for two to six treatments.

6.6.4 Radiation Treatment of Benign Tumours

Lymphocytoma cutis has been successfully treated with low-dose radiation therapy. Doses of 100–250 cGy can give him 1–3 week intervals. Response is seen in as few as one treatment. Rarely more than 4 or 5 fractions are needed. This tumour was previously thought to be benign; however, recent studies have suggested that some may be a low-grade lymphoma. Successful treatment of keloids is best done immediately post excision or within the first 6–12 months of development of the lesion. Dosage schedules vary but 100–300 cGy given one to three times weekly with total dose between 400 and 2,000 cGy give best results. Doses over 1,500 cGy may result in pigmentation telangiectasia and atrophy.

6.7 Radiation Sequelae

Radiation effects on the skin will not be discussed in detail here. An expected acute radiodermatitis is produced by cancer treatment utilising the schedules as outlined above. Erythema begins usually after the fourth or fifth treatment and then a third- to fourth-degree reaction ensues which lasts 2–4 weeks after the last treatment. Treatment of the nose and lips can cause mucositis of underlying tissues which may precede the cutaneous reaction and last for several weeks after the skin has healed. Plain water compresses and lubricating ointments are soothing and antibiotic ointments may prevent secondary infection. Hair will be permanently lost from the radiation field. Some patients can develop comedones in the periphery of radiation fields on the nose, cheeks and ears. This reaction can respond to topical retinoids. Sometimes keratosis like nodules can develop usually in the periphery – so-called pseudorecidivism – these usually settle spontaneously. Occasionally a tumour may still be present 6 weeks or more after completion of therapy treatment. A biopsy at this time may still show basal cell carcinoma. But this may be delayed tumour regression, and with time the tumour can slowly shrink. If after 6 months of observation the tumour is still persistent, then it should be excised.

Although repeated small-dose X-ray over long time can induce new tumours in irradiated areas (as used in the past for some benign conditions), it is very rare for cancericidal treatment to cause secondary cancer. Ehring and Honda reported one of 2005 patients treated for basal cell carcinoma developed a second tumour 40 years after initial treatment, whereas 5 % of their patients treated had basal cell carcinoma developing in radiodermatitis caused by previous radiation therapy for benign conditions [9].

6.8 How We Perform Radiotherapy

At the Skin and Cancer Foundation Victoria, we calculate the time to turn on the radiotherapy machine for a given treatment by using the following formula:

$$\text{Time}(\text{min}) = \frac{\text{Dose}(\text{cGy})}{\text{BSF} \times \text{CCF} \times \text{output}(\text{cGy}/\text{min})}$$

where *dose* is the desired individual fraction dose, *BSF* is the backscatter factor, *CCF* is the cone correction factor and *output* is the measured dose rate produced by the X-ray machine under the conditions of use (i.e. including any filters placed in the beam)

The backscatter factor is determined by (a) the treatment area, (b) half-value layer (HVL) and (c) underlying tissue thickness which is usually assumed to be maximum (unless treating thin structures such as alar nasi, lip or ear where lead shields are placed deep to the incident beam to protect underlying structures such as nasal septum, gum or scalp, respectively). In this case, a bolus of wet gauze is used to aid stabilising the

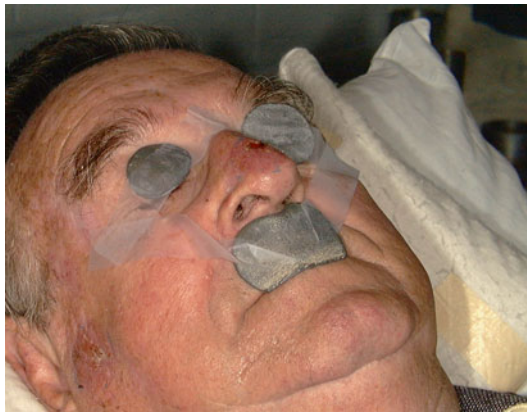

Fig. 6.5 Dorsum and supratip of nose BCC treatment – initial phase: external lead eye shields, upper lip protection

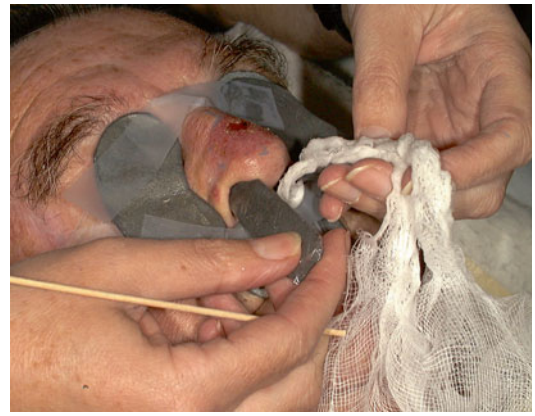

Fig. 6.6 Dorsum and supratip of nose treatment – second phase: insertion of internal nasal lead shields (wrapped in cellophane), insertion of moistened gauze to act as a bolus, cheek protection

treatment site and to maximise the backscatter factor. The underlying tissue thickness is gained from the thickness of the tumour, its underlying tissue and the bolus up to the lead shield.

The backscatter factor can then be read off from published tables.

CCF is cone correction factor and describes the attenuation of the beam caused by the use of the cones. This factor is given by the physicist or manufacturer of the equipment and is a constant for each of the treatment cones (although this seems complex, in practice backscatter factor multiplied by cone correction factor often is close to one). Output is calibrated by the physicist for a given machine at a specific focus-skin distance (FSD), also known as target-skin distance (TSD).

At other distances, output varies by the inverse square law (except in Grenz rays where X-ray attenuation area in air cannot be ignored). In certain situations, the FSD will need to be adjusted in treating concave surfaces such as the medial canthus, as it may not be possible to get the cone right down onto the skin level. There will therefore be a "stand off" which can be measured in situ, then the output of machine can be adjusted accordingly. For example, output of 15 cm is Y output of 15 cm plus 1 cm stand off is $Y \times 15^2 \div 16^2$.

In treating convex surfaces, e.g. tip of nose, edges of the treatment field will receive less cGys (as by inverse square law) – this is referred to as fall off. The effect of this can be minimised by extending the FSD as the difference will be less with longer FSD, e.g. $15^2/16^2$ is less than $30^2/31^2$ if assuming a fall off of 1 cm. and FSD 15 cm. Unfortunately, the greater homogeneity achieved comes at the price of far longer treatment times (four times longer in this example). (Radiation oncologists usually solve this problem differently, by custom building a bolus box to sit on the tip of the nose and treating with two cross-firing higher-energy beams).

Lead cutouts are fashioned to protect surrounding skin around the treatment area.

We use external eye shields and lead blankets routinely. Internal eye shields are also mandatory for lid lesions. Lead shields are used to protect nasal septum, when treating nose; protect gums when treating lips; and protect scalp, when treating ears. We use cellophane to decrease the effect of any characteristic X-rays induced by radiation of the lead. Lead cutout is fashioned to protect surrounding skin around the treatment area. For inner canthus areas, a round cutout with a slit in one side can be fashioned into a conical shape cutout to provide protection to surrounding areas. We generally select a cone at least 1 cm diameter larger than the cutout applied. This allows for patient movement during treatment. To ensure even irradiation of the treatment area, the maximum diameter of the field should be less than one third of the FSD. Example setups are shown in the accompanying figures (Figs. 6.5, 6.6, 6.7, 6.8, 6.9, 6.10, 6.11, 6.12, 6.13, 6.14, 6.15, 6.16, and 6.17).

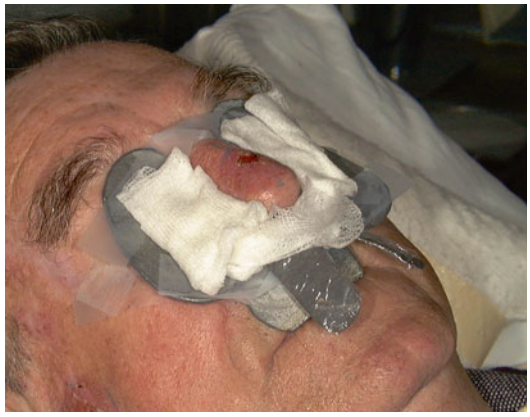

Fig. 6.7 Dorsum and supratip of nose treatment – third phase: moistened gauze (bolus) sides of nose

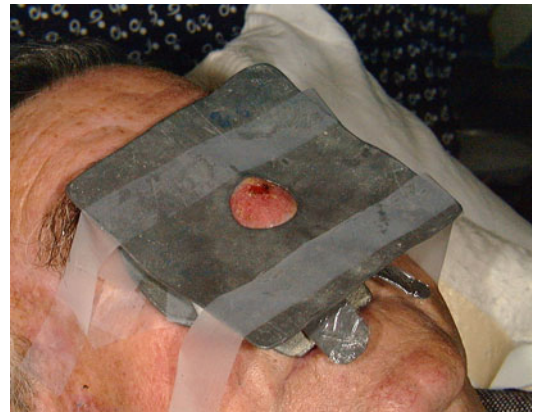

Fig. 6.8 Dorsum and supratip of nose treatment – final phase: cutout in place; treatment cone will sit on the cutout

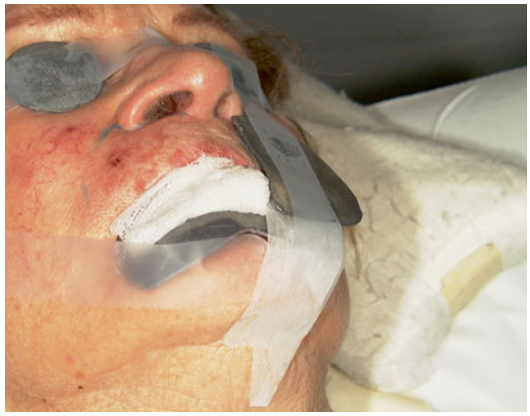

Fig. 6.9 Extensive upper lip BCC treatment – initial phase: external eye shields, internal mouth shield to protect gums, external upper lip shield, moistened gauze (bolus) to stabilise lip, increase backscatter factor and a surface for the lead cutout to sit on

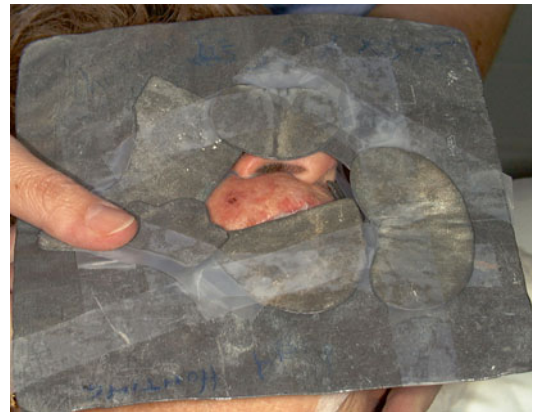

Fig. 6.10 Extensive upper lip BCC treatment: full lead shielding in place. Cone sits on this

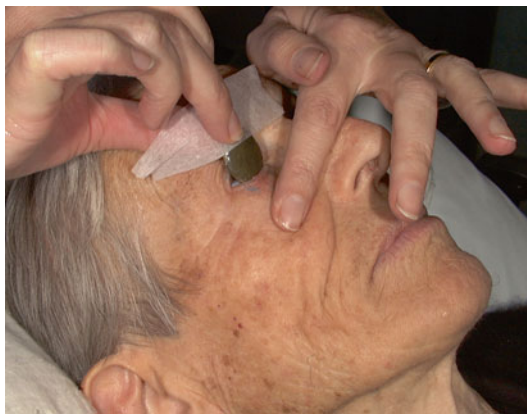

Fig. 6.11 Right lower eyelid BCC treatment: insertion of internal eye shield after local anaesthetic installation. This sits over the upper eyelid. Note surgical paper tape applied to help prevent shield popping out

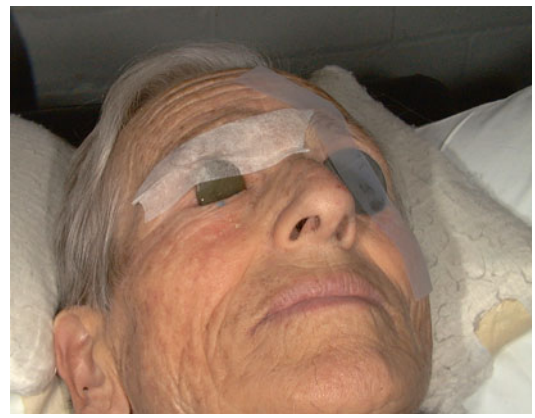

Fig. 6.12 Right lower eyelid BCC treatment: internal eye shield in place, external eye shield for left eye

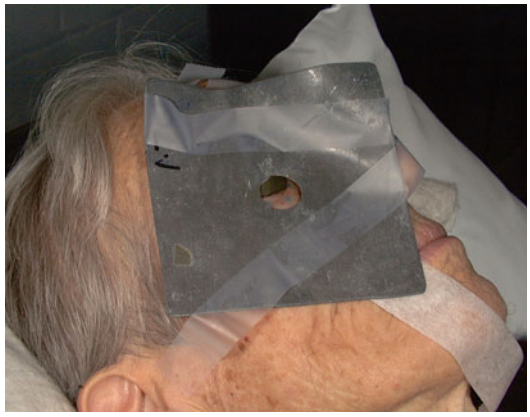

Fig. 6.13 Right lower eyelid BCC treatment: lead cutout in place which cone will sit on

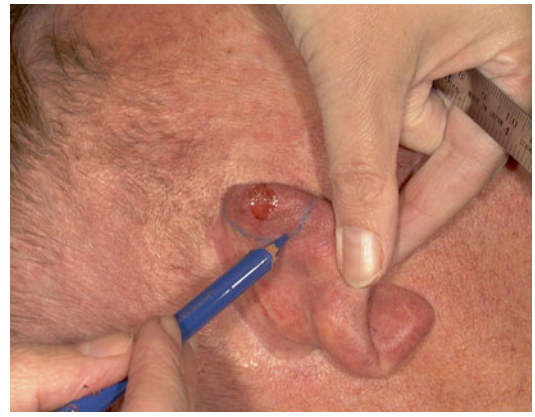

Fig. 6.14 Right ear superior helix BCC treatment: marking out area of treatment

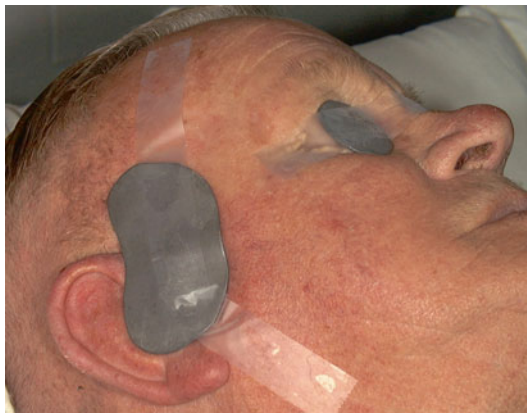

Fig. 6.15 Right ear superior helix treatment: preauricular lead shield (to protect sideburn hair), external eye shields

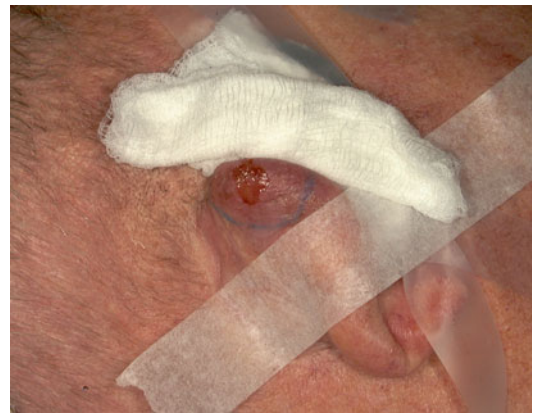

Fig. 6.16 Right ear superior helix treatment: ear turned forward, gauze bolus to allow treatment right up to edge of ear, to stabilise ear and to maximise backscatter

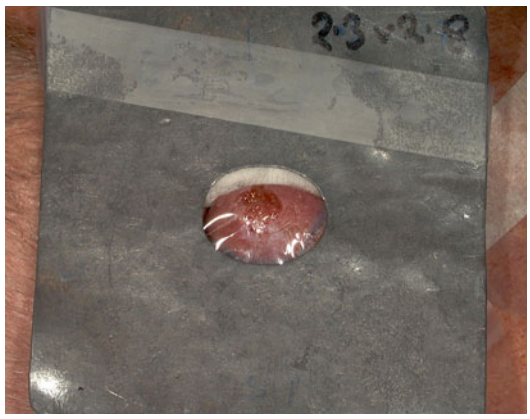

Fig. 6.17 Right ear superior helix treatment: lead cutout in place

Conclusion

The art of dermatological radiotherapy needs to be preserved, and if we can demonstrate knowledge, compliance and expertise in the area, it will ensure our future. Who best treats skin disease but those who are most familiar with its appearance and pathophysiology?

Acknowledgements The authors gratefully acknowledge the assistance of Robin Smale, radiotherapy technician at the Skin and Cancer Foundation Victoria, and Kathy Teagno, medical photographer, Skin and Cancer Foundation Victoria.

Appendix 1. A Comparison of Guidelines in the USA and Australia

Caution: The precise rules that govern the use of radioactive materials and X-ray-generating equipment vary from jurisdiction to jurisdiction. What follows is a generalised concept and *cannot* be substituted for the *exact* requirements of a specific location.

Training and Certification: USA

In the USA, the operator is required to obtain a licence from the appropriate city, state or national agency, which we will call the Department of Health here for simplicity. The licencee is responsible for all administrative requirements and implementation. A list of requirements is usually available from the Department of Health, Radiation Control Section. The Radiation Control Section evaluates the applicant and issues the licence. The licencee must be certified in radiology (common previously, but now rare) or therapeutic radiology (radiation oncology) by the American Board of Radiology or is active in the practice of therapeutic radiology and has completed 200 h of instruction in basic radiation techniques applicable to the use of an external beam radiation therapy unit, 500 h of supervised work experience and a minimum of 3 years of supervised clinical experience.

In addition, a licencee for any therapeutic machine of less than 500 kV may also submit the training of the prospective authorised user physician for department review on a case-by-case basis. The International Dermatological Radiotherapy Society is currently developing a certification exam for prospective clinicians.

Records

The licencee is required to maintain the following information in a separate file for each therapeutic radiation machine: (1) a report of acceptance testing; (2) records of all surveys, calibrations and periodic quality assurance checks; (3) records of all major maintenance or modifications; (4) the signature of the person authorising return of the machine to clinical use; (5) a log of all treatments done; (6) an individual patient record of the written directive and daily prescribed doses; and (7) recalibrations following maintenance or modification.

Protection Survey

The licencee is to ensure that radiation protection surveys of all new facilities (and existing facilities not previously surveyed) are performed with an operable radiation measurement survey instrument, which has been properly calibrated. The radiation protection survey shall be performed by or under the direction of a qualified medical physicist. Radiation physicists can often be found in radiation oncology departments.

Quality Management Program

A quality management program should be established to include written procedures and policies to meet the following objectives. (1) Before administration of a dose, a written directive is prepared to include the total dose, individual doses and fractionations. Any revisions should be noted, dated and signed by the authorised user; (2) the patient's identity should be verified by more than one method; and (3) treatment should be in accordance with the written directive.

Procedures are to be developed to review the quality management program. The reviews are to be conducted at least every 12 months. The reviews are to include (1) a representative sample of patient administrations, (2) all recordable events and (3) all misadministrations to verify compliance with all aspects of the quality management program. The reviews are to be evaluated to determine effectiveness of the quality management program and, if necessary, to make modifications to meet requirements. Records are to be kept for each review, including evaluations of findings and reviews.

Recordable Events

Recordable events include (1) any weekly administered radiotherapy dose 15 % or more greater than weekly prescribed dose, (2) radiotherapy delivered without a written directive, (3) radiotherapy delivered without recording the daily dose and (4) radiotherapy dose differs by more than 10 % of the dose outlined in the written directive.

In the event of a misadministration the licencee shall:

1. Notify the department by the next calendar day of the misadministration.
2. Submit a written report to the department within 15 days of discovery. The report is to include the licencee's name, the prescribing physicians name and a brief description of the event; why the event occurred; the effect on the patient; what improvements are needed to prevent event recurrence; actions taken to prevent recurrence; whether the licencee notified the patient or patients guardian and if not why not; and what information the patient was provided.
3. Notify the referring physician and also notify the patient of the misadministration within 24 h of the occurrence.
4. Retain a record of the misadministration.
5. Send a written report to the patient within 15 days.

Treatment Room Requirements

The treatment room should have continuous audible communication with the patient as well as continuous observation of the patient from the treatment control panel. Most therapeutic machines below 100 kV use cones and filters to ensure safety and limit over exposure. The site survey will ensure the safety of the surrounding areas. An indicator light should be in place to notify the operator and others that the machine is in use. Most machines have the required built-in timer and lock switch.

Site Inspection

Radiation diagnostic and treatment sites are subject to annual inspection by an official from the Department of Health to ensure compliance with all the administrative guidelines [10].

Training and Certification: Australia

In Australia, in all states, except South Australia, upon qualification, dermatologists are entitled to obtain a licence to operate radiotherapy apparatus of the superficial therapy type (less than 120 kVp). An operating licence is purchased from the relevant state health authority. The operator licence is provided subject to conditions; and in the case of dermatologists, in Victoria, this is for dermatological treatments. The conditions restrict the operating licencee to use an appropriately calibrated ionising radiation apparatus to ensure correct dosage administered to patients and that the operating licencee must ensure the radiation beam is collimated to the area of interest.

All machines even those in storage are licenced to a registered person. Disposal of an X-ray unit without notification to the Department is an offence. The use of individual machines is governed by conditions of the registration. The registered person must:

1. Provide appropriate radiation shielding in doors, walls, floors and ceilings of treatment rooms and appropriate shielding for operators is necessary to ensure no person receives radiation dose in excess of relevant radiation protection limit specified in Schedule 1 of the Health (Radiation Safety) Regulations 1994 [11].
2. Provide personal monitoring devices.
3. Be responsible for maintaining radiation safety.
4. Ensure apparatus is operated only by persons holding relevant operator licences.
5. Ensure that X-ray tube is fixed in housing so that the absorbed dose rate in air from the leakage radiation.
   (a) Does not exceed 10 mGy per hour at a distance of 1 m from the focus
   (b) Does not exceed 300 mGy per hour at any position accessible to the patient at a distance of 50 mm from the surface of the housing or accessory equipment

(c) In the case of an x-ray tube which is operated at potential 60 kV peak or below, does not exceed 1 mGy per hour at any position 50 mm from the surface of the housing or its accessory equipment

6. Ensure that any cones or diaphragms used comply with leakage exposure requirements as set above.
7. Control panel shows filtration used and kVp and MA, when these can be varied.
8. Ensure that any limiting diaphragm transmits less than 5 % of useful beam at maximal operating kV and filter in position.
9. Ensure the X-ray tube is fixed in housing and remains stationary during stationary treatment.
10. Ensure the control panel shows when X-rays are being produced and if beam is controlled by shutter, an indicator that this is open or closed.
11. Ensure automatic timer de-energises X-ray tube after exposure has elapsed and preserves its accumulated response.
12. All beam therapy equipment is tested and calibrated by a qualified expert before use and at regular intervals, as specified by the Department of Human Services. (annually).
13. Ensure tube is not held by hand and is held in position mechanically.
14. Ensure that if the tube has a beryllium window, an audible signal or warning light is prominently mounted in the housing which indicates when the tube is energised.

Most of the requirements above will be met by qualified site survey and by calibration by a qualified physicist. Record keeping and incident and radiation protection incident reporting are defined by the HRSR 1994. Penalties can be levied if there are breaches of the regulations.

Other countries will have their own guidelines which may vary more or less, but every effort should be made to identify and comply with local guidelines and laws in order to ensure patient safety.

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Tumor Staging in Dermatology

7

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7.1 Tumor Staging in Dermatology

The TNM staging system categorizes tumors by the anatomical extent of the disease in different groups and thus facilitates information exchange between medical centers. It also helps clinicians with the treatment plan and aids to determine the prognosis [1], although some tumors because of their unique characteristics cannot be categorized with this staging system.

In this system, the TNM abbreviation stands for T, primary tumor; N, regional lymph node; and M, distant metastasis.

In this chapter, we introduce the more relevant skin tumors and their staging.

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7.2 Basal Cell Carcinoma

Nonmelanoma skin cancers (SCC together with BCC) are the most common cancers in humans and the incidence is on the rise [2]. Basal cell carcinoma (BCC) originates from the basal cells of the epidermis. BCC is the most common neoplasm in the Caucasian population. Unfortunately, there is a variation in nonmelanoma cancer registry in most countries mostly due to the high incidence and a lot of times patients being treated without histologic confirmation. Nevertheless, it is well known that the incidence of BCC is on the rise for the past few decades despite increased public awareness on unfavorable effects of sun exposure. The lifetime risk for BCCs is estimated to be approximately 30 % in comparison to less than 10 % for SCCs. Duration and intensity of sun exposure especially the UVB radiation seems to be the main responsible factor for BCC pathogenesis. Skin type, genetic alterations such as seen in DNA-repair deficiency, and hereditary syndromes (i.e., Gorlin syndrome, xeroderma pigmentosum, albinism, Rombo syndrome, and Bazex-Dupre-Christol syndrome) are important predisposing factors. Other risk factors include ionizing radiation, intensive photochemotherapy, and arsenic intoxication [3].

7.2.1 Diagnosis

The clinical presentation of BCC varies within a wide spectrum from small, pearly, or erythematous patch to black nodules or a rodent ulcer.

Histopathologically BCC is categorized into different subtypes: Nodular is the most common subtype usually presenting on the head and neck, superficial occurs most frequently on the trunk, micronodular, infiltrating, fibroepithelial, basosquamous carcinoma, and sclerosing/morphoeiform BCC. However, diagnosis and differentiation between the subtypes of BCC and also other cutaneous benign or malignant tumors remains challenging, at times.

7.2.2 Staging

To reflect a multidisciplinary effort to provide a mechanism for staging nonmelanoma skin cancers according to evidence-based medicine, the American Joint Committee on Cancer and Union for International Cancer Control (AJCC/UICC) guidelines has come up with a new staging system in 2009 as shown in Table 7.1.

Table 7.1 Cutaneous squamous cell carcinoma and other cutaneous carcinomas staging excluding the eyelid [1]

Tx	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ
T1	Tumor 2 cm or less in greatest dimension
T2	Tumor more than 2 cm in greatest dimension
T3	Tumor invades to deeper extradermal structures like musculoskeletal, bone, cartilage, jaw, and orbit
T4	Tumor invades to skull bone or axial skeleton
Nx	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Regional lymph node metastases in one lymph node 3 cm or less in greatest dimension
N2	One lymph node metastases more than 3 cm, but no more than 6 cm, in greatest dimension or multiple lymph node metastases, but none more than 6 cm in the greatest dimension
N3	Metastases in regional lymph node more than 6 cm
M0	No distant metastasis
M1	Distant metastasis

Stage grouping			
0	Tis	N0	M0
I	T1	N0	M0
II	T2	N0	M0
III	T3	N0	M0
	T1, T2, T3	N1	M0
IV	T1, T2, T3	N2, N3	M0
	T4	Any N	M0
	Any T	Any N	M1

In the new AJCC classification, stage I tumors with more than one high-risk feature is as stage II classified
High-risk features are:
Primary anatomic site of ear or hair-bearing lip
Greater than 2 mm depth
Clark level greater than or equal to IV
Perineural involvement

7.2.3 Treatment

Several evaluations of BCC treatment have shown that the histologic subtype is an important risk factor for recurrence [3], which can affect the choice of treatment.

Although excision with negative margins has been the most effective approach to cure, at times radiation therapy is chosen as the first choice considering preservation of function, cosmesis, and patients' preferences.

Topical drug therapy with imiquimod, 5-fluorouracil (5-FU), tazarotene, vigorous cryotherapy or photodynamic therapy are other options in low-risk superficial BCC patients or when surgery and radiation therapy are contraindicated [4, 5].

7.2.4 Follow-Up

Close follow-up after local disease is needed by examining the skin and regional lymph nodes every 3–6 months for the first 2 years after diagnosis, then 6–12 months for the next 3 years, and then annually for life. If there was also regional lymph node involvement, then closer follow-up is needed as every 1–3 month for the first year, 2–4 month for the second year, 4–6 month for the third year, and 6–12 month annually for life [5]. Finally, routine sun-protection and self-examination is recommended.

7.3 Cutaneous Squamous Cell Carcinoma

Squamous cell carcinoma originates from the suprabasal epidermal keratinocytes [6]. SCC is the second most common skin cancer accounting for approximately 20 % of nonmelanoma skin cancers. Both BCC and SCC tend to spread mostly locally, but SCC in contrast to BCC has a higher rate of metastasis. Fair-skinned people are more susceptible compared to the general population and the incidence increases with advanced age. Actinic keratosis and Bowen's disease (squamous cell carcinoma in situ) are believed to be the precursors of SCC. Cumulative UV exposure especially UVB is the most important risk factor and hence accounting for the higher incidence of this cancer in sun-exposed areas mostly including the head, neck, and arms. There are also other known extrinsic and intrinsic risk factors for SCC such as ionizing radiation exposure; exposure to environmental carcinogen, e.g., arsenic; scars; burns; chronic wounds; human papillomavirus infection especially HPV-16 and HPV-18 which are associated with squamous cell carcinoma of the genital region; and also extensive immunosuppression such as seen in solid organ transplant patients or leukemia [6–8].

7.3.1 Diagnosis

Squamous cell carcinoma is usually described as a firm, flesh-colored, or erythematous papule or plaque with crust or ulceration [6].

SCC has many clinicopathological variants such as verrucous carcinoma, spindle cell, keratoacanthoma, Bowen's disease, and erythroplasia of Queyrat. The details of the histopathologic differences are out of the scope of this chapter, but it is important to recognize that these differences influence the prognosis. A common invasive SCC consists of invasion of epidermal cells of the spinous layer into the underlying dermis. Usually signs of keratinisation can occur as single cell dyskeratoses or concentric horn pearls [9].

7.3.2 Staging

To reflect a multidisciplinary effort to provide a mechanism for staging nonmelanoma skin cancers according to evidence-based medicine, the AJCC/UICC guidelines has come up with a new staging system in 2009 as shown in Table 7.1.

7.3.3 Treatment

Treatment options include topical imiquimod, topical 5-fluorouracil, photodynamic therapy, cryotherapy, curettage, and electrodessication, all of which can be especially considered for precursor lesions. For invasive squamous cell carcinoma, the treatment of choice remains excision with negative margins or MOHS micrographic surgery; the latter has been shown to have lower rate of reoccurrence [10].

Although radiation therapy sometimes is chosen as primary treatment when preservation of

functionality and cosmesis is a priority, radiation therapy alone has a lower success rate when compared to surgery and a higher local reoccurrence rate [11]. Radiation therapy can be used as adjuvant to surgery especially when there is lymph node involvement or for perineural disease [5].

Chemotherapy usually with cisplatin or EGFR-targeted drugs, as a single agent or in combination with chemotherapeutic agents, should be reserved for more advanced stages of disease.

7.3.4 Follow-Up

The recommended guidelines for follow-up are the same as mentioned in the BCC follow-up. Additionally, during these follow-up visits, patient should be checked for development of new precursor lesions.

7.4 Melanoma

Melanoma accounts for the most lethal skin tumor, causing 90 % of skin cancer mortality.

The incidence rates in the white population have increased three- to fivefolds. This increase ranges from 10 to 60 cases per 100,000 inhabitants and year depending of the region, but the highest reported rates are from Australia and the southern states of the United States [12]. The expectations are that this rising trend will continue at least for the next two decades. The main risk factors include sun exposure, atypical nevi, positive family history for melanoma, and fair skin type.

This heterogenous disease presents mainly as four different subtypes, including superficially spreading (SSM), nodular (NMM), lentigo maligna (LMM), and acrolentiginous melanoma (ALM). Eyes, meninges, and mucosal tissue affectation exists as well but is rare.

Arising from melanocytic cells, the majority of melanoma types show clear pigmentation except for the rare amelanotic melanoma type.

Metastases can involve any organ, but there is a preference for skin, lungs, liver, brain, and lymph nodes.

7.4.1 Diagnosis and Staging

The latest European consensus-based interdisciplinary guidelines for melanoma are reviewed and published by Garbe et al. in 2010 [13].

According to the AJCC (American Joint Committee on Cancer) system, in 2001 a new TNM classification was defined for cutaneous melanoma (Table 7.2) [13–15].

Histopathologic analysis helps identify the clinicopathological subtype, tumor thickness in mm (also known as Breslow depth), the ulceration status, the level of invasion (Clark I–V), presence of potential microsatellites, and lateral and deep excision margins [13].

7.4.2 General Staging Recommendations

Chest X-ray and regional lymph node and abdominal (including pelvis and retroperitoneum) ultrasound are recommended as staging procedures at initial and follow-up examinations. Positron emission tomography- computed tomography (PET-CT) scans or magnet resonance imaging (MRI) is indicated in higher-risk patients. As a follow-up tool, LDH and serum S-100 levels are analyzed [16, 17] (refer to Table 7.3 for further details).

7.4.3 Staging and Follow-Up in Melanoma Stage I (<1 mm: Low-Risk Scheme)

Recent changes of the AJCC guidelines include the mitotic rate (MR) as a relevant prognostic factor. Hence, if the primary lesion is equal or less than 1 mm in the presence of ulceration or at least 1 mitosis/mm^2, SNLB is recommended (T1b–T4b). The 10-year survival is expected to be over 90 % [18, 19]. Please refer to Table 7.4 for further details.

Table 7.2 TNM staging categories for cutaneous melanoma [15]

Classification	Thickness (mm)	Ulceration status
Tis	NA	NA
T1	<1.00	(a) Without ulceration and mitosis < 1/mm^2 (b) With ulceration or mitosis > 1/mm^2
T2	1.01–2.00	(a) Without ulceration (b) With ulceration
T3	2.01–4.00	(a) Without ulceration (b) With ulceration
T4	>4.00	(a) Without ulceration (b) With ulceration
N	No. of metastatic nodes	Nodal metastatic burden
N0	0	NA
N1	1	(a) Micrometastasis[a] (b) Macrometastasis[b]
N2	2–3	(a) Micrometastasis[a] (b) Macrometastasis[b] (c) In-transit metastases/satellites without metastatic nodes
N3	+4 metastatic nodes, or matted nodes, or in-transit metastases/satellites with metastatic nodes	
M	Site	Serum LDH
M0	No distant metastases	NA
M1a	Distant skin, subcutaneous, or nodal metastases	Normal
M1b	Lung metastases	Normal
M1c	All other visceral Metastases Any distant metastasis	Normal Elevated

NA not applicable, *LDH* lactate dehydrogenase
[a]Micrometastases are diagnosed after lymph node biopsy
[b]Macrometastases are defined as clinically detectable nodal metastases confirmed pathologically

7.4.4 Staging and Follow-Up in Melanoma Stage I + II (>1 mm: Intermediate-Risk Scheme)

According to Morton et al., the radical lymph node dissection of positive sentinel lymph nodes prolongs the disease-free survival, but not the overall survival [20].

SNLB is recommended for T1b–T4 with clinically or radiographically uninvolved lymph nodes [21].

According to the recent AJCC updates, T1b is referring to the degree of ulceration and the mitotic rate, but no longer the Clark level. The mitotic rate is the second most relevant factor determining prognosis after the tumor depth.

7.4.5 Staging and Follow-Up in Melanoma Stage III + IV (>4 mm + N + M: High-Risk Scheme)

Currently radical lymph node dissection is recommended following micrometastases in sentinel lymph nodes. Since the overall survival benefit of this procedure is very controversial, instead ultrasound follow-up of the lymph node basin can be considered [13].

Table 7.3 Staging of melanoma [13]

Stage	Primary tumor (pT)	Regional lymph node metastases (N)	Distant metastases (M)
0	In situ tumor	None	None
IA	<1.0 mm, no ulceration	None	None
IB	<1.0 mm with ulceration or Clark Level IV or V 1.01–2.0 mm, no ulceration	None	None
IIA	1.01–2.0 mm with ulceration 2.01–4.0 mm, no ulceration	None	None
IIB	2.01–4 mm with ulceration >4.0 mm, no ulceration	None	None
IIC	>4.0 mm with ulceration	None	None
IIIA	Any tumor thickness, no ulceration	Micrometastases	None
IIIB	Any tumor thickness with ulceration Any tumor thickness, no ulceration Any tumor thickness, +/−ulceration	Up to 3 macrometastases None but satellite and/or in-transit metastases	None
IIIC	Any tumor thickness with ulceration Any tumor thickness, +/−ulceration	Up to three macrometastases Four or more macrometastases or lymph node involvement extending beyond capsule, or satellite and/or in-transit metastases with lymph node involvement	None
IV			Distant metastases

The lactic dehydrogenase (LDH) level, being a relevant predictor of survival, has been recently included in the M category of the TNM staging system [15].

7.4.6 Therapy

Surgery is the first treatment choice of localized melanoma in any stage. But surgery is always not feasible for multiple reasons including the anatomical site. For example, lentigo maligna and lentigo maligna melanoma are mostly seen in the elderly population in the face area. If the lesion is small and the location is favorable, Mohs surgery with careful follow-up of the margins should be performed, but many times the anatomical site is not suitable, e.g., the eyelid, nose, or ear or the patient is high risk for surgery. In such cases, studies have shown that superficial radiotherapy with Grenz or soft X-rays is a reliable treatment option [22].

According to the melanoma subtype and stage, radiation therapy, adjuvant INF-alpha, and other immunotherapies and palliative chemotherapy serve as main therapeutic options [13]. The EORTC (European Organization for Research and Treatment of Cancer) 18991 phase II clinical trail showed pegylated interferon-alpha can be beneficial as adjuvant therapy for patients with stage II and III melanoma with microscopic nodal disease [23].

Small molecules targeting specific proteins are broadly investigated in pre- and clinical trials [24].

7.5 Merkel Cell Carcinoma

Merkel cell carcinoma (MCC) is a rare, aggressive malignancy of the skin, with tripling incidence during the past two decades. This neuroendocrine skin tumor has a high local, regional, and metastatic recurrence potential [26, 27].

Potential risk factors for developing Merkel cell carcinoma include advanced age, ultraviolet exposure, fair skin, and immune suppression. The mnemonic acronym "AEIOU" may increase awareness for Merkel cell carcinoma: **a**symptomatic/lack of tenderness, **e**xpanding rapidly (doubling in <3 months), **i**mmunosuppression, **o**lder than 50 years, and **u**ltraviolet exposed skin site [28].

Table 7.4 Follow-up [25]

	Physical examination (months)	Physical examination (months)	Physical examination (months)	Locoregional lymph node ultrasound (months)	S-100 (months)	Abdominal ultrasound and chest X-ray (months)	CT, MRI, PET, or PET-CT (months)
Stage (TNM)	Years 1–3	Years 4–5	Years 6–10	Years 1–5	Years 1–5	Years 1–5	Years 1–5
I (<T1N0)	6	12	12	–	–	–	–
I (T2N0), IIA + B	3	6	6–12	6–12	6–12	Individual	–
IIC, III	3	3	6	6	6	Individual	6–12
IV	Individual	Individual	Individual	Individual	Individual	Individual	Individual

7.5.1 Diagnosis and Staging

Histologically, MCCs are small, round, blue cell tumors. The most difficult differentiation is often between primary MCC and metastatic small cell carcinoma of the lung. Until recently, different staging systems for MCC described in the literature were leading to significant confusion among patients, physicians, and researchers. In 2009, a new consensus staging system was adopted by the AJCC/UICC (Table 7.5). This new staging system is based on prognostic factor analysis of 5,823 MCC patients in the United States using information from the national cancer data base. Using this staging system, the extent of disease is highly predictive of survival with 5-year survival rates of 64 % for local, 39 % for regional nodal, and 18 % for distant metastatic disease [29].

7.5.2 Therapy

Surgery is the primary treatment modality for MCC. SLNB for clinically normal regional lymph node basins is recommended as well as postoperative radiation therapy for the primary tumor, draining lymphatics, and/or regional lymph node basins.

For stage 4 disease, various chemotherapeutics are administered such as platin derivates, anthracyclines, or cyclophosphamide [30–32].

7.5.3 Follow-Up

Suggested follow-up schedules have low level of evidence and are the same regardless of whether patients are N0, N+, or M1. The NCCN guidelines suggest a physical examination including a complete skin and regional lymph node examination every 1–3 months for the first year, every 3–6 months in the second year, and annually thereafter [30]. The German guidelines further suggests performing ultrasound of regional lymph nodes at every visit and abdominal ultrasound as well as chest X-ray once per year [33].

Table 7.5 TNM criteria and stage groupings of new American Joint Committee on Cancer staging system for Merkel cell carcinoma [34]

T			
Tx, primary tumor cannot be assessed			
T0, no primary tumor			
Tis, in situ primary tumor			
T1, primary tumor <2 cm			
T2, primary tumor >2 but <5 cm			
T3, primary tumor >5 cm			
T4, primary tumor invades bone, muscle, fascia, or cartilage			
N			
Nx, regional nodes cannot be assessed			
N0, no regional node metastasis[a]			
cN0, nodes not clinically detectable[a]			
cN1, nodes clinically detectable[a]			
pN0, nodes negative by pathologic examination			
pNx, nodes not examined pathologically			
N1a, micrometastasis[b]			
N1b, macrometastasis[c]			
N2, in-transit metastasis[d]			
M			
Mx, distant metastasis cannot be assessed			
M0, no distant metastasis			
M1, distant metastasis[e]			
M1a, distant skin, distant subcutaneous tissues, or distant lymph nodes			
M1b, lung			
M1c, all other visceral sites			
Stage			
0	Tis	N0	M0
IA	T1 p	N0	M0
IB	T1 c	N0	M0
IIA	T2/T3	pN0	M0
IIB	T2/T3	cN0	M0
IIC	T4	N0	M0
IIIA	Any T	N1a	M0
IIIB	Any T	N1b/N2	M0
IV	Any T	Any N	M1

[a]"N0" denotes negative nodes by clinical, pathologic, or both types of examination. Clinical detection of nodal disease may be via inspection, palpation, and/or imaging; cN0 is used only for patients who did not undergo pathologic node staging

[b]Micrometastases are diagnosed after sentinel or elective lymphadenectomy

[c]Macrometastases are defined as clinically detectable nodal metastases confirmed pathologically by biopsy or therapeutic lymphadenectomy

[d]In-transit metastasis is tumor distinct from primary lesion and located either (1) between primary lesion and draining regional lymphnodes or (2) distal to primary lesion

[e]Because there are no data to suggest significant effect of M categories on survival in Merkel cell carcinoma, M1a–c are included in same stage grouping

7.6 Cutaneous Lymphoma

Primary cutaneous lymphomas (CL) are malignancies of skin homing lymphocytes and by definition develop in and remain confined to the skin for months and typically years. Their incidence has increased over the last 30 years and is now roughly estimated at 1/100,000 yearly in Europe, varying by race and sex, with slight predominance in male gender [35–37]. Recent progress in the classification and staging of these disease entities has led to increased awareness and might explain increasing frequency of certain subtypes of CL [38].

CL include a broad range of heterogeneous disorders: 75 % are cutaneous T-cell lymphomas (CTCL), 25 % cutaneous B-cell lymphomas (CBCL), and a few percent other uncommon forms. Secondary cutaneous lymphomas stand for involvement of skin by primary nodal or non-cutaneous extranodal lymphomas.

Discrimination between cutaneous and non-cutaneous lymphomas is crucial, since CL differ dramatically in clinical behavior and outcome and require special therapeutic strategies.

7.6.1 Diagnosis

In 2005, the World Health Organization (WHO) and European Organization for Research and Treatment of Cancer (EORTC) published a classification for CL, the WHO-EORTC classification (Table 7.6) that is clinically useful and internationally reproducible and thus widely accepted. The diagnosis of cutaneous lymphomas (CL) requires high clinical expertise as well as thorough histologic and immunohistochemical analysis and assessment of clonality in lesional skin. Mycosis fungoides lesions usually show superficial band-like or lichenoid infiltrates, mainly consisting of atypical lymphocytes and histiocytes. Epidermotropism is a characteristic feature, whereas the presence of intraepidermal collections of atypical cells (Pautrier microabscesses) is observed in only a minority of cases [39, 40].

Table 7.6 WHO-EORTC classification 2005 [39]

Cutaneous T-cell and NK-cell lymphomas
Mycosis fungoides
MF variants and subtypes
Folliculotropic MF
Pagetoid reticulosis
Granulomatous slack skin
Sézary syndrome
Adult T-cell leukemia/lymphoma
Primary cutaneous CD30+ lymphoproliferative disorders
Primary cutaneous anaplastic large-cell lymphoma
Lymphomatoid papulosis
Subcutaneous panniculitis-like T-cell lymphoma
Extranodal NK-/T-cell lymphoma, nasal type
Primary cutaneous peripheral T-cell lymphoma, unspecified
Primary cutaneous aggressive epidermotropic CD8+ T-cell lymphoma (provisional)
Cutaneous gamma/delta T-cell lymphoma (provisional)
Primary cutaneous CD4+ small-/medium-sized pleomorphic T-cell lymphoma (provisional)
Cutaneous B-cell lymphomas
Primary cutaneous marginal zone B-cell lymphoma
Primary cutaneous follicle center lymphoma
Primary cutaneous diffuse large B-cell lymphoma, leg type
Primary cutaneous diffuse large B-cell lymphoma, other
Intravascular large B-cell lymphoma
Precursor hematologic neoplasm
CD4+/CD56+ hematodermic neoplasm (blastic NK-cell lymphoma)

7.6.2 Staging

Recently, a proposal for a revised TNM staging for mycosis fungoides (MF) and Sézary syndrome (SS) was published by the International Society for Cutaneous Lymphomas (ISCL) and EORTC Table 7.7 [41]. In addition a TNM staging system for CL other than MF and SS was presented in Table 7.8 [42]. These two TNM-based tools today allow the reproducible description of the tumor load in CL patients facilitating the precise description of patient populations—a prerequisite for the comparison of clinical trials.

Table 7.7 TNM staging for MF and SS by EORTC and ISCL [41]

Skin	
T1	Limited patches,[a] papules, and/or plaques[b] covering <10 % of the skin surface. May further stratify into T1a (patch only) vs. T1b (plaque ± patch)
T2	Patches, papules, or plaques covering ≥10 % of the skin surface. May further stratify into T2a (patch only) vs T2b (plaque ± patch)
T3	One or more tumors[c] (≥1 cm diameter)
T4	Confluence of erythema covering ≥80 % body surface area
Node	
N0	No clinically abnormal peripheral lymph nodes[d]; biopsy not required
N1	Clinically abnormal peripheral lymph nodes; histopathology Dutch grade 1 or NCI $LN_{0–2}$
N1a	Clone negative[g]
N1b	Clone positive[g]
N2	Clinically abnormal peripheral lymph nodes; histopathology Dutch grade 2 or NCI LN_3
N2a	Clone negative[g]
N2b	Clone positive[g]
N3	Clinically abnormal peripheral lymph nodes; histopathology Dutch grades 3–4 or NCI LN_4; clone positive or negative
Nx	Clinically abnormal peripheral lymph nodes; no histologic confirmation
Visceral	
M0	No visceral organ involvement
M1	Visceral involvement (must have pathology confirmation[e] and organ involved should be specified)
Blood	
B0	Absence of significant blood involvement: ≤5 % of peripheral blood lymphocytes are atypical (Sézary) cells
B0a	Clone negative[g]
B0b	Clone positive[g]
B1	Low blood tumor burden: >5 % of peripheral blood lymphocytes are atypical (Sézary) cells but do not meet the criteria of B2
B1a	Clone negative[g]
B1b	Clone positive[g]
B2	High blood tumor burden: ≥1,000/μL Sézary cells[f] with positive clone[g]

[a]For skin, patch indicates any size skin lesion without significant elevation or induration. Presence/absence of hypo- or hyperpigmentation, scale, crusting, and/or poikiloderma should be noted

[b]For skin, plaque indicates any size skin lesion that is elevated or indurated. Presence or absence of scale, crusting, and/or poikiloderma should be noted. Histologic features such as folliculotropism or large-cell transformation (25 % large cells), CD30 or CD30, and clinical features such as ulceration are important to document

[c]For skin, tumor indicates at least one 1-cm diameter solid or nodular lesion with evidence of depth and/or vertical growth. Note total number of lesions, total volume of lesions, largest size lesion, and region of body involved. Also note if histologic evidence of large-cell transformation has occurred. Phenotyping for CD30 is encouraged

[d]For node, abnormal peripheral lymph node (s) indicates any palpable peripheral node that on physical examination is firm, irregular, clustered, fixed, or 1.5 cm or larger in diameter. Node groups examined on physical examination include cervical, supraclavicular, epitrochlear, axillary, and inguinal. Central nodes, which are not generally amenable to pathologic assessment, are not currently considered in the nodal classification unless used to establish N3 histopathologically

[e]For viscera, spleen and liver may be diagnosed by imaging criteria

[f]For blood, Sézary cells are defined as lymphocytes with hyperconvoluted cerebriform nuclei. If Sézary cells are not able to be used to determine tumor burden for B2, then one of the following modified ISCL criteria along with a positive clonal rearrangement of the TCR may be used instead: (1) expanded CD4 or CD3 cells with CD4/CD8 ratio of 10 or more and (2) expanded CD4 cells with abnormal immunophenotype including loss of CD7 or CD26

[g]A T-cell clone is defined by PCR or Southern blot analysis of the T-cell receptor gene

Table 7.8 TNM staging for cutaneous lymphomas other than mycosis fungoides and Sézary syndrome [42]

T	
T1	Solitary skin involvement
T1a	A solitary lesion <5 cm diameter
T1b	A solitary >5 cm diameter
T2	Regional skin involvement: multiple lesions limited to 1 body region or 2 contiguous body regions[a]
T2a	All-disease-encompassing in a <15-cm-diameter circular area
T2b	All-disease-encompassing in a >15- and <30-cm-diameter circular area
T2c	All-disease-encompassing in a >30-cm-diameter circular area
T3	Generalized skin involvement
T3a	Multiple lesions involving 2 noncontiguous body regions
T3b	Multiple lesions involving ≥3 body regions
N	
N0	No clinical or pathologic lymph node involvement
N1	Involvement of 1 peripheral lymph node region[b] that drains an area of current or prior skin involvement
N2	Involvement of 2 or more peripheral lymph node regions[b] or involvement of any lymph node region that does not drain an area of current or prior skin involvement
N3	Involvement of central lymph nodes
M	
M0	No evidence of extracutaneous non-lymph node disease
M1	Extracutaneous non-lymph node disease present

[a]Definition of body regions

Head and neck: inferior border, superior border of clavicles; T1 spinous process

Chest: superior border, superior border of clavicles; inferior border, inferior margin of rib cage; lateral borders, midaxillary lines, glenohumeral joints (inclusive of axillae)

Abdomen/genital: superior border, inferior margin of rib cage; inferior border, inguinal folds, anterior perineum

Lateral borders, midaxillary lines

Upper back: superior border, T1 spinous process; inferior border, inferior margin of rib cage; lateral borders, midaxillary lines

Lower back/buttocks: superior border, inferior margin of rib cage; inferior border, inferior gluteal fold, anterior perineum (inclusive of perineum); lateral borders, midaxillary lines

Each upper arm: superior borders, glenohumeral joints (exclusive of axillae); inferior borders, ulnar/radial-humeral (elbow) joint

Each lower arm/hand: superior borders—ulnar/radial-humeral (elbow) joint. Each upper leg (thigh): superior

Borders, inguinal folds, inferior gluteal folds; inferior borders, mid-patellae, midpopliteal fossae

Each lower leg/foot: superior borders—mid-patellae, midpopliteal fossae

[b]Definition of lymph node regions is consistent with the Ann Arbor system

Peripheral sites: antecubital, cervical, supraclavicular, axillary, inguinal-femoral, and popliteal. Central sites: mediastinal, pulmonary hilar, para-aortic, iliac

Staging procedures differ depending on diagnosis. For MF and SS patients, usually a complete physical examination, skin biopsy with evaluation of clonality, blood tests including Sézary cell counts, radiologic tests ranging from ultrasound of peripheral lymph nodes up to PET-CT scans, and lymph node biopsies are suggested [41].

7.6.3 Therapy

Most CL are indolent neoplasms. For MF and its variants, a mild stage-adapted therapy is recommended. In early stages, skin-directed therapies such as topical steroids, PUVA, skin-applied cytostatic drugs, or irradiation therapy are first-line treatment options. In advanced stages, a

combination of topical and systemic treatment options is recommended, comprising cytostatic drugs as well as novel molecules or even stem cell transplantation [43–45].

7.6.4 Follow-Up

The time-frame for follow-up visits of patients with cutaneous lymphomas is adjusted individually according to clinical findings. In patients with early disease (stage Ia, Ib), longer intervals of 6–12 months are reasonable, whereas in advanced disease stages, patients often have to be followed every 4–6 weeks to assess therapeutic response.

7.7 Soft Tissue Tumors

Soft tissue tumors are a highly heterogeneous group of tumors that are classified based on their histology. Some of the malignant soft tissue tumors (sarcomas) like DFSP are slow growing with rare metastases in contrast to other sarcomas like angiosarcomas or malignant fibrohistiocytoma that are locally very aggressive with high rate of metastases [46].

The fact that sarcomas are rare and usually start as a painless mass among other factors makes their diagnosis difficult and delayed.

The grading and staging system of soft tissue sarcomas has been challenging and beyond the scope of this chapter, but the two well-accepted staging systems are the Union for International Cancer Control and the American Joint Committee on Cancer (UICC/AJCC) and the Musculoskeletal Tumor Society with each systems having its advantages and pitfalls Table 7.9 [46].

Here we will focus on few types of cutaneous sarcomas.

Table 7.9 TNM staging for soft tissue sarcomas [1] (both angiosarcoma and dermatofibrosarcoma protuberans due to their individual characteristics are excluded from this table)

T
Tx primary tumor cannot be assessed
T0 no primary tumor found
T1 tumor ≤5 cm diameter
T1a: superficial
T1b: deep
T2 tumor >5 cm diameter
T2a: superficial
T2b: deep
N
Nx cannot be assessed
N0 no regional lymph node involvement
N1 regional lymph node involvement
M
Mx cannot be assessed
M0 no distant metastasis
M1 distant metastasis

7.7.1 Dermatofibrosarcoma Protuberans

Dermatofibrosarcoma protuberans (DFSP) is a rare intermediate malignancy of mesenchymal origin. DFSP is locally aggressive and has a tendency of reoccurrence after excision, but metastases and lymph node involvements are rare. Like in many other sarcomas, most distant metastases are to the lungs.

7.7.1.1 Diagnosis

DFSP consists of monotonous spindle-shaped cells in a storiform pattern with low mitotic activity [47]. Dermatofibrosarcoma protuberans cells usually are derived from amplification of t(7,22) containing a specific fusion of COL1A1 (collagen1alpha1) with PDGFB (platelet-derived growth factor-B) genes. This fusion gene product stimulates the tumor growth [48, 49]. These tumors cells are commonly positive for CD34.

DFSP is seen as a slow-growing, skin-colored, firm lesion that can be flat or raised, typically involving the trunk or shoulder girdle. The incidence is higher in men in their third to fourth decade of life.

DFSP can be sometimes confused with a scar or keloid, so a slow-growing lesion without a history of trauma should be biopsied. Also in its differential diagnosis are atypical dermatofibroma

(benign), leiomyosarcoma, atypical fibroxanthoma, and malignant fibrous histiocytoma.

Variants rarely seen are Bednar tumor with melanin-pigmented dendritic cells [50] and juvenile giant cell fibroblastoma.

Incisional biopsy is needed for diagnosis. MRI can be considered in reoccurring lesions to evaluate deeper invasion of tumor [51].

7.7.1.2 Treatment

The treatment of choice is micrographic surgery or wide excisions to aim for negative margins, which have shown to lower the rate of local reoccurrence. The success of radiotherapy alone in treatment of DFSP has been controversial, but it should be considered as adjuvant therapy (usually in 50–60 Gy doses) to resection if margins are positive [52] or when wide excision or recurrent excision can cause cosmetic or functional morbidity or for local control when there is an unresectable tumor. Another treatment option is imatinib a selective inhibitor of PDGR-alpha and PDGFR-beta tyrosine kinases. Imatinib studies on locally advanced or metastatic disease have shown to be successful in the treatment of DFSP by targeted inhibition of PDGFR. At this time, it can be used in treating unresectable, recurrent, and/or metastatic DFSP that are not eligible for surgery [53].

Follow-up is recommended every 6 months.

7.7.2 Angiosarcoma

Cutaneous angiosarcoma is a rare highly malignant vascular tumor with poor prognosis. It is more common in elderly men on the face, scalp, at the site of previous radiation therapy, or lymphedematous regions. The risk of angiosarcoma postradiation therapy is especially higher in women with breast cancer. The incidence peaks between 5 and 10 years postradiation therapy [54]. This tumor is locally aggressive and has a high rate of metastases especially through hematogenous spread.

7.7.2.1 Diagnosis

Angiosarcoma initially can present itself as a bruise or red-purple multifocal papule, but then it can evolve to fungating tumor penetrating to deeper tissue and causing ulceration.

Angiosarcoma consists of atypical pleomorphic endothelial cells forming vascular sinusoids. Mitotic bodies are common [55].

Other vascular tumors such as hemangioma or Kaposi's sarcoma and also systemic lupus erythematosus and pyogenic granuloma have been mentioned in the differential diagnosis of angiosarcoma [56, 57].

7.7.2.2 Treatment

Treatment options are limited and less successful; therefore, it usually has a poor prognosis. Advanced age and advanced disease at the time of diagnosis contribute to poorer prognosis. For local disease, wide excisional surgery with or without radiation therapy has been approached, but due to the invasive nature of this tumor to deeper tissue and positive margins even after wide excisions, the rate of local reoccurrence is high [58].

Although in some retrospective studies chemotherapy has been shown to improve survival by a few months [59], considering that most patients with this tumor are elderly with multiple comorbidities, for the most part, chemotherapy has been ineffective and might be only an option for palliation in some cases.

7.7.3 Malignant Fibrous Histiocytoma (MFH)

Due to the heterogenousity of this category of sarcomas, their existence as a single entity is very controversial. This group of tumors is seen more in the elderly with a high rate of metastases and local reoccurrence. MFH consists of pleomorphic cells and mitotic figures. Often this tumor appears at the postirradiation site with a 5–20 years interval.

MFH is not only a cutaneous malignancy but also seen in retroperitoneal and musculoskeletal areas. Treatment of choice is micrographic surgery with or without radiation and close follow-up afterwards.

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Treatment of Precancerous Lesions

8

Stephan Lautenschlager

Contents

8.1 Introduction

The recommendation of radiotherapy (RT) for precancerous skin lesions is usually limited to patients where the cosmetic and/or functional outcome is likely to be better with radiotherapy compared with surgery or other various treatment modalities. Important advantages of grenz or soft X-rays (12–50 kV) compared to cryotherapy, photodynamic therapy, electrodesiccation, or topical agents (e.g., 5-fluorouracil or imiquimod) include predictable cure rates, predictable penetration of tissue, and minimal wound care and morbidity. Significant disadvantages such as treatment duration, low availability of experienced centers, and in some cases higher costs limit its use in dermatology. Modern radiotherapy is especially suited for elderly patients with various comorbidities suffering from extensive and widespread actinic keratoses of the scalp, Bowen's disease, and lentigo maligna.

8.2 Actinic Keratoses

Actinic keratoses (AK) are seen in up to 25 % of adults in the northern hemisphere, mostly seen in the older fair-skinned population with a worldwide increase [1–3]. Mostly therapy of AK is simple, but widespread actinic keratoses of the scalp, especially in the elderly population, can be a therapeutic challenge. These lesions can be treated with a great variety of modalities [4], but success may be

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Table 8.1 Recommended parameters for treating precancerous lesions by radiotherapy

Diagnosis	kV	Diameter (cm)	Dose (Gy)	Interval (days)
Actinic keratoses	12–20	<2	2–3×8	4–7
		>2	5–7×4	3–4
Bowen's disease	12–20	<2	3–4×8	3–4
		>2	8–10×4	
Lentigo maligna	12	>2	12×10	2–7

limited due to inadequate cure rates, significant pain, and morbidity. Especially for elderly patients meticulous wound care for second intention healing (e.g., after electrodesiccation and curettage, cryotherapy, or CO_2 laser) is not feasible. Severely delayed wound healing is known to occur for months after chemical peel, cryotherapy, and CO_2 laser [5]. Suboptimal cure rates can be influenced further by periadnexal atypia, which is an especially important problem on the scalp due to the abundance of hair follicles and might not be treated by topical agents [6]. In particular for giant or widespread lesions, fractionated grenz or superficial soft X-ray radiation is very efficient [6–8]. As radiation may induce dose-dependent alopecia and even more important secondary tumors, younger patients have to be excluded [9], although the risk of developing radiogenic ulcers and tumors after soft X-ray therapy is not very high [9]. Usually the required total dose varies from 20 to 28 Gy with single-dose 4–8 Gy once or twice per week with 12–20 kV (Table 8.1) [8]. If the entire scalp is affected, the required field has to be subdivided in different sections (Fig. 8.1a, b). The prolonged treatment time and higher costs compared to cryotherapy, electrodesiccation, or topical agents are offset by the durable remission time with less future treatments [8]. Patients have to be advised that transient inflammatory reactions occur during treatment and that future consistent sun protection is absolutely essential. In rare cases of actinic cheilitis, radiotherapy may be considered when other treatment options failed.

8.3 Bowen's Disease

First described in 1912, Bowen's disease (BD) is a form of intraepidermal squamous cell carcinoma (in situ SCC) [10]. In two thirds of patients, a solitary, sharply demarcated erythematous and scaly or crusted plaque ranging in size from a few millimeters to several centimeters can be found, mostly located on the head, neck, hands, and lower leg [11–13]. Often the pilosebaceous apparatus is involved [14]. Less common sites or variants include pigmented BD, subungual/periungual, palmar, genital, perianal, and verrucous BD. Its mucosal variant is called erythroplasia of Queyrat. A minority (<5 %) become invasive although this figure may be higher (10 %) in genital lesions (erythroplasia of Queyrat) [15]. Various radiotherapy techniques (soft X-rays, orthovoltage, or electron therapy) and regimens have been used to treat BD, but there are no studies directly comparing other treatments with RT, and data are sparse regarding dosing and toxicity. RT is advantageous in patients who refuse surgery, for lesions in cosmetically sensitive areas, for large and multiple lesions (Fig. 8.2a, b), and for patients with keloid formation [13]. Several retrospective studies indicate local control rates from 89 to 100 % (Table 8.2) despite wide ranges in doses used. Local recurrences seem to be equally low in patients treated with high- and low-dose regimens. Patients with grade 4 toxicities according to Cox et al. [16] (necrosis of cartilage/bone damage and/or ulceration with an additional requirement for a duration of >3 months) more often had hypofractionated regimens (dose per fraction >4 Gy) in an extremity location. In the study of 59 lower extremity BD lesions by Cox and Dyson [17], one fifth also failed to heal after RT. Dupree et al. [12] reported nonhealing ulcers in 25 % of patients with BD after a median of 27.5 months following RT, all of them on the lower extremity. Most patients with this side effect were treated with orthovoltage X-rays. Recent review articles on managing patients with

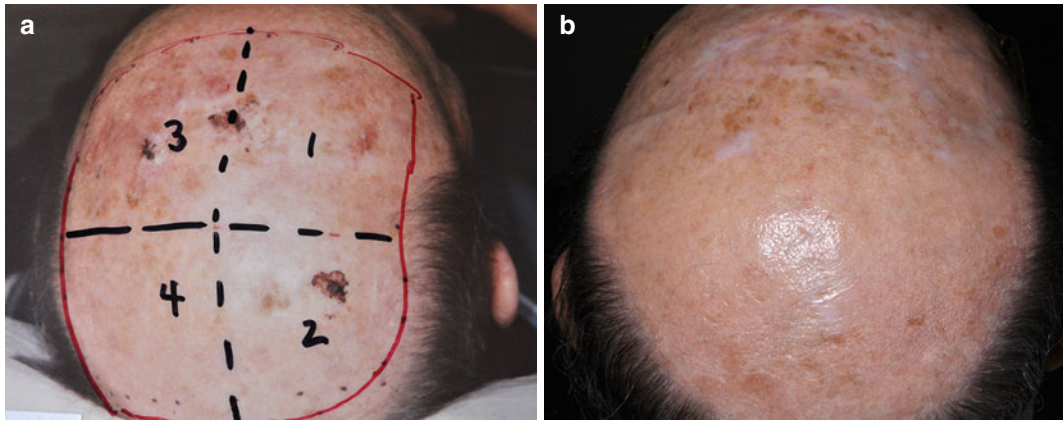

Fig. 8.1 (**a**) A 66-year-old patient with disseminated actinic keratoses on the scalp with four treatment fields (6×4 Gy, 12 kV, time interval 3–4 days). (**b**) Same patient 7 years after radiation treatment with durable remission

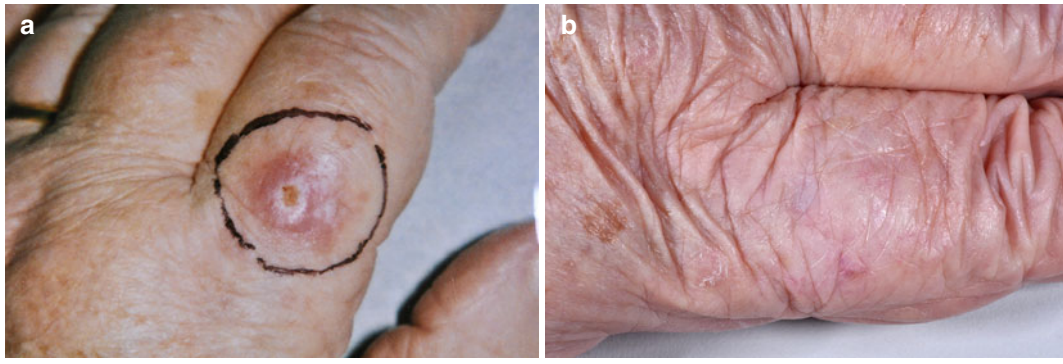

Fig. 8.2 (**a**) A 82-year-old patient with Bowen's disease on her left index. (**b**) Same patient 5 years after radiation treatment (8×4 Gy, 20 kV, time interval 3–4 days)

Table 8.2 Summary of publications to treat Bowen's disease with radiation therapy

Authors	Year	Number of lesions	Dose/fraction Gy	Total dose Gy	Local control (%)
Schoefinius et al. [28]	1974	33	2–5	40–60	100
Stevens et al. [29]	1977	19	5	50	89
Panizzon [30]	1983	41	4	40	100
Blank and Schnyder [31]	1985	73	2–8	40–48	97
Cox and Dyson [17]	1995	59	12–18	10–42	100
Caccialanza et al. [32]	1999	62	2–5	40–70	98
Dupree et al. [12]	2001	16	2.5–3.5	44.2–52.5	100
Lukas Vanderspek et al. [13]	2005	42	3–15	10–52	100

BD emphasize the multitude of treatments for these patients [15, 18]. Despite this, RT remains an excellent and well-tolerated therapeutic option in selected patients with BD (in particular on digital, penile, or perianal sites), but risk factors for poor healing on the lower leg, such as poor vascularity, size of the lesion (>4 cm), and large fraction size (>4 Gy), should be taken into account [12, 13, 15]. When other treatments have failed, RT can be effective [19].

8.4 Lentigo Maligna

Lentigo maligna (LM), first described by Hutchinson in 1892, is a macular pigmented skin lesion usually found in the seventh or eighth age decade in patients with actinic skin damage and is located in 90 % in the head and neck region. LM is regarded as a form of melanoma in situ with slow horizontal growth and, if untreated, may progress to lentigo maligna melanoma [20]. For this reason, early treatment is mandatory, but the diffuse nature of melanocytic overgrowth makes LM difficult to treat, with recurrence rates ranging up to 50 % [20]. Surgical excision with clear margins was previously considered as the first-line treatment [21]. Since patients seem to be unsuitable for excision, especially because of advanced age, large size of the lesion (Fig. 8.3a–c), and proximity of the eye, ear, or nose, RT has been used in Europe for decades as the primary treatment with control rates of 95 % [22]. Using the Miescher technique, high doses of grenz or soft X-rays are applied, affecting only the epidermis and the upper dermis [23]. This technique often induces a severe acute radiodermatitis with only limited long-term side effects with excellent cosmetic results when used on the face. Farshad et al. [22] reported a recurrence rate of 7 % after a mean time of 45.6 months in 101 treated patients with LM and LMM. They emphasized a safety margin of at least 10 mm. Schmid-Wendtner et al. [24] reported in 42 patients a success rate of even 100 % (10×10 Gy, 14.5 kV, 50 % depth dose 1.1 mm, mean follow-up 23 months). The recommended RT parameters are listed in Table 8.1. Since LM may harbor areas of early invasive melanoma, seen histologically in about 16 % [25], Miescher technique theoretically could fail if the lesions are thicker than 1 mm (50 % depth dose). Since recurrences are rare, the brisk inflammation induced by RT may

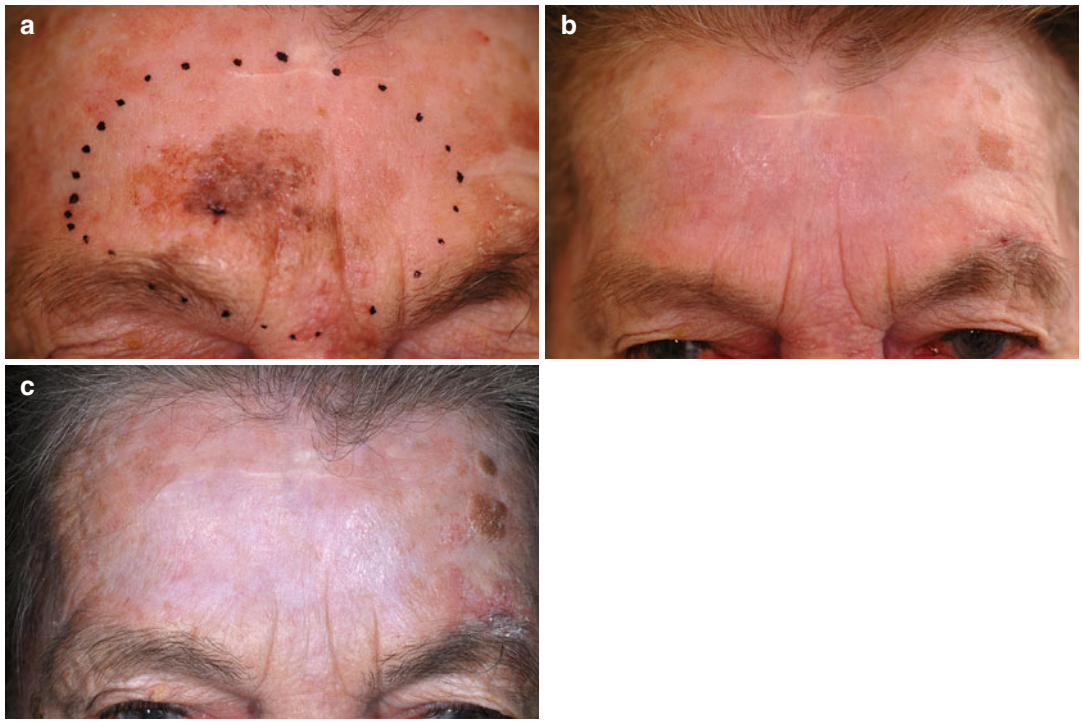

Fig. 8.3 (**a**) A 71-year-old patient with frontal lentigo maligna. (**b**) Same patient 3 months after radiation treatment with fading erythema (12×10 Gy, 12 kV, time interval 3–4 days). (**c**) Same patient 5 years after radiation treatment with slight hypopigmentation

destroy precancerous melanocytes in the dermis or augment an immunologic response [24]. In the USA, conventional orthovoltage RT has been used for LM with good results [26, 27]. One drawback of this treatment technique with high-energy X-rays are the possible side effects on the underlying tissue in the treated field, especially radionecrosis of the bone. Based on the excellent cosmetic result, the low recurrence rate, and the lack of systemic side effects, RT can be seen as the first-line treatment for elderly patients with facial LM.

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Electron Therapy of Skin Carcinomas

9

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9.1 Introduction

Epithelial skin cancers are very common neoplasms. The majority of them are basal cell carcinoma followed by squamous cell carcinoma [1, 2]. Among the different treatment options (surgery, Mohs' surgery, radiotherapy, cryotherapy, curettage, electro-desiccation, photodynamic therapy, topical treatment, etc.), surgical excision and radiation therapy are the most effective modalities to achieve local control [3].

Indeed, radiation therapy is one of the best treatment modalities available to treat skin carcinomas and represents a particularly important option when the preservation of normal tissue and the cosmetic result are essential. It allows treating the tumor and the area of subclinical spread with a margin without significant damage to normal tissues [4, 5]. Radiation therapy can be administered by superficial X-rays, brachytherapy, megavoltage photons, or electron beams.

Since 1949, electron beam therapy has been used for cutaneous malignancies [6]. Its applications in the treatment of mycosis fungoides are well known and described in the literature, but only few articles are available on their use for skin carcinomas. The main advantage of electron beam therapy is to make the treatment of epithelial skin cancers easier when their size and/or localization presents difficulties in their management, as described by Friedman and Pearce and by Braun-Falco et al. [7, 8]. Generally speaking, the electron beam therapy is preferred for large

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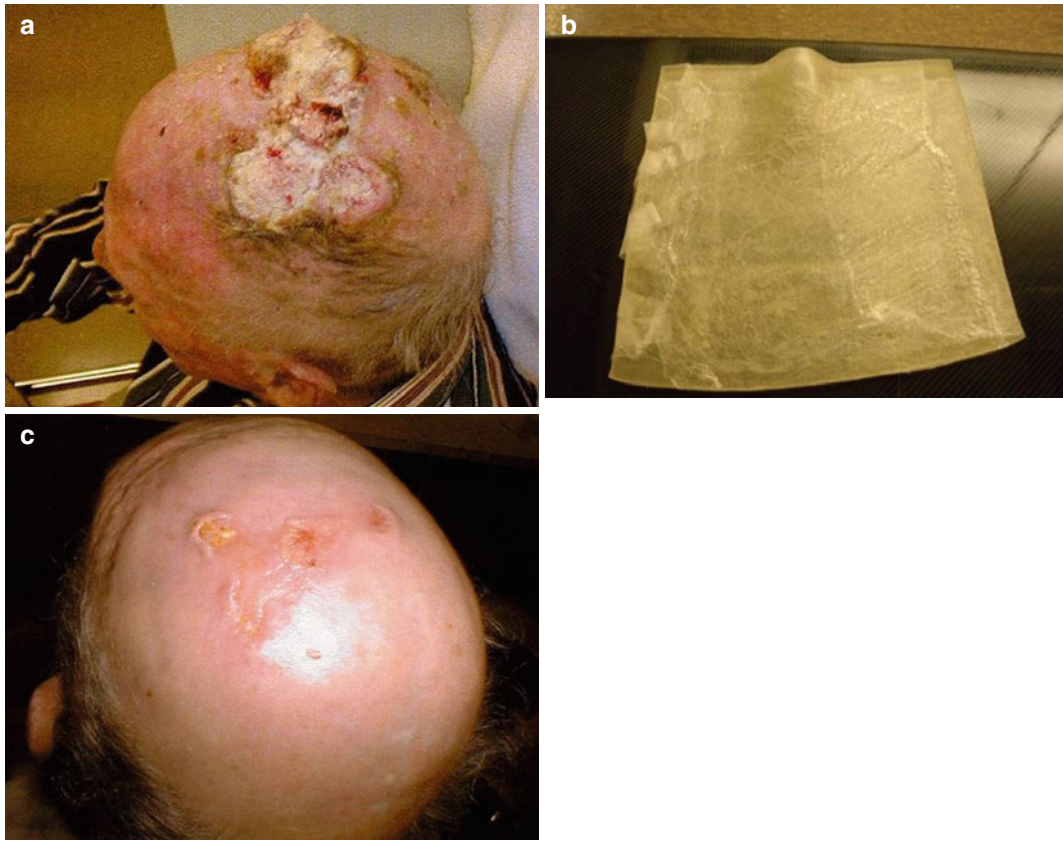

Fig. 9.1 (**a**–**c**) Large squamous cell carcinoma on the scalp treated with electrons and bolus. Result 6 weeks after the end of the treatment

lesions to decrease the radiation exposure to subcutaneous tissues compared with X-rays treatments [9] (Fig. 9.1) or when their thickness is too important to allow a treatment with X-rays. To avoid large dose inhomogeneities observed with superficial X-ray treatments on irregular surface (i.e., the pinna or the nasolabial fold), electron beams are also preferable [10] (Fig. 9.2).

9.2 Electron Beam Characteristics

Some characteristics of the electron beams make them interesting for the treatment of certain skin carcinomas, especially when their localization makes the surgery or the treatment by X-rays less relevant. Electron beams are characterized by a rapid isodose falloff at depth below the skin surface, which means that there is little or no radiation exposure beyond a defined depth. The range of the depth to be irradiated is controlled by the selection of the appropriate energy. Although differences in body densities represent important inhomogeneities for electrons, the additional problem of strong atomic number dependence is not an issue here. So a high dose of radiation can be delivered to superficial skin lesions with limited damage to underlying and adjacent normal tissues. This can be particularly advantageous when the skin cancer to be treated is located over bone or cartilage. In contrast, the high density of bone and cartilage is responsible for a high relative absorption of radiation when X-rays are used, and these tissues are therefore more at risk to develop radionecrosis. For low energy electron beams (2–10 MeV), the dose distribution to the level of 80 % isodose is uniform.

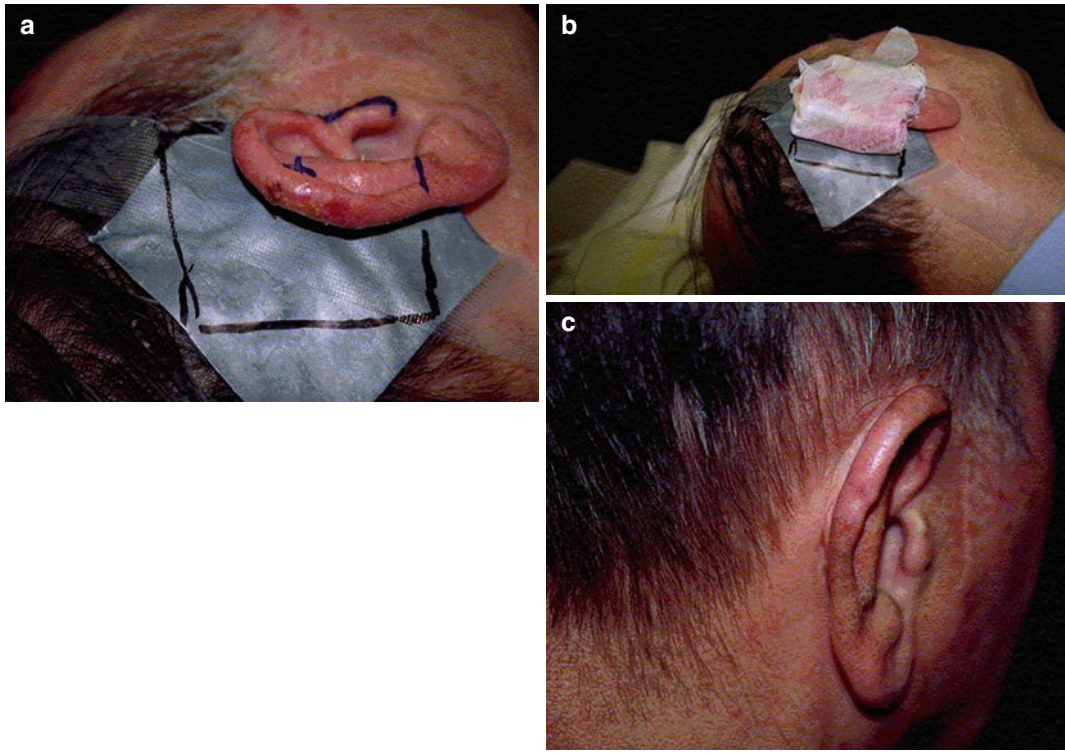

Fig. 9.2 (**a**–**c**) Basal cell carcinoma treated with electron beam. A wax mold is placed to diminish the dose inhomogeneity. Result 6 months later

As their energies are higher than those of X-rays, electrons can treat thicker lesions much more efficiently [4, 11].

9.3 The Margins

The determination of the margins for lesions treated with electron beams must absolutely take into account the fact that the area of high dose intensity is constricted inside the borders of the radiation fields by as much as 1 cm (blurred field edge). A larger field size than the one used with superficial X-rays may be necessary to cover the target area adequately to counterbalance the penumbra region of the electron beams [4]. To underestimate this physical fact can be responsible for a higher recurrence rate after treatment with electron beams. Tumor localization near the eye is a relative contraindication to perform an electron beam treatment because of the lack of sharpness at the edge of the electron fields. In this case, superficial X-rays are preferable for a better eye protection.

9.4 The Buildup

Because of the electrons' buildup, the maximum dose is localized under the surface of the skin, and its depth depends on the electron energy. As the target for epithelial carcinomas is the skin, it is essential to use a bolus (tissue-equivalent material) to be placed on the skin. The thickness of the bolus depends on the depth of the buildup [4].

9.5 Local Control and Treatment Modality

Griep et al. have presented a retrospective analysis of 389 basal or squamous cell carcinomas treated either with superficial X-ray (99) or

electrons (290). Local or loco-regional recurrence was 4.9 %. The local control of the 99 lesions treated with superficial X-rays was 97 %, whereas it was 94.5 % for the 290 lesions treated with electrons ($p=0.30$). Similar rates of local control are reported in the literature [12]. The overall local tumor control rate in the study reported by Locke et al. in 531 patients was 89 % with a median follow-up of 5.8 years [2]. Tapley and Fletcher [2] have reported a local control of 86 % in 156 patients treated for epithelial skin carcinomas with electron beam therapy, with follow-up between 2 and 8.5 years [13]. In Zablow et al.'s analysis, the local control of 115 skin cancers (99 patients) was 88 % with a follow-up between 24 and 47 months [14]. In Miller and Spittle's study, a primary control of 82 % in 29 patients was found with a follow-up between 2 and 6 years [11].

The results reported above on the local control with electron beam therapy contradict the initial data reported by Lovett et al. in their retrospective analysis on 339 basal (242) and squamous cell (97) carcinomas treated with either superficial X-rays (187), electrons (57), megavoltage photons (15), or combined treatment (80). Overall, local control was achieved in 86 % of the patients: 91 % for basal cell carcinoma and 75 % for squamous cell carcinoma. They found that local control was dependant both on the tumor size and on the modality of treatment. Regarding superficial X-rays, the local control was 98 % for lesions less than 1 cm, 93 % for lesions 1–5 cm, and 100 % for lesions more than 5 cm. Regarding electrons, the tumor control was 88, 72, and 78 %, respectively, whereas for megavoltage photons (60Co, 4 MV photons) tumor control was 100, 67, and 33 % respectively. Finally with mixed treatments, local control was 90, 76, and 64 %, respectively [5]. In an updated analysis after more than 10 additional years, Locke et al. have reported an overall local tumor control rate of 94 % for superficial X-rays modality, of 82 % for electron beam, of 82 % for mixed treatment, and of 50 % for megavoltage photons. Nevertheless, in multivariate analysis, the treatment modality was not significant (electron versus other treatment modalities, $p=0.345$). On one hand, these results may reflect an improvement over the years in the use of electrons as a modality of treatment for epithelial skin cancer. On the other hand, electrons were generally used for more advanced tumors than those treated with superficial X-rays, and this can explain the poorer local control in that group [2].

Silva et al. from the Princess Margaret Hospital have reported their experience in the treatment of carcinoma of the pinna. Among the 334 lesions treated, 278 (83 %) were treated with orthovoltage radiotherapy and 39 (12 %) with electron beams. The local control was worse in the group treated with electrons. However, after the correction of the RBE (relative biological effectiveness), there were no more statistically significant increased local failure rates with electrons [15]. The different results reported in the literature for treatment with electron beam therapy are summarized in Table 9.1.

9.6 Prognostic Factors

9.6.1 Tumor Size

One of the main prognostic factors for local control is the tumor size: the larger the tumor, the higher the recurrence rate. Irradiated region of less than 10 cm^2 had a local recurrence rate of 2.2 %, versus 13.8 % for irradiated areas of more than 50 cm^2 [12]. Lovett et al. found also a relationship between the tumor size and local control. Tumor control was 97, 87, and 87 % for basal cell less than 1 cm, 1–5 cm, and greater than 5 cm, respectively, versus 91, 76, and 56 %, respectively, for squamous cell carcinoma [5]. In Silva's study, a tumor size of more than 2 cm had a statistically significant worse local control ($p=0.02$) [15].

9.6.2 Previously Treated Skin Cancer

Other factors are also important regarding local control, such as previous treatments and histology. Patients treated with radiation therapy for relapse showed a recurrence rate of 9.9 %, while

Table 9.1 Studies on skin carcinomas including electron beam therapy

Literature	Number of patients	Follow-up	Local control	Local control in basal cell carcinoma	Local control in squamous cell carcinoma
Locke J 2001[a,b]	531	5.8 years	89 %	92 %	80 %
Superficial X-rays	317		94 %		
Electron beam	100		82 %		
Combination of treatment	108		82 %		
Megavoltage photon	6		50 %		
van Hezewijk M 2010	434	3.6 years (median)	96.5 %		
54 Gy (18 fractions) electron beam	159	5.4 years	97.5 % (actuarial at 3 years)	97.6 % (actuarial at 3 years)	97 % (actuarial at 3 years)
44 Gy (10 fractions) electron beam	275	2.6 years	96.1 % (actuarial at 3 years)	96.9 % (actuarial at 3 years)	93.6 % (actuarial at 3 years)
Griep C 1995	389	1.98 years (average)	95.1 %	95.9 %	92.5 %
Electron beam	290		Actuarial 93 % at 2 years		
Superficial X-rays	99		Actuarial 90 % at 2 years		
Lovett RD 1990[a]	339	min 2 years	86 %	91 %	75 %
Superficial X-rays	187		95 %		
Electron beam	57		77 %		
Combination of treatment	80		76 %		
Megavoltage photon	15		67 %		
Silva JJ 2000, carcinoma of the pinna	334	3.3 years (median)	86.6 % (actuarial at 2 years)	93 % (actuarial at 2 years)	82 % (actuarial at 2 years)
Orthovoltage X-rays	278		79.2 % (actuarial at 5 years)	83 % (actuarial at 5 years)	79 % (actuarial at 5 years)
Electron beam	39				
Other	17				
Zablow AI 1992	115	3.9 years (mean)	88 %		
Electron beam					
Tapley Ndu V 1975	111/156	2–8.5 years	86 %		
Miller RA 1982	29	2–6 years	82 %		
Electron beam					

[a]Studies from the same institution (Mallinckrodt Institute of Radiology, Washington University Medical Center, St. Louis. MO)
[b]In multivariate analysis, the treatment modality was not significant (electrons versus other types, $p = 0.345$)

patients primarily treated with radiation therapy had a recurrence rate of only 3.1 % [12]. Lovett et al. have reported a local control rate for untreated lesions of 93 %, versus 75 % for previously treated lesion. The recurrence rate for basal cell carcinoma previously treated was 18 % versus 5 % for untreated basal cell carcinoma and 35 % versus 13 %, respectively, for squamous cell carcinoma [5]. In their 10-year updated analysis, Locke et al. found a local control rate of 93 % for previously untreated cancer and 80 % for recurrent lesions. Previously treated basal cell cancer had a local control rate of 86 % compared to 94 % for untreated lesions and 68 % for previously treated squamous cell carcinoma compared to 89 % for untreated lesions [2].

9.6.3 Histology

In Griep's study, the local control rate was 95.9 % for basal cell carcinoma versus 92.5 % for squamous cell carcinoma [12]. Locke et al. reported a local control of 92 % with basal cell carcinoma versus 80 % with squamous cell carcinoma [2]. In contrast, van Hezewijk et al. found no difference in local control between basal and squamous cell carcinoma [16].

In morpheaform basal cell carcinoma, the limits of the lesion are difficult to assess as they are mostly poorly defined. Surgery allows having a better assessment of the margin since the pathologist will analyze the entire lesion. However, if the radiation therapy indication is confirmed, an appropriate margin (at least 1.5 cm) should be given [17].

9.7 Dose and Fractionation

The same total dose and fractionation should be used with electron beam and superficial X-ray therapy. In the literature, different schedules are found such as 6–10-times 6–10 Gy, 33–35 Gy in five fractions, 42.5–45 Gy in 10 fractions, 50–60 Gy in 20–30 fractions, or the more standard 60–66 Gy in 2 Gy per fractions. Usually the same treatment schedule is prescribed both in basal cell carcinoma and in squamous cell carcinoma [2, 11, 12, 15, 16]. These different schedules found in the literature make a comparison between these treatment modalities difficult. Usually small lesions are treated with lower total dose and higher fractionation, whereas larger tumors are irradiated with higher total dose and lower fractionation [2, 5].

van Hezewijk et al. have compared two different electron beam fractionations for epithelial skin carcinoma. Their standard treatment was 54 Gy in 18 fractions of 3 Gy (159 lesions) and their hypofractionated schedule was 44 Gy in 10 fractions (275 lesions). The actuarial 3-year local recurrence-free rate was 97.5 % in the group treated with 54 Gy versus 96.1 % in the group treated with 44 Gy ($p = 0.22$). They neither found any differences between the two schedules in the basal cell carcinoma (97.6 % vs. 96.9 %, respectively) nor in the squamous cell carcinoma subgroups (97 % vs. 93.6 %, respectively) [16]. Locke et al. found a better local control with higher total dose and with a higher fraction size ($\leq$2 Gy vs. 2.01–3, 3.01–4, >4 $p = 0.01$) [2].

9.8 Tissue Reaction

The same tissue reactions are observed after electron beam or X-ray therapy. The importance of the reaction depends on the total dose, the fractionation (dose/fraction), and the field size. Most common acute reactions are erythema, dry desquamation, and moist desquamation. With a treatment on the nose, one can observe a vestibular irritation, sometimes with minor nosebleeds. The late reactions comprise hypopigmentation, subcutaneous fibrosis, skin atrophy, teleangiectasia, and epilation [18]. Residual scarring depends on the initial lesion. Complications can affect soft tissues, they can also include cartilaginous and bone necrosis, but they are altogether very rare (0–6 %), as are the radiation-induced malignancies (1/1,000). For young patients, surgery is a better choice than radiation therapy, particularly for lesions developed on burn scars. Radiation oncologists are concerned with the risk of radiation-induced malignancies even if the probability is very small, but it is an important issue in younger patient treated for skin cancers which have a very good prognostic [18].

9.9 Cosmetic

Good to fair cosmetic and functional result are observed in the majority of patients, namely, between 75 and 97 % [12, 14, 16, 19]. Locke et al. have reported excellent to good cosmetic results in 92 % of their patients. They found worse cosmetic results in patients treated with high total dose, in lesions previously treated, and lesions treated with electrons [2]. Griep et al. have reported a better cosmetic result with electrons, probably due to the fact that in their institution, lesions were treated with small dose per fraction because of their large size [12]. van Hezewijk et al. found no significant difference in terms of cosmetic result between the various dose and fractionation schedules [16].

Conclusion

Radiotherapy is an excellent treatment modality for skin cancer. Electron beam therapy proves to be a good option in skin carcinoma when there is a large and/or thick lesion or because its localization makes surgery more difficult.

As the tumor's local control depends on the tumor size, an early diagnostic is an important issue. Patients with recurrent skin cancers experience a poorer local control. So, early detection and treatment intervention improve the local control and the final cosmetic result.

With electron beam treatment, special knowledge in treatment techniques is mandatory in order to provide the best tumor control, with special attention to the margins, the bolus, the energy's choice, and the total dose and fractionation.

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Radiotherapy of Kaposi's Sarcoma

10

Massimo Caccialanza and Roberta Piccinno

Contents

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10.1 Introduction

Kaposi's sarcoma (KS) is a locally aggressive endothelial neoplasm which typically presents with cutaneous lesions in the form of multiple patches, plaques, nodules or tumours, but may also involve mucosal sites, lymph nodes and visceral organs. Very rarely KS is seen in skeletal muscles, brain and kidney.

After the first description of the disease by Moritz Kaposi in 1872 [1], four clinical forms have been defined:

1. Classic (Mediterranean)
2. Endemic (African)
3. Transplant-related (iatrogenic)
4. HIV-related (epidemic)

These forms have peculiar clinical, epidemiologic and histopathologic characteristics [2–5]. For most of them the therapeutical approach includes radiotherapy.

10.2 Clinical and Epidemiologic Aspects

10.2.1 Classic (Mediterranean) KS

The annual incidence in the USA is estimated to be 0.02–0.06 % of all malignant tumours [2]. The male to female ratio is 3:1, and the mean age of onset is 65 years. Clinically it is characterized by indolent tumours in the distal extremities, especially in males of Mediterranean area or eastern

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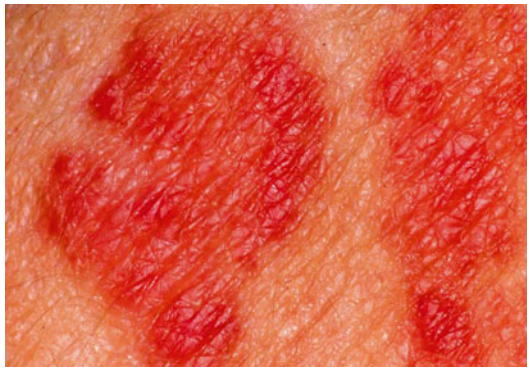

Fig. 10.1 Macular lesions

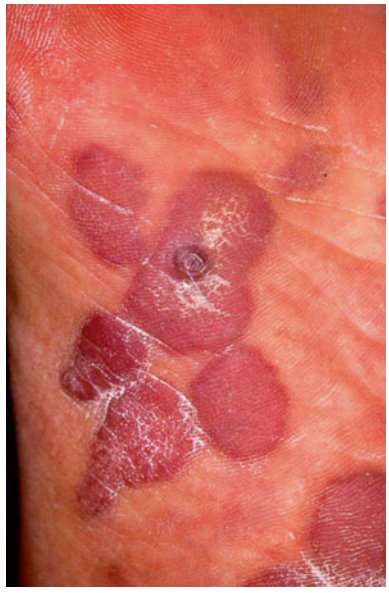

Fig. 10.2 Plaque lesions

Europe of Jewish origin. The lesions can be painful. A portion of cases is accompanied by lymphoedema. Far less commonly lesions are localized on the arms and hands and rarely on the mucosa of oral cavity.

Generally, the disease is confined to the skin (it uncommonly spreads to regional lymph nodes and very rarely can involve bones) and usually develops very slowly.

Clinically, the lesions are blue-red to violet macules that may coalesce to form large plaques or develop into nodules or tumours (Figs. 10.1, 10.2, 10.3, and 10.4).

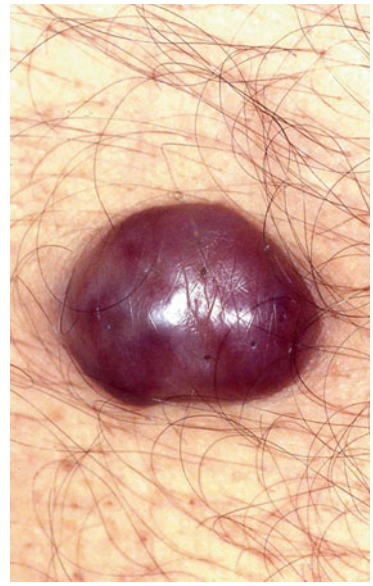

Fig. 10.3 Nodular lesion

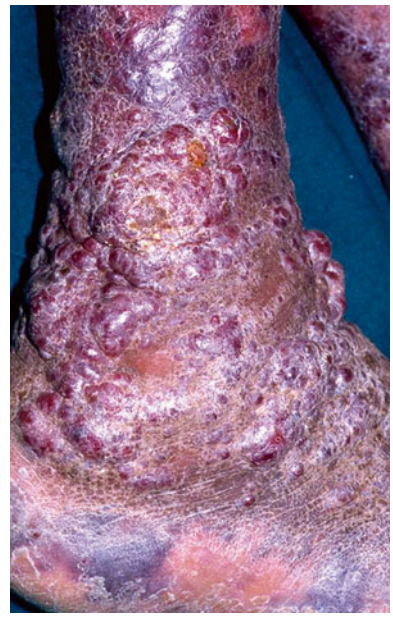

Fig. 10.4 Tumoral lesions

10.2.2 Endemic (African) KS

It accounts for up to 9 % of all malignancies in central Africa, with a male to female ratio of 18:1 (adults). The mean age of onset is of 36 years in females and 40 years in males. Clinically the

disease is often similar to classic KS. The form that arises in middle-aged adults commonly follows an indolent course favouring the lower limbs. In children it is described a lymphadenopathic form rapidly progressive and generally fatal, with a male to female ratio of 3:1.

10.2.3 Transplant-Related (Iatrogenic) KS

It is a rare form of KS, presenting as an indolent or, rarely, aggressive disease in patients receiving immunosuppressive therapy, with organ transplants, cancer or autoimmune diseases.

Clinically the lesions are similar to those observed in classic KS. Both systemic and cutaneous involvement may occur. It may resolve completely upon ending of immunosuppressive therapy.

The progression of the disease may be aggressive, causing the death of the patient.

10.2.4 HIV-Related (Epidemic) KS

The outburst of the disease began in the late 1970s and in the pre-HAART (Highly Active Antiretroviral Treatment) era, about 40 % of AIDS-affected homosexual men developed KS, compared with less than 5 % in other risk groups.

It has declined substantially after the introduction of HAART (1997) and for the avoidance of high-risk sexual practices.

Clinically, it is characterized by either small round or oval pink to reddish macules.

Initial lesions frequently develop on the face and on the trunk. In prolonged courses, KS lesions may be disseminated, often coalescing to form large plaques. The oral mucosa, primarily the palate, is the initial site of localization in 10–15 % of all HIV-KS patients (Fig. 10.5a–c). The involvement of viscera, including the gastrointestinal tract, lymph nodes and lungs is frequent.

10.3 Histopathology

To the different clinical expressions of the disease correspond the distinct histopathologic pictures [3].

In the patch stage a dermal proliferation of small, thin-walled, irregular lymphatic-like channels is prevalent around pre-existing normal blood vessels and adnexal structure.

In the plaque stage there is an exaggeration of the patch stage features with involvement of the whole reticular dermis and even the subcutis.

The nodular stage is characterized by well-defined mostly dermal tumours composed of intersecting fascicles of uniform spindle cells

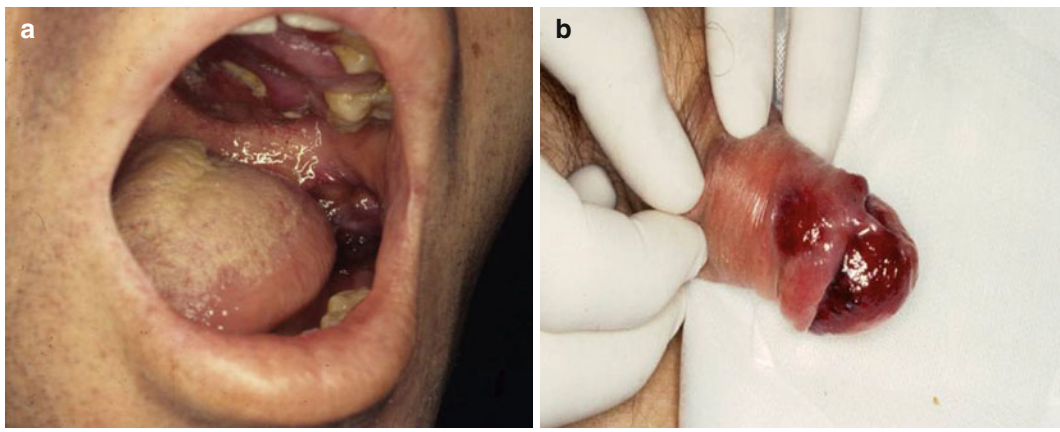

Fig. 10.5 (**a**–**c**) Typical presentations of HIV-related KS lesions

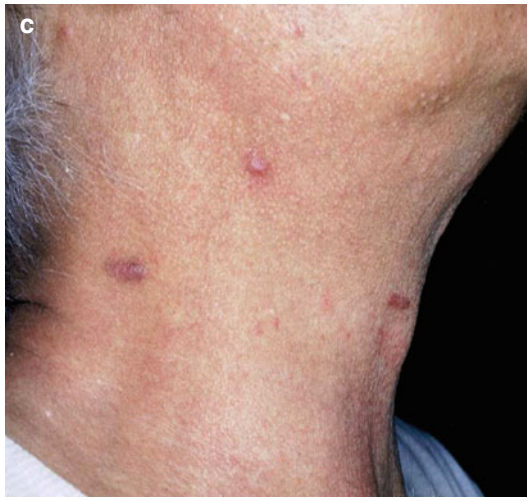

Fig. 10.5 (continued)

which show only mild cytological atypia and frequent mitotic figures. Immunohistochemical and ultrastructural studies have firmly established the endothelial nature of KS.

10.4 Aetiology

In recent years the role of HHV-8 tumorigenesis of all forms of KS has been hypothesized, after the detection of viral DNA sequences in many cases. This virus was first identified in KS cells of a patient with AIDS and now is known to be present in most patients with all clinical types of KS [6].

10.5 Differential Diagnosis

The differential diagnosis includes many clinical pictures also according to the stage of the disease.

In macular stage one would consider angiosarcoma, benign lymphangiomatosis, microvenular haemangioma and hobnail haemangioma; in nodular stage Kaposiform haemangioendothelioma and spindle cell haemangioma; and in late stage acroangiodermatitis of chronic venous insufficiency and Stewart-Bluefarb syndrome (pseudo-Kaposi's sarcoma) [2].

10.6 Staging

To assess the stage of the disease, the more common investigations performed are the following: involved tissues biopsy with histopathological examination, haematological and biochemical studies, chest radiography and, when clinically indicated, gastrointestinal radiography or endoscopy, abdominal ultrasound or computerized tomography scan [7].

10.7 Radiotherapy

Radiotherapy, as all therapies for KS, must be individualized and its planning depends upon size, location and number of lesions, presence or absence of symptoms, overall state of health including comorbidities and goals of therapy (palliation vs. cure).

KS is a tumour relatively radioresponsive. Radiotherapy can be used for different scopes: curative, as far as possible in spite of the multicentric features for classic KS, and palliative or reducing the extent of the disease in HIV-related KS. It is a treatment option for the patients presenting with multifocal but relatively localized KS. Furthermore, typical indications for radiotherapy are palliation of pain, bleeding or lymphoedema and improvement of cosmetic appearance. It is the treatment of choice for the majority of patients with nodular disease of the extremities.

After the introduction of HAART (1997), the employ of radiotherapy in the HIV-related KS has become sporadic.

Local irradiation of KS includes the lesion plus a marginal tissue border in healthy skin of approximately 1–2 cm, whereas a larger margin is necessary for lesions whose edges are poorly defined. The thickness of the lesion dictates the type of radiation required. Thin cutaneous lesions can be effectively treated either by superficial X-ray therapy (50–150 kV) or relatively low-energy electron beams (4–6 MeV) and bolus. Six MeV beam penetrates approximately 2 cm into tissue with 90 % of its intensity before becoming markedly attenuated. The bolus ensures that the most superficial aspect of the tumour receives the

prescribed dose and, because the bolus material absorbs some of the beam, simultaneously limits the degree of penetration of the beam into underlying tissues. Palliation of swollen and painful extremities can be achieved by covering the limb with bolus or by placing it in a water bath and applying irradiation by parallel-opposed photon portals.

High dose rate brachytherapy techniques have also been published: they are useful for lesions with a diameter not bigger than 2.5 cm; the median dose administered is 24 gray (Gy) in 3 fractions. Complete response of all lesions with no relapse is reported [8].

The literature supports the use of a wide range of doses and fractionation patterns. As long as a sufficient dose is delivered, e.g. 20–30 Gy in 10 fractions or, for small lesions, 6–8 Gy in 1 fraction [9] or 8 Gy in single dose to 30–40 Gy in 10–20 daily fractions [10], a salutary outcome is likely [11]. A conventional fractionation regimen was compared with a hypofractionated regimen in the treatment of epidemic Kaposi's sarcoma (24 Gy in 12 fractions/20 Gy in 5 fractions). The two treatment regimens produced equivalent results for treatment response, local recurrence-free survival and toxicity [12]. As far as regards the optimal "biologic dose" of ionizing radiation to be administered, we share with other authors the opinion that the dose is around 30 Gy in 10 fractions over 2 weeks. Such value appears to provide an optimal balance between tumour control and rapidity of treatment [13].

Usually, the same dose schedules are used for all the forms of KS (equally radioresponsive).

The outcome of irradiation shows that more than 90 % of lesions respond to radiotherapy and approximately 70 % respond completely [14–18].

Some residual purple pigmentation remains in about 55 % of treated patients, especially in HIV-related KS [19].

Side effects are rare, and radiation is usually well tolerated, with minimal skin reactions, except for mucositis reaction occurring as a rule in patients with HIV-related KS and mucosal (oropharyngeal) lesions, after transcutaneous radiotherapy [20, 21]. The employ of intracavitary contact X-ray radiotherapy (ICX RT) can avoid or reduce the mucositis reactions as it has been demonstrated by a study of ours [22]. The same results may be obtained with brachytherapy to the hard and soft gum palate, using individual dental plates [23].

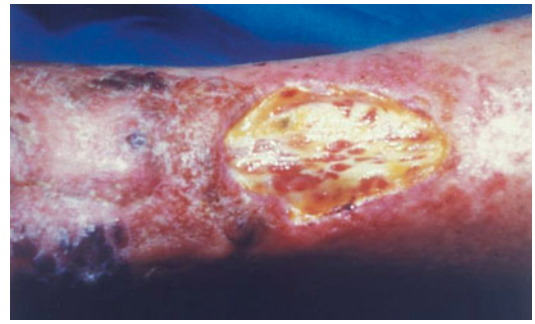

Fig. 10.6 Extensive chronic radiodermatitis of the pretibial area on nodular classic KS, irradiated elsewhere

Yet it has been frequently observed that patients treated with extended field irradiation suffer from severe skin reactions (exudative epidermitis with skin ulcerations) in 5 % of cases [16]. Such toxicity of radiotherapy, more evident in patients affected by HIV-related KS, obviously caused by the condition of immune depression, is related to the need of treating extensive lesions or to the intention of obtaining a preventive action on disease dissemination [24].

On the skin of the pretibial area, the appearance of radiodermatitis (chronic and acute) is more frequent (due to thinning of the skin, vascular alterations and trauma possibilities). Therefore, particular attention has to be paid in the irradiation of KS lesions localized on that area, by limiting the total dose and performing small-sized irradiation fields (Fig. 10.6).

10.8 Clinical Results

Our experience is relative to a retrospective study of 711 lesions of classic KS and 771 lesions of HIV-related KS treated with radiotherapy in the period from 1976 to 2003 [25].

Table 10.1 Techniques of radiotherapy

	Voltage	Amperage	FSD	Field diameter	HVD	Filtration
Contact X-ray therapy (CXRT)	55–60 kV	4 mA	1.5–5 cm	2–4.4 cm	2–12 mm	–
Half-deep X-ray therapy (HDXRT)	100–120 kV	6 mA	30 cm	Maximum 10×12 cm	30 mm	2 mm Al
Soft X-ray therapy (SXRT)	50 kV	25 mA	15 cm	1–4.2 cm	10.5 mm	1 mm Al

kV kiloVolt, *mA* milliAmpère, *FSD* focus skin distance, *HVD* half-value depth (tissue layer reducing the surface dose to 50 %)

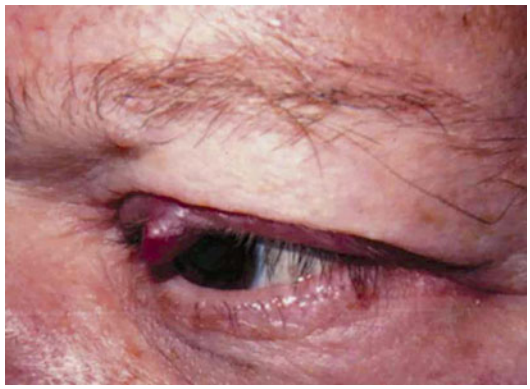

Fig. 10.7 Classic KS. Nodular eyelid lesion before radiotherapy

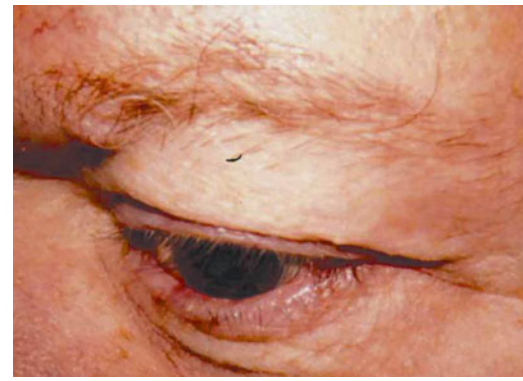

Fig. 10.8 The same case as in Fig. 10.7, 3 years after CX RT. Total dose 25 Gy, complete remission

10.8.1 Radiotherapy Techniques

Traditional radiotherapy techniques were used (Table 10.1).

When the lesions were localized next to critical organs, those were shielded with layers of lead-rubber (6-mm Pb equivalent) and in case of lesions localized on eyelids, special cup-shaped internal eye shields made of an alloy of lead, zinc and nickel were employed to protect the lens [26]. Forty-nine patients with HIV-related KS of the oral mucosa were treated with ICX RT [22]. In three of them the Göttingen method, which reduces reactions of irradiated tissue thanks to an inherent filter able to remove the component of lower energy of the irradiation, was employed [27].

10.8.2 Classic KS

Seventy patients with histologically proved KS underwent radiotherapy. In 19 cases other treatments were administered before the beginning of radiotherapy (surgery, intralesional chemotherapy, laser therapy and cryotherapy). A clinical classification of these patients has not been done, since it is not available [28]. A total of 711 lesions were treated with 711 fields of radiotherapy. Of these 699 were done with contact X-ray therapy (CX RT), ten with half-deep X-ray therapy (HDX RT) and two with soft X-ray therapy (SX RT). The total dose ranged from 10 to 40 Gy with a mean dose of 29.24 Gy (one or two weekly dose fractions of 5 Gy each for CX RT and SX RT and two weekly fractions of 2 Gy each for HDX RT). Follow-up from the end of the treatment ranged from 1 to 324 months (mean 92.63 months). A complete remission (CR) was obtained in 701 lesions (98.59 %) and partial remission (PR) in seven lesions (0.98 %), whereas three lesions (0.42 %) resulted not evaluable (Figs. 10.7, 10.8, 10.9, 10.10, 10.11, and 10.12). These data did not change with time; therefore, the 5-year cure rate from the end of radiotherapy was 99.4 %, 99 % after 10 years and 98.7 % after 13.5 years. The

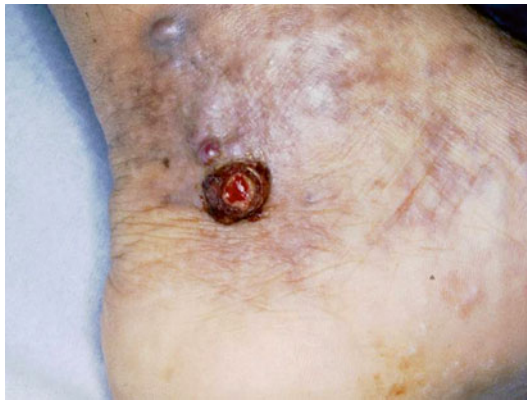

Fig. 10.9 Classic KS. Nodular lesion of the ankle before radiotherapy

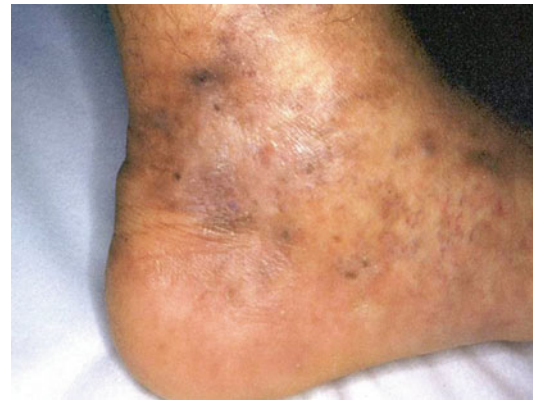

Fig. 10.10 The same case as in Fig. 10.9, 6 months after CX RT. Total dose 30 Gy, complete remission

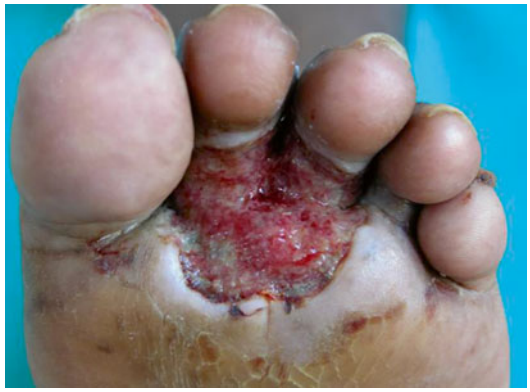

Fig. 10.11 Classic KS, lymphangiomatous type on the plantar surface before radiotherapy

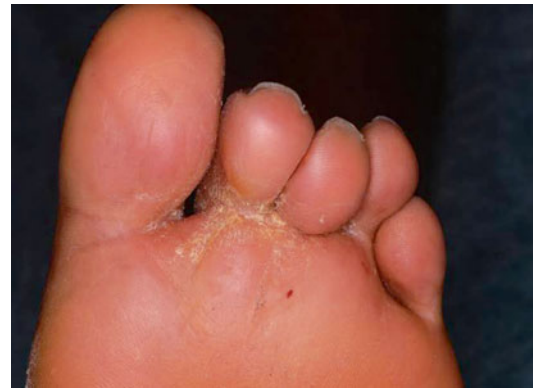

Fig. 10.12 The same case as in Fig. 10.11, 1 year after CX RT. Total dose 30 Gy, complete remission

cosmetic results relative to 701 lesions in CR were judged as good in 530 lesions (75.60 %) and as acceptable in 171 (24.39 %). We considered as "good" the cases characterized by no visible radiation injury and as "acceptable" the cases characterized by a mild skin dystrophy and/or light skin dyschromia. In the painful lesions there has been always an effective palliative action. The treatment has been always well tolerated and there were no skin reactions of such severity as to stop the treatment. In three lesions (0.42 %) of a same patient, localized at the ankle, an acute radiodermatitis occurred after traumatic action of a shoe while walking, shortly after the end of radiotherapy (total dose 30 Gy, CX RT). All three lesions healed with medical therapies.

10.8.3 HIV-Related KS

One-hundred sixty-eight patients with histologically proved KS underwent radiotherapy in the period 1986–1996. Twenty-nine patients were not included either because of insufficient follow-up (<1 month from the end of the treatment) or because of discontinuation of therapy as a result of complications or death (six patients dead, one for disseminated KS and the other five for AIDS). Therefore, the case series is made of 139 patients (132 males and 7 females). A total of 771 lesions were treated. When first observed the patients with KS were classified according to the system of Mitsuyasu [29]. None was stage III, whereas 49 cases of mucosal lesions were

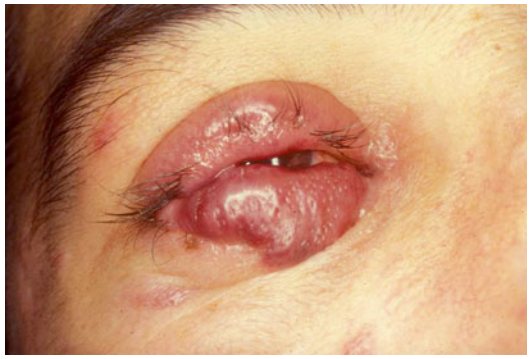

Fig. 10.13 HIV-related KS of eyelids, before radiotherapy

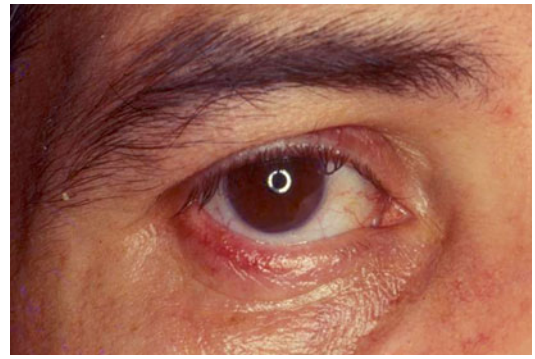

Fig. 10.14 The same case as in Fig. 10.13, 2 years after CX RT. Total dose 15 Gy, complete remission

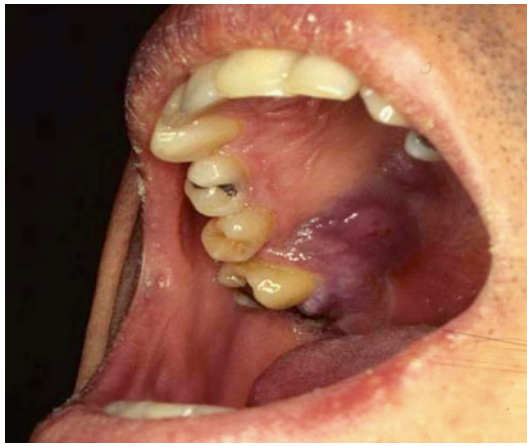

Fig. 10.15 HIV-related KS, hard palate, before radiotherapy

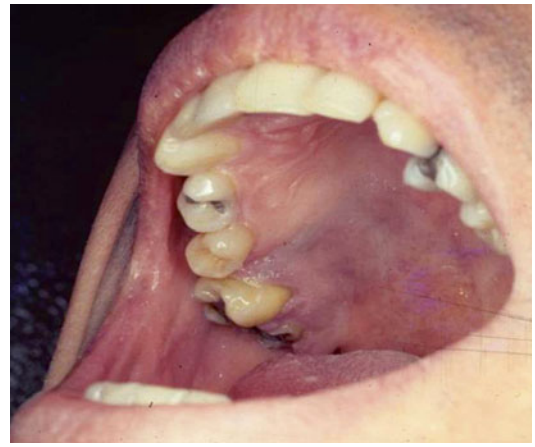

Fig. 10.16 The same case as in Fig. 10.15, 6 months after the end of ICX RT. Total dose 20 Gy, complete remission

classified as stage IV. In many patients A and B substages could not be retrospectively determined. When first examined 53 patients were receiving other treatments (antiretroviral therapy, α-interferon, systemic chemotherapy). In all patients treated, also with regard to their immunological condition, the whole clinical evaluation found appropriate the employ of radiotherapy with the aim of palliation and reduction of the tumour burden. Seven hundred seventy-one irradiation fields were performed: 752 with CX RT, 19 with HDX RT. The total dose administered ranged between 5 and 45 Gy (one or two weekly fractions of 5 Gy each) for CX RT and between 5 and 20 Gy (two to three weekly fractions of 1.5–2 Gy each) for HDX RT. The actual weekly dose administered was a function of lesion site (hyperfractionation in cases involving the eyelid, oral cavity and penis) and the extent of skin and mucosal reactions. The cosmetic purpose of the treatment in some cases required special care in minimizing cutaneous reactions to irradiation. The purpose of HDX RT was mainly palliative, to reduce pain and the size of plaques on lower limbs. It was discontinued when an acceptable result was obtained, with consequent variability in the total dose administered. Follow-up from the end of the treatment ranged from 1 to 46 months (mean 7.9 months). CR was obtained in 705 lesions (91.43 %), PR in 52 (6.74 %) and nonresponse (NR) in 4 (0.51 %) (Figs. 10.13, 10.14, 10.15, and 10.16). A relapse occurred in ten lesions (1.29 %), after 3–9 months from the end of radiotherapy (mean 4 months). The cos-

metic results obtained in 705 lesions with CR were good in 141 lesions (20 %) and acceptable in the remaining 564 (80 %), since there was hyperpigmentation in 560 and hypopigmentation in 4. Radiotherapy was always well tolerated. In case of employ of ICX RT, mucous membrane reaction was always mild and never required discontinuation of therapy. In case of pre-existing pain, there was always an improvement or disappearance of the symptom. No sequelae were observed, except in two patients (lower limbs, pretibial lesions). One had received HDX RT (total dose 10 Gy) and developed an ulceration at the site of irradiation 1 month later. The other patient, who had undergone CX RT (total dose 25 Gy), had remission of the lesion 1 month later. A small ulceration, probably caused by trauma, developed 4 months after the end of irradiation. The two lesions healed after medical treatment.

In our series of classic KS, made up mostly by patients affected by small-sized lesions (treated with irradiation fields of limited extension), the following considerations could be done: (1) the nearly total lack of side effects, (2) the suppression of pain and (3) a very high cure rate. As far as regards the optimal "biologic dose" of ionizing radiation to be administered (mean total dose 29.24 Gy in our series), it is noteworthy that it corresponds to that prescribed by other authors with results as good as ours, even if not able to modify the virological status [30] in the radiotherapy of classic KS.

The results obtained in the treatment of HIV-related KS could be judged as good, with a follow-up limited by the severity of the general health status of the patients (mean follow-up: 7.9 months). In some localizations such as eyelid and penis, the response to radiotherapy has been particularly satisfactory. In our opinion the possibility of irradiating some lesions of the oral mucosa directly with ICX RT, avoiding the employ of external beam radiotherapy endowed with high mucosal toxicity, is of great practical interest.

While many systemic therapies are available for more extensive KS forms [2, 3], a detailed and reliable comparison between radiotherapy and the other topical therapies for both classic KS and HIV-related KS is hard to do, mostly because of the numerical disequality of the series and of the difference in duration of the follow-up in the reports of patients treated with several therapeutic methods found in the literature [2, 5].

Yet, the study we have done on a relevant number of irradiated lesions and with long follow-up has confirmed that radiotherapy is a safe and effective method, as established by some of the most reliable reports of the literature [7, 16, 17, 31–33].

Conclusion

In our experience and in agreement with comparable series reported in the literature, radiotherapy, when scheduled with caution and personalized on the basis of the clinical and immunological features of the patient, has demonstrated to be a therapeutic tool endowed with an advantageous benefit/risk rate, that is a feature of great importance in the global strategy of KS treatment.

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Radiation Treatment of Cutaneous T-Cell Lymphomas: Indian Experience

11

Kaushal K. Verma and Dillip K. Parida

Contents

11.1 Background

Cutaneous T-cell lymphoma (CTCL) is a group of lymphoproliferative disorders characterized by proliferation of neoplastic T-lymphocytes primarily affecting the skin. Several disorders which are considered to be cutaneous T-cell lymphomas have been found to differ widely in biologic course, histological appearance, immunologic and cytogenetic features, as well as in their response to appropriate treatment. Mycosis fungoides and Sézary syndrome(SS), the erythrodermic variant of MF, are the commonest of them.

Mycosis fungoides d' emblée is a low-grade chronic lymphoproliferative disorder of the skin, usually having an indolent course, caused by abnormal proliferation of CD4+T-cells [18]. MF itself is often an epidermotropic disorder characterized by evolution of patches into plaques and tumors composed of small- to medium-sized skin-homing T-cells, some (or rarely all) of which have convoluted, cerebriform nuclei. The condition was first described by Alibert in 1806 (pian

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fungoides), initially thinking that the signs and symptoms were related to yaws. Sézary and Bouvrain described a leukemic variant called Sézary syndrome (SS) in 1938. Lutzner and Jordan elucidated the ultrastructure of Sézary cells in 1968 [47]. The clinical term "cutaneous T-cell lymphoma" (CTCL) was introduced by Eldelson in 1975 to bring together various lymphoproliferative disorders of the skin which were previously known as MF, SS, reticulum cell sarcoma of the skin, and some other cutaneous lymphocytic disorders [10, 11]. In clinical practice, the terms MF and CTCL are often used interchangeably, although MF constitutes only about 50 % of all CTCLs. The clinical presentations and therapy are also different for each subtype of CTCL [35].

11.2 Epidemiology

CTCLs have a worldwide distribution. MF, the most common variant of CTCL, affects men more commonly than women (2:1). Individuals affected are usually in their 50s or 60s. Children are rarely affected. According to the Leukemia and Lymphoma Society in the United States, there are about 1,500 new cases of cutaneous T-cell lymphoma every year. Surveillance, Epidemiology, and End Result (SEER) Program has shown an increase in incidence of CTCL by 3.2 fold between 1973 and 1984. The overall incidence of MF is about 4 per 100,000 [69, 70]. Over the past three decades, the incidence rate of MF is showing an increasing trend, may be because of improved diagnostic tools and techniques. However, the exact incidence may still be underreported because of difficulty in diagnosis or misdiagnosis.

Some studies have identified an increase in prevalence of MF in industrial populations (e.g., among workers who use machine cutting oils) [16]. Viruses like HTLV-1 and HTLV-V are presumed to be associated with MF. Retroviral core proteins have also been isolated from these patients [62, 49]. Almost 70 % of CTCL are T-cell type and immunophenotype wise they are CD4+.

11.3 Aetiopathogenesis

The exact molecular biology of development of MF is still unclear. It may be preceded by a T-cell-mediated chronic inflammatory skin disease. Genetic typing of cutaneous and peripheral blood lymphocytes has shown several genetically aberrant T-cell clones. Thus, one hypothesis is that the development of genotraumatic T-lymphocytes may be involved in the etiopathogenesis of the disease and its progression. The T-cell receptor antigen is encoded with gamma-delta and alpha-beta gene complex. During T-cell maturation, rearrangement occurs first in the gamma-delta complex, and after a successful rearrangement, the lymphocytes become mature CD3+, gamma-delta+, CD4-, and CD8+ cells. In the absence of such activity, however, the alpha-beta complex undergoes rearrangements to produce an alpha-beta T-cell receptor chain and CD3+, alpha-beta+, CD4+, and CD8+ cells. Some of these cells migrate to the skin and others circulate within the blood. These cells undergo further maturation that may take place in the skin under the influence of various factors including skin-specific cellular adhesion molecules. One study has implicated rearrangement or deletion of the tal-1 and NFkB2/lyt-10 encoded transcription factors in a subset of CTCL patients with very aggressive disease [52]. The exact pathogenesis of MF is still poorly understood, but two most common hypotheses regarding its pathogenesis are as follows: (1) MF is a disorder of CD4+ helper T-cells with a single clone present from the initiation of the disease process; (2) there is an initial antigen stimulation phase triggering a benign polyclonal proliferation of T-cells through which a neoplastic clone is established either as a result of a polymerase error or by the action of exogenous mutagens. These activated T-cells have cutaneous lymphoid antigens (CLA) on their surface, and E-selectin on endothelial cells allows these abnormal cells to adhere to the walls of cutaneous venules. The cells then leave the circulation and enter the skin, causing profound epidermotropism [45]. These cells produce interferon-y which stimulates keratinocytes to express the intercellular adhesion

molecule-1 (ICAM-1) on their surface [54]. ICAM-1, a physiological ligand for antigen-1 associated lymphocyte function, is expressed on the surface of all T-cells; the CTCL cells adhere to the keratinocytes exposed to IFN-y [53]. In addition to this mechanism, there is evidence of binding of CTCL cells to keratinocytes by other non-ICAM-1-dependent pathways also. Besides producing cytokines, CTCL cells are exposed to a complex paracrine environment composed of many growth factors and cytokines produced by keratinocytes and stromal fibroblasts, macrophages, endothelial cells, and normal and neoplastic T-lymphocytes. Preformed interleukin-1 (IL-1) is released by proliferating keratinocytes to stimulate both keratinocytes and benign as well as neoplastic T-cells to release granulocyte macrophage colony-stimulating factor (GM-CSF) [42] and macrophage colony-stimulating factor (M-CSF). These two cytokines enhance the antigen-presenting capabilities of Langerhans cells (LC) and activate resting macrophages which respond by releasing a complex mixture of cytokines acting on keratinocyte, fibroblast, endothelial, and lymphohematopoietic cells [3]. In more advanced stage of disease, CTCL cells lose their dependence on epidermal cell adhesion molecules and cytokines, so their epidermotropism either diminishes, resulting in development of tumor nodules that extend deep into the dermis, or is lost completely to permit dissemination of neoplastic cells to nodal and visceral sites. The epidermotropic collections of CTCL cells called "Pautrier's microabscess" may represent congregation of malignant T-cells around Langerhans cells (LC), the dendritic antigen-presenting cells (DC) of epidermis. Chronic exposure to occupational chemicals, pesticides, tobacco, etc., has also been reported to initiate the development of CTCL [65, 72]. Ultraviolet (UV) rays too have the ability to damage LC, thereby initiating the growth signals for CTCL cells. A viral etiology has also been proposed because individuals infected with human T-cell leukemia virus type-1 (HTLV-1) often develop T-cell leukemia with skin involvement, but in all the patients of MF, the evidence of virus has not been confirmed and also the causal relationship between viral exposure and development of MF has not been clearly established [56, 76]. The relationship between immunosuppression and the progression of MF is well known, but its mechanism is not clearly understood. In the presence of progressive disease, infiltrates may become monomorphic, and normal immunity may be further impaired because of lack of regulation and immunological evasion by the neoplastic cells. Modulation of the host immune system also allows progression of neoplastic cells to lymph nodes, blood, and other organs [4, 20–22]. Majority of MF patients are immunosuppressed when the disease is at an advanced stage, resulting in development of disseminated herpes, fungal, or bacterial infection.

11.4 Clinical Presentations

Mycosis fungoides is the neoplasm of T-cell lymphocytes, which is home to skin and to the T-cells of the lymphoid structures but not generally to the bone marrow. The clinical importance of classifications for various stages of MF is twofolds; (1) it highlights the relationship between distinct clinical phases that evolve into each other or can coexists and (2) various phases emphasize the clinical relevance of advances in the understanding of the biology of malignant T-cells. MF usually has an indolent course. The median duration from appearance of symptoms to diagnosis may take as long as 5 years. Majority of the patients (75 %) present with limited patch and plaque stage of disease. Rarely, however, they may have tumor or more advance stage of the disease. The symptoms vary according to the stage of the disease and degree of skin involvement. Weight loss, night sweats, and rise in temperature are uncommon findings in patients of MF. The classical MF progresses through following five distinct phases; premycotic, patch, plaque, tumor, and erythroderma.

11.4.1 Premycotic Phase

Mostly the lesions begin as dry scaly erythematous ill-defined flat lesions often seen over covered areas with itching as the most prominent symptom. The

lesions wax and wane over a period of years and then proceed to plaque stage or may persists for months to years and the patient may remain asymptomatic. This stage of the disease is very difficult to diagnose clinically as well as histopathologically.

11.4.2 Patch Phase

These lesions manifest as hypo- or hyperpigmented, severely itchy erythematous, occasionally eczematous, and barely palpable patches occurring anywhere on the body but are more often seen on the trunk, pelvis, buttocks, groin, under the arms, and proximal parts of extremities. Some areas in the patches may be raised as plaques. This phase may persist for years as nonspecific dermatitis. However, the disease can be diagnosed histopathologically.

11.4.3 Plaque Phase

The lesions are well-demarcated, erythematous indurated plaques with well-defined borders which may coalesce or exhibit central clearance. The palms and soles may be thickened and fissured. This stage of MF may coexist with patch phase of the disease.

11.4.4 Tumor Phase

The patches and plaques progress to indurated nodules which may arise on normal skin [41]. In this stage of disease, erythematous violaceous raised dome-shaped nodules and a mushroomlike tumors or ulcerated nodular lesion may be present. The tumors represent vertical growth and are most common over the face, digits, perineum, and scrotal skin. Infrequently, this phase exists in the absence of patch or plaque phase. This phase of MF has histopathological infiltration of CTCL cells below the papillary dermis.

11.4.5 Erythrodermic Phase

Erythrodermic phase of MF may arise de novo or it may develop from any other stage of MF. During this phase, in addition to the patches and tumors, the patients develop large red areas which are very itchy and scaly. There may be thickening of skin with prominent skin folds on the face and fissuring as well as thickening of the skin of palms and soles. The patients present with generalized erythema with infiltration of the skin and intense pruritus, which is difficult to control with conservative measures. Very painful erythroderma may arise de novo or may coexists with any of the phases of MF. This stage is not always associated with Sézary syndrome.

11.4.6 Sézary Syndrome (SS)

Leukemic involvement with erythrodermic phase occurs in a small proportion of MF patients called Sézary syndrome (SS). Sézary syndrome has been historically defined as a triad of erythroderma, generalized lymphadenopathy, and the presence of neoplastic T-cells (Sézary cells) in the skin, lymph nodes, and peripheral blood. The patients of SS have erythroderma with more than 10 % malignant T-cells in peripheral blood called Sézary cells (SC) and lymphadenopathy. The clinical findings may also include edema and tumors involving the face, severe fissures over palms and soles, intense pruritus, and cutaneous tenderness. The minimal criteria required for the diagnosis of SS are demonstration of a T-cell clone (same clone in skin and peripheral blood) in combination with one of the cytomorphological or immunophenotypical criteria.

11.5 Internal Organ Involvement

Extracutaneous involvement occurs in approximately 10–20 % of MF patients. Up to 25 % of the patients with plaque or tumor stage have detectable circulating SC in their blood, and over 90 % of patients with generalized erythroderma have varying number of SC in their blood [17]. Although MF may be a systemic disease from the onset, the clinical behavior seems to suggest that progressive skin involvement progresses to lymph nodes and then to visceral involvement [12]. The most common organs involved are lymph node, bone

marrow, lungs, gastrointestinal tract, and liver. Visceral involvement in MF is often subclinical and does not routinely have a fatal termination. Neoplastic T-cells however are observed in nearly every organ in patients with advance stage disease involving blood and lymph node. Approximately 30 % of newly diagnosed MF patients present with lymph node metastasis. The involved lymph nodes are usually between 1 and 4 cm, mobile, and non-tender. Lymphadenopathy increases with the stage of the disease and is associated with a poor prognosis. Bone marrow involvement is observed in less than 5 % of the patients.

11.6 Diagnosis

The skin biopsy sample is examined to identify lymphoma cells. A number of other tests including tests for lymphoma markers (immunohistochemistry) and lymphoma genes are required to determine the type of lymphoma and to confirm histological findings. Clinically MF can be confused with certain benign cutaneous disorders like lymphoid papulosis (LP), alopecia mucinosa follicular mucinosis (AM-FM), and pagetoid reticulosis (PR) [5, 48, 71, 75]. Adult T-cell leukemia-lymphoma (ATLL) and CD30+ anaplastic large-cell lymphoma are two malignant conditions which resemble and share many common pathological features with that of CTCL. Histopathologically, MF has an upper dermal mononuclear cell infiltrate, which is intimate with the epidermis and obscures the dermo-epidermal junction. Demonstration of epidermal collection of lymphocytes with hyperchromatic, irregular nuclei lacking spongiosis is considered to be diagnostic for MF. The presence of Pautrier's microabscess is the hall mark of the disease; however, at times it may not be detected. Sézary syndrome is diagnosed by presence of >10 % SC in the peripheral blood. The cells are recognized by deeply convoluted cerebriform nuclei and high nuclear cytoplasm ratio. These cells may contain PAS positive cytoplasmic vacuoles. In a diagnosed CTCL patient, the presence of large number (>10 %) of Sézary cells in the peripheral blood with erythroderma is diagnostic of Sézary syndrome. Pathological confirmation of MF may be difficult in the early stage because the majority of lymphocytes in the epidermis may be inflammatory and nonneoplastic. Many CD4+ and CD8+ T-lymphocytes within the dermis are also nonneoplastic and are present as a result of activation of the immune response. Therefore repeated and multiple skin biopsies may be helpful in the diagnosis. Molecular biological markers like CLA and CD45RO (memory T-cell marker) are expressed by CTCL cells. Hence, molecular biological techniques have become more important for confirmation of the diagnosis. In fact MF was among the first lymphomas to be characterized immunologically [6]. The most appropriate mean to optimally diagnose the condition is to combine clinical, pathological, pathobiological, and immunophenotypic evaluation results. There must be a good interaction between the dermatologist, radiation oncologist, dermatopathologist, and dermatobiochemist with experience in dealing with MF patients to make an accurate diagnosis and decide further course of management.

11.7 Prognosis

The principal prognostic factors are the (1) percentage of the total skin surface involved and phase of disease, (2) lymphadenopathy and visceral involvement, and (3) presence of lymphoma cells in the peripheral circulation [50]. In the early stage of disease, the prognosis has also been independently associated with pathobiological findings like depth of cutaneous infiltration, total contiguous and non-contiguous infiltrative cell density, and the proportion of reactive CD8+ cells and dermal infiltrate [26, 33, 40, 60]. However, the prognosis is generally poor in advanced stage of the disease. Patients with very advance dermal or systemic disease may lose various cell-surface antigens and have chromosomal changes. But whether these changes have an independent prognostic significance apart from their presence in advance stage disease is still unclear [9]. The distribution of skin tumors affect the ultimate prognosis in stage IIB as does the presence of circulating cells in the blood in stage III [17, 33]. Transformation of MF cells to large-cell lymphoma also implies a poor

prognosis. In all the large studies, the median survival of patients of mycosis fungoides is shown be about 10 years [28].

11.8 Principles of Management

A number of therapeutic modalities have been used to treat MF. Many of them have a good response, but often the disease recurs and progresses. Patients with stage IA and IB disease (patch and plaque stage only) account for about 75 % of all new patients. Therefore, early-stage disease that is mostly localized in the skin has an excellent chance of cure with skin-directed therapies alone. However, in the advanced stage, adjuvant systemic therapies may also be needed for better results. In metastatic and disseminated disease, palliation can be achieved with both local and systemic chemotherapy. Skin-directed therapies include topical chemotherapeutic agents like carmustine (BCNU), nitrogen mustard, narrow band UVB, systemic PUVA, electrons, and X-ray therapies. All these agents primarily affect disease confined to the skin by destroying the neoplastic T-cells directly, probably by triggering T-lymphocyte apoptosis and by inhibiting the production of cytokines from the epithelial and stromal cells, which are necessary for neoplastic T-cell survival and proliferation [8]. The options of different topical modalities should be exhausted before the disease progresses enough to require systemic therapy. Certain topical agents offer excellent palliation even in advanced disease. Photopheresis, a systemic immunological therapy that acts by both directly killing T-lymphocytes by the cytotoxic actions of psoralen/UVA light and also indirectly by eliciting antitumor cell immune responses, has been used in CTCL. Similarly, other systemic agents such as retinoids and biological response modifiers like IFN-alpha have been shown to exert their therapeutic effects by modifying the production of cytokines from keratinocytes and dermal fibroblasts in this disease. Also, these agents have direct effects on benign as well as malignant T-lymphocytes [23]. The detail outline of treatment strategies has been given in Table 11.1.

Table 11.1 Treatment strategies by stage

T1: Topical
T2: Topical+/– TSEI
T3: TSEI+/– topical+/– local radiation boost
T4: PUVA/photopheresis/systemic chemotherapy +/–TSEI
Extracutaneous disease: megavoltage photon irradiation+/– Systemic chemotherapy

11.9 Skin-Directed Radiation Therapies

11.9.1 Local External Beam Irradiation

Local radiotherapy was first described by Schultz in 1902. But the techniques of treatment were developed in late 1950s. There were practical problems in treating large field skin surface having oblique contours [28]. The cutaneous lesions are extremely radio responsive, and a dose-response relationship has been demonstrated [7, 23, 24, 39, 66]. Superficial, orthovoltage radiations as well as electrons in doses of 20–40 Gy are very effective in controlling the disease and have been used to treat localized primary or relapsed patches, plaques, and tumors. The fraction size may vary between 1 and 2 Gy, depending on the site and the size of the lesions. The complete remission rates with this therapy may be as high as 90–100 % in localized lesions. Local external beam radiation can be considered for patients having very localized disease. This is also very useful in the patients who either do not respond or have residual disease after PUVA/narrow band UVB therapy. Cotter et al. have even demonstrated 100 % remission with a radiation dose in excess of 30 Gy [7]. Wilson et al. have reported a remission rate of 97 % with external beam radiotherapy [73]. Isolated residual or relapsed lesions after PUVA therapy can also be effectively treated by this method with excellent results. In disseminated disease, a dose between 5 and 20 Gy provides adequate and effective palliation.

11.9.2 Teleroentgentherapy or Total Skin Electron Irradiation (TSEI)

Although radiation as a therapy was used for the treatment of localized/limited lesions of MF in

1902, large areas of skin or the entire skin with low-energy X-rays or electrons could not be treated due to lack of equipment and technical shortcomings. Therefore, a technique was developed, as total skin electron irradiation therapy, which was first used in the clinical practice in 1952.

Teleroentgentherapy or total skin electron irradiation (TSEI) is still a technically and practically challenging procedure; hence not many centers around the world use it. The setup for performing TSEI requires a proper infrastructure, and the treatment procedure requires close coordination among the radiation oncologist, medical physicist, and dermatologist. A variety of technical and clinical issues related to TSEI and its effects were reviewed by Reavely et al. [63]. A model of TSEI treatment using the "six-dual-field" technique was reviewed by Faj et al. [14]. The procedure has been modified several times during the process of developing the TSEI program at Stanford University to make it more technically refined and clinician as well as patient friendly, which was widely accepted by many centers, and at the same time, many centers tried to improve upon the dose-schedule of the technique. Trump et al. first described the application of the TSEI in 1953 [66]. Since then, many modifications to the technique and dose fractionation have been done to obtain better results, which have been documented in many studies [15, 19, 25, 29, 31, 32, 34, 37, 38, 46, 51, 55, 64, 67, 68]. In a study by Jones, data of more than 2,000 patients is presented [31]. His subsequent publication on these patients included historical information, definition of target volume, different techniques, dosimetric aspects, updated clinical results from both Stanford University and Hamilton Regional Cancer Center and also an attempted meta-analysis of the worldwide literature [34]. At the Hamilton Regional Cancer Center, out of a total of 621 patients treated between 1956 and 1996, 401 patients received TSEI with/without any adjuvant modality of treatment or concurrent therapies, and another 52 patients received TSEI plus adjuvant mechlorethamine or concurrent systematic chemotherapy, retinoids or interferon [34, 36, 61].

A dose of 4–7 MeV is usually used to treat epidermal and dermal lesions homogeneously. As most of the dose (80 %) is delivered at a depth of 1 cm and less than 5 % beyond 2 cm, structures below the deep dermis are spared. Shadowed regions like the scalp, perineum, sole, and other skin folds are boosted later with local electron fields. TSEI produces excellent results in patients with diffuse cutaneous involvement with patches, plaques, or tumors and especially in such patient's refractory to PUVA or other skin-directed therapies. The results are also good in symptomatic erythroderma. The stage of the disease and the total dose of the electron irradiation determine the end result, such as the response to therapy and diseases-free survival. In a study by Hoppe et al. the initial complete response ranged from 86 % in early-stage diseases to 44 % in the tumor stage. Kuten et al. have reported a cure rate of 95–100 % with TSEI [43]. Ysebeart et al. have described that TSEI produces excellent results in T1, T2 stage of MF [77]. The probability of complete remission is high with TSEI, and it offers good palliation in advanced disease [13]. Regardless of the technique used, the most important factors to get the best results in TSEI remain the electron energy, which should be 4 MeV and the total dose which should be more than 30 Gy [34, 57, 58]. Published literature also shows the benefit of TSEI on SS which reduces the burden of circulating T-cells in peripheral blood [30].

11.9.3 The Indian Experience

We have been using this therapeutic modality in MF patients since 1985, and in our experience, TSEI is an excellent treatment modality in both early and advanced disease [57, 58]. Between 1985 and 1998, we have treated 14 such patients, all males between 27 and 82 years of age with a disease duration of 4 months to 2 years [57]. The duration of disease was <6 months in two patients, 6–12 months in four, and 1–2 years in the rest. Out of 14 patients, 7 had T2 and the other 7 had T3 stage disease. Seven patients had more than 90 % skin involvement, whereas the remaining patients had 60–90 % involvement.

Nine patients had predominantly plaque lesions with diffuse involvement, while the rest had tumors and plaques. Two patients had lymph node involvement at the time of presentation. TESI was carried out using a high-energy linear accelerator (Clinac-20) with 6 MeV electrons. The patients were made to stand on a stationary platform with the legs wide apart behind a polystyrene screen (to reduce the beam energy to 4 MeV) at a distance of 10 ft from the isocenter of the accelerator. Two large overlapping fields were used to irradiate the whole length of the body. The central axis of the fields pointed 15° upwards and downwards from the horizontal plane to minimize photon contamination, as described in the Stanford technique. All the patients were treated in six positions (anterior, posterior, left anterior oblique, left posterior oblique, right anterior oblique, and right posterior oblique). The total dose of radiation varied from 8 to 36 Gy with a daily fraction size of 120 cGy, given over 5 days in a week. During irradiation the eyes and nails were shielded with a 3 mm-thick lead shield. A supplementary boost dose of 10 Gy was given to self-shielding areas like the scalp, perineum, and soles. Only seven patients could tolerate a total dose of 36 Gy, while three patients received a dose between 24 and 36 Gy, and one patient was treated with a palliative dose of 8 Gy. Three patients did not come back for treatment after the initial eight treatment sessions; hence they were excluded from the analysis. The total follow-up period ranged between 4 and 110 months (median 52 months) [57]. Ten patients had complete remission with no evidence of disease following TSEI. Histopathology repeated in three patients also did not show any evidence of MF. Relapse of the cutaneous lesions occurred in three patients over the shaded area. All of them had received a total dose of less than 30 Gy. The relapse was noticed after a minimum follow-up period of 2 months. One patient developed visceral metastasis involving the liver 6 months after radiotherapy. Two patients died due to progression of the disease. Five patients were alive without any evidence of the disease at the end of 5 years of follow-up.

At present we perform TSEI using Elekta (SL-20) dual energy linear accelerator having a special attachment which delivers electron at a very high-dose rate (30 Gy/min) at the isocenter [58]. The high-dose-rate (HDR) mode delivers a 4 MeV electron beam with acceptable beam uniformity and adequate depth dose while maintaining a low level of X-ray contamination. The HDR mode is a useful treatment modality with good results and reduced treatment time while retaining proper functioning of the accelerator dosimetry systems and interlocks. Between 1998 and 2000, we have treated seven clinically diagnosed and histopathologically proven CTCL patients using HDR mode TSEI. All seven patients were male between 40 and 64 years of age, who had the disease for 9–18 months. Three patients had T2 and four patients had T3 stage disease with more than 90 % involvement. In three patients, the lesions were confluent, ulcerated and bleeding on manipulation. Extracutaneous sites were not involved in any of the patients. All patients were evaluated and treated with TSEI with a total radiation dose of 36 Gy. Thermo luminescent dosimeter (TLD) measurements of the prescribed skin dose were obtained in these patients at the lateral margins, dorsum of the foot, perineum, and scalp. The patients were given hydration before treatment and advised to take high calorie diet throughout the treatment. The treatment time taken for an individual setting with this modality was only about 15 min, which is significantly shorter than conventional TSEI time, which takes about 2 h. Four out of seven patients had complete remission both clinically and histopathologically following TSEI. In the other two patients, the lesions healed with a few ulcers, which healed within 2 months after TSEI. One patient died during the course of treatment owing to rapid progression of the disease. There were treatment interruptions for various durations in all patients because of radiation-associated morbidities such as the decrease in hemoglobin and total leucocytes count, development of blister, desquamation of the skin, and poor general condition of the patients. One patient developed pericardial effusion leading to generalized edema,

Table 11.2 Results of total skin electron irradiation therapy ($n=25$)

Response	No. of patients
Complete remission	20
Progressive disease	2
Death	3
Recurrence	5
Lost to follow-up	3

who was managed for cardiac disease and treated like other patients. The patients were followed up at an interval of every 6 weeks in the first year, every 3 months during the second year, and every 6 months there after following TSEI. The total follow-up period ranged from 4 to 26 months (median 9 months) [58]. In one patient, the lesions relapsed on the trunk after 10 months, and in the other patient who did not received the boost treatment, the lesions relapsed over the eyelid and the perineum after 4 months. He was treated with 10 Gy of radiation dose to these regions. At the end of 2 years, all six patients were alive. The combined results have been outlined in Table 11.2.

Now there is enough evidence to suggest that TSEI alone can achieve remission rate of 80–97 % in newly diagnosed MF patients. The patients with stage IA, where the lesions persist or relapse after treatment, and in those with stage IB – IV disease also have reduced risk of clinically significant progression, transformation, and dissemination of disease following TSEI, leading to higher rates of cause-specific and overall survival.

11.9.4 Toxicities Associated with TSEI

TSEI is a well-tolerated therapy by most of the patients; however, radiation-associated acute toxicities like erythema, pruritus, alopecia, xerosis, edema of the lower limbs, hypohidrosis, bullae of the hands and feet, and loss of nails may occur in majority of the patients. On long- term follow-up, the most common symptoms observed are telangiectasia, atrophy, xerosis, alopecia, and hypohidrosis. Secondary cutaneous malignancies following TSEI have also been reported, which may be partly due to previous therapies used for the disease, particularly potent carcinogens like PUVA and mechlorethamine which may have contributed to the increased risk [1, 44]. Systemic side effects following TESI are usually not observed, as electrons do not penetrate beyond dermis.

At our centers, the therapy was tolerated well by most of the patients; however, radiation-associated changes like nausea, general fatigue, complete loose of hair, edema over the joints of the extremities, and tenderness over the hand and feet were observed in all patients who received more than 20 Gy of radiation. Patients receiving more than 20 Gy radiation also developed different grades of skin desquamation (grade III-3, grade II-7). Moist desquamations as well as blisters over the dorsa of the feet and lateral body surfaces were more often encountered with a higher dose. The desquamation was visible in the third week of the treatment. The treatment had to be interrupted for some periods in these patients to allow the desquamation to heal. The patients who developed acute toxicities were taken off the radiation therapy, admitted and managed with antibacterial therapy, parenteral nutrition, and blood transfusion where indicated and other conservative measures were instituted [57]. Four and two patients had edema of the hands and feet and conjunctivitis, respectively. One patient had dystrophy of the nails of the hands. However, none of the patients developed skin necrosis or a corneal ulcer.

The response to radiation therapy in MF is dependent on the total radiation dose and duration of treatment. Prolonged overall treatment duration can spare the tumor cells and lower the chance of cure, whereas delivering the total dose over a shorter duration provides greater radiobiological benefit and offers better tumor control [7, 25]. Hence, it is very important not to have more treatment interruptions and to complete the total treatment within shorter duration.

In order to reduce TSEI-related toxicities and treatment interruptions, we tried to modify the treatment schedule. The treatment was carried out using a HDR mode delivering 4 MeV electron at

Table 11.3 Comparison of treatment schedules

	Conventional TSEI	Modified alternate day TSEI
Total radiation dose, Gy	36	36
Total treatment duration, wks	14	10
Treatment schedule	5 fractions/week until completion of total dose	5 fractions/week for 2 week then 3 fractions/week. On alternate days until completion of total dose
Treatment-related toxicity		
Mucositis	++	+
Desquamation	++	+
Blisters	+++	+
Edema of the limbs	++	+
Treatment interruptions	2–3	Nil

a dose rate of 30 Gy/min at isocenter. In this protocol, the patients were treated with Stanford technique, 120 cGy/field/day, to a total dose of 36 Gy. The treatment was delivered 5 days/week for first 2 weeks and then on alternate days until completion of total radiation dose. At the end of the treatment, a booster dose of 10 Gy was delivered to self-shielding areas such as sole, scalp, and perineum. Rest of the evaluation and follow-up protocols were similar to previous group of patients. This modification in the treatment protocol resulted in much less occurrence of radiation-associated toxicities like wet desquamation, swelling of joints, etc., with no treatment interruptions. The toxicities were limited to small blisters and mild swelling and pain of small joints. All the patients could complete the radiation treatment of total dose of 36 Gy within 10 weeks, compared to 14 weeks by conventional treatment schedule. Four patients were treated with this protocol and all of them had complete remission [59]. They were followed up for 60–84 months with no relapse of the disease. Comparative details of conventional Stanford technique and modified protocol are given in Table 11.3.

11.9.5 Re-irradiation with TSEI

The patients who experience relapse of the disease with diffuse cutaneous involvement after TSEI, which is not amenable to other topical modalities, may be offered a second course of TSEI. In our series of 25 patients, five patients relapsed, out of which two patients were treated with an additional dose of 10 Gy to recurrence sites [58]. In a study from Yale, 14 patients received two, and five patients received three courses of TSEI. The median dose was 36 Gy for the first course, 18 Gy for the second, and 12 Gy for the third course. The median total dose after these additional courses was 57 Gy. After a second course of TSEI, 86 % of the patients achieved complete remission with a median disease-free interval of 11.5 months [2, 74]. The criteria for re-irradiation include a long disease-free interval following the first course of TSEI, diffuse cutaneous involvement, and failure of other adjuvant modalities.

TSEI therefore is a proven and effective treatment modality for MF patients with diffuse involvement with plaques or cutaneous tumors and for patients with symptomatic erythoderma, and it is a good palliative therapy in advanced stage of the disease. It also offers good results in patients with extensive patches or thin plaques refractory to PUVA or other skin-directed therapies. Technical innovations in recent years with high-dose-rate mode of electron delivery have made TSEI easier, less time consuming, and more patient compliant. A better understanding of the pathophysiology of MF, proper infrastructure, optimum dosimetry, and dose fractionation will further improve the disease control rate.

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Merkel Cell Carcinoma: The Sydney Experience

12

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12.1 Introduction

Merkel cell carcinoma (MCC) is an aggressive cutaneous neoplasm with malignant neuroendocrine differentiation. It predominantly afflicts the elderly white population with a male predominance [7]. MCC has early local invasion, nodal involvement, distant metastases and a high rate of recurrence [22]. It is sensitive to radiotherapy [20, 21]. Polyoma virus-positive MCC may have a better prognosis [8]. Sentinel lymph node biopsy can help direct regional treatment [9]. Despite aggressive therapy, MCC has a higher mortality than melanoma [5, 15].

It is regarded as a rare tumour [6]. However, the incidence is rising [15]. There is an association with increased statin use [18] and in the immunosuppressed [3, 17]. The highest incidence in the world is in Australia [5]. Given this scenario, we decided to retrospectively investigate the MCC experience in our institution. Particular emphasis was put on the impact of radiotherapy (RT).

12.2 Methods

12.2.1 Patient and Tumour Factors

Patients with a histologically proven diagnosis of MCC who presented between January 1996 and June 2007 to St. Vincent's and Mater Hospitals, Sydney, Australia, were identified. Patient tumour

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and treatment characteristics were collected and analysed. Patient factors include age, sex and any history of immunosuppression. Immunosuppressed patients were either six transplant patients (heart [3], lung [2] and kidney [1]) or eight patients that had been on long-term steroids. They included seven patients with connective tissue diseases (ulcerative colitis, pyoderma gangrenosum, scleroderma, myasthenia gravis, psoriatic arthritis, rheumatoid arthritis and multiple myeloma) and one patient with long-term kidney cancer.

Tumour factors recorded included tumour site, size and involvement of regional lymph nodes, distant metastatic disease and overall staging. Treatment characteristics recorded included whether wide local excision (WLE) is used or not, regional dissection, RT to the primary and regional sites and the use of chemotherapy both in the adjuvant and definitive settings. For staging, most patients underwent computed tomography (CT) of the chest, upper abdomen and regional nodes. Patients were staged by a four-tiered staging system developed by Memorial Sloan Kettering Cancer Center (MSKCC) [1].

12.2.2 Radiotherapy Technique

Patients were treated according to the following protocol. The primary site was treated with 46–50 Gy in 2 gray (Gy) fractions to an area of skin that includes the lesion or scar with a 5 cm margin. Compromise may have been needed for nearby dose-limiting organs, e.g. eyes. An electron or superficial/orthovoltage technique was often used. Regional treatment target was to the draining lymph nodes and was given with same dose using megavoltage techniques. Gross disease may have been boosted to a higher dose, e.g. to 60 Gy. Bolus was used to cover any scars or drain sites to achieve full dose on operated skin that is thought to be at risk. The field treating the primary site was junctioned to the regional field if field edges are within 5 cm and there is no danger of unnecessary toxicity. Axillary fields are treated as per Fogarty et al. [4].

12.2.3 Statistical Analysis

IBM SPSS Statistic v 19.0 was used to conduct all statistical analyses. Local recurrence-free survival was defined as the time from initial diagnosis to the first local recurrence or date of last follow-up. Regional recurrence-free survival was defined as the time between the initial diagnosis and first regional recurrence. The disease-free interval was defined as the months between the date of initial diagnosis with MCC and the patient's first recurrence of MCC and date of last follow-up. MCC-specific survival (MCCSS) was defined as the interval between initial diagnosis and the date of last follow-up; death from MCC was considered an event, and all other cases were censored. Overall survival (OS) was assessed as the interval between initial diagnosis and date of last follow-up; death from MCC or other causes was considered an event.

12.3 Results

12.3.1 Patient Characteristics

Sixty-seven patients with MCC were identified. Five patients presented stage IV disease. These five patients were treated with palliative intent and were excluded from the analysis. The reported analysis is therefore a study of radical treatment of 62 patients with stage I–III disease. Patient and clinicopathological characteristics are listed in Table 12.1. The overall analysed cohort of 62 patients was 68 % male and 32 % female, with a median age at diagnosis of 74 years. Forty-two cases (68 %) were stage I or II. Twenty cases (32 %) were initially diagnosed with involved lymph nodes (stage III).

12.3.2 Recurrences

Nine patients (14 %) experienced a local recurrence of their MCC. Sixteen (26 %) developed a regional recurrence; all locoregional recurrences were observed in stage I or II patients. No stage III

Table 12.1 Summary characteristics for the patient cohort

Factor	Value	*N*
Patient sex	Male	42
	Female	20
Age at initial diagnosis	(years)	Median = 74 (range 47–88)
Immunocompromised at initial diagnosis	Yes	14
	No	48
Types of immunosuppression	Long-term steroids	8
	Transplantation	6
Primary site of MCC	Head and neck	32
	Upper limb	8
	Lower limb	9
	Trunk	3
	Buttocks	1
	Not known	9
Primary macroscopic size	(mm)	$n = 53$; median = 15 (range 5–60 mm)
Stage	I	38
	II	4
	III	20
Lymphadenectomy	Yes	17
	No	45
Final surgical treatment for primary	Incisional biopsy	3
	Excisional biopsy	21
	WLE	29
	Not applicable	9
Adjuvant RT to the primary site	Yes	43
	No	10
	Not applicable	9
RT to the regional node site	Yes	43
	No	19
Local recurrence	Yes	9
	No	53[a]
Regional recurrence	Yes	16
	No	46
Distant recurrence	Yes	16
	No	41
	Not known	5
Status at last follow-up	Alive	22
	Died of disease	20
	Died of other/unknown	20

[a]Out of 53 with no local recurrence, 9 unknown primaries are included

patients had regional relapses observed with a median follow-up of 44 months (range 7–115 months). Distant recurrence status was known for 57 patients and, of these, 16 (28 %) recurred in a distant site (11 stage I/II; 5 stage III).

12.3.3 Impact of RT to the Primary Site

Local recurrence-free survival was assessed. For the subset of 42 stage I and II patients, those that

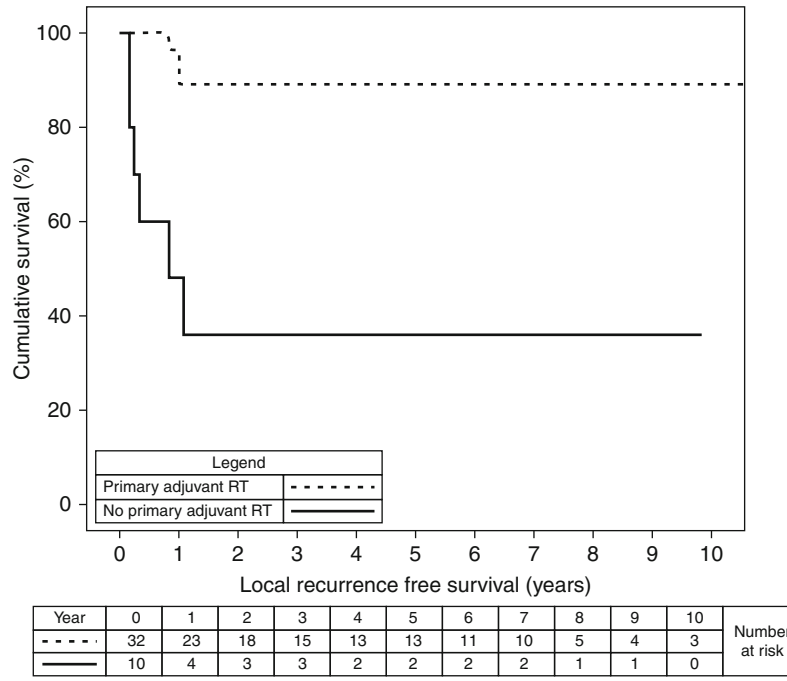


Fig. 12.1 Local recurrence-free survival of 42 stage I and II patients

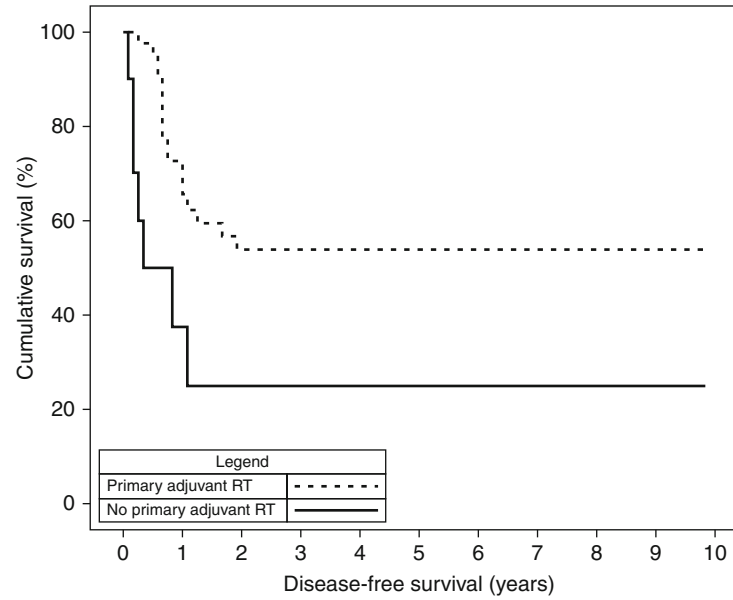
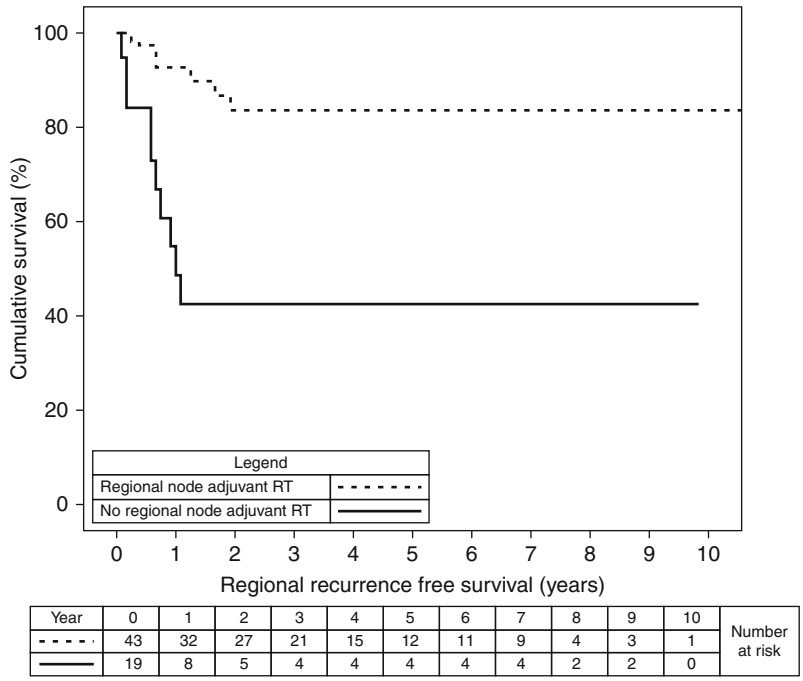


Fig. 12.2 Disease-free survival for the overall cohort of patients having adjuvant RT to their primary site ($p = 0.009$)

had RT to their primary site ($n = 32$) had a 2-year local recurrence-free survival of 89 % compared with 36 % for patients ($n = 10$) not receiving RT (Fig. 12.1, $p < 0.001$).

Disease-free survival for RT to primary site was assessed. Disease-free survival (DFS) was significantly improved for patients having RT to their primary site. This result was observed in the overall cohort (Fig. 12.3, $p = 0.009$) and also the subset of patients having stage I and II disease ($p = 0.048$). For the overall cohort, the cumulative 2-year DFS was 54 % for the RT group compared with 25 % for the no-RT group (Fig. 12.2).



Year	0	1	2	3	4	5	6	7	8	9	10	Number at risk
- - - - -	43	32	27	21	15	12	11	9	4	3	1	
———	19	8	5	4	4	4	4	4	2	2	0	

Fig. 12.3 Regional recurrence-free survival for the overall cohort for patients having adjuvant or prophylactic RT to their regional nodes ($p<0.001$)

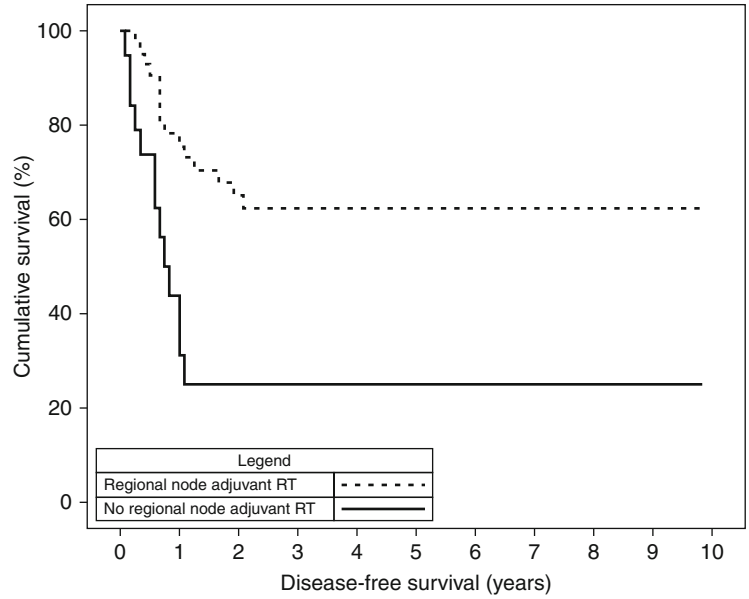


Fig. 12.4 DFS for the overall cohort for patients having adjuvant or prophylactic RT to their regional nodes ($p=0.001$)

12.3.4 Impact of RT to the Regional Site

Regional recurrence-free survival was assessed. The cumulative 2-year regional recurrence-free survival for patients ($n=43$) having regional RT was 84 % compared with 43 % for patients ($n=19$) not receiving this treatment (Fig. 12.3, $p<0.001$).

Disease-free survival for RT to regional site was assessed. Similarly, RT to the regional nodes was found to significantly improve DFS for the overall cohort (Fig. 12.4, $p=0.001$). The

cumulative 2-year DFS was 64 % for the RT group and 25 % for the no-RT group.

However, neither MCC-specific survival nor overall survival was improved by either RT to the primary site or to the regional nodes. Multivariate analysis of the influence of other factors on survival found only immune status at diagnosis impacted on overall survival (HR = 2.096, 95 %CI: 1.002–4.385, $p = 0.049$).

Conclusions

This study confirmed that RT is an important part of the treatment paradigm of MCC. Local recurrence-free survival and regional recurrence-free survival were significantly increased with the addition of RT to the primary site and regional lymph nodes, respectively. The addition of these fields was associated with increased DFS for the whole cohort. However, the addition of RT was not found to influence overall or MCCSS. This may be due to small numbers but may also be because this group of older patients has significant competing risks of death and has a disease that metastasizes early to distant sites out of the treatment volumes of locoregional RT.

The relative roles of surgery and RT in MCC are controversial. There are proponents of a predominantly surgical approach whilst others favour minimal surgery followed by RT [1, 10]. Postoperative RT has been strongly recommended by other studies due to its aggressiveness and high risk of recurrence [12]. MCC is known to be highly radiosensitive [2]. In a review done by Medina-Franco et al. which had 1,024 patients, the mean relapse rate with RT was 10 % and 53 % without ($p = 0.000001$). The average disease-free period for local recurrence was 7.4 months (range, 4–10 months) [13].

Other studies have found RT and adjuvant chemotherapy to be associated with better survival rates [19]. Due to the high metastatic potential of MCC, others have suggested systemic therapy and RT rather than radical surgery only [1, 16]. In patients from the Queensland Radium Institute who were treated with surgery only, all of them had locoregional relapse, and disease-free survival rate at 36 months was 0 % [14]. A French trial has recently published that RT to lymph node basin showed a low probability for regional recurrence compared with the observation group who had no regional RT [11]. This trial was unfortunately terminated early due to inadequate accrual.

This study suggests that local and regional RT are worthwhile treatments for MCC. Stratification for immunosuppression should be factored into any future trial design. The limitations of this study include a small sample size and lack of inclusion of new technologies such as positron emission tomography and sentinel lymph node biopsy and the knowledge of the polyoma virus status of our patients. Randomized studies are needed to guide management and should include RT as treatment and should stratify for immune status at diagnosis.

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Cutaneous Melanoma

13

Lukas J.A. Stalpers and Maarten C.C.M. Hulshof

Contents

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13.1 Introduction

13.1.1 Epidemiology

Melanoma is a relatively rare tumour, arising from the melanocyte in the basal layer of the skin, but can sporadically also arise in the squamous epithelium and in the neuroepithelium, i.e. the retina of the eye.

The incidence of melanoma is more than doubled in the past 20 years. For example, in the Netherlands, the incidence has increased from 10 to >25 per 100,000 persons; the incidence is lower in Southern European countries and somewhat higher in the Northern European countries but two- to threefold higher amongst Caucasians in Australasia. The incidence increases with age.

As a consequence of the higher incidence rate, also the absolute mortality rate from melanoma increased from 2.2 to 3.6 per 100,000 persons [1]. However, the 5-year survival rate improved slightly to about 88 % and is strongly dependent of the tumour stage (Table 13.1) [2].

A genetic predisposition, particularly a Nordic Caucasian family trait with a white skin, fair or red hair and dimples, is the most important risk factor, a risk which is exaggerated by exuberant UV exposure, i.e. sunbathing and sun bench (Fig. 13.1).

13.1.2 Staging and Prognosis

See Tables 13.1 and 13.2.

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Table 13.1 Melanoma stage [TNM, 7th edition, 2010] [35], relative incidence and 5-years survival by stage

Stage	Description				5-year survival (%)
		T	N	M	
I	A	Clinical T1a	N0	M0	~100
	B	Clinical T1b or T2a		M0	95
II	A	Clinical T2b or T3a	N0	M0	85
	B	Clinical T3b or T4a	N0	M0	77
	C	Clinical T4b N0 M0	N0	M0	65
III	A	Any clinical T Pathological T1-4a	N1-3 N1a or N2a	M0	78
	B	Pathological T1-4a Pathological T1-4b	N1b, N2b or N2c N1a, N2a, or N2c	M0	62
	C	Pathological T1-4b Any T	N1b or N2b N3	M0	50
IV		Any T	Any N	M0	12
All stages					88

Source: Netherlands Cancer Registry [1]

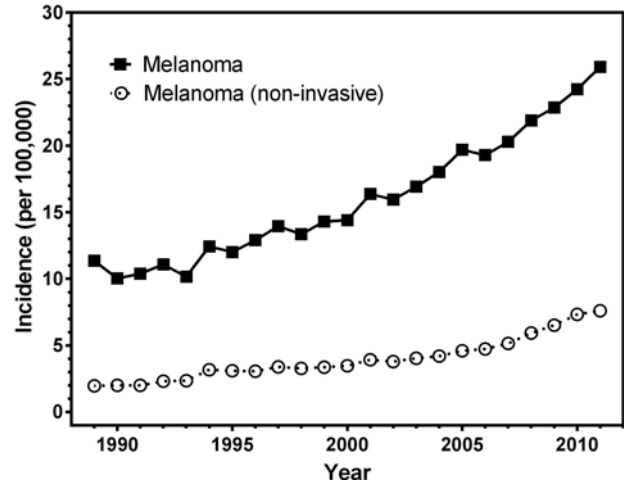

Fig. 13.1 Incidence of invasive and non-invasive melanoma in the Netherlands from 1989 until 2011 (*ESR* European Standardized Rate per 100,000 persons per year, adjusted for age and sex) (Source: Netherlands Cancer Registry [1])

Table 13.2 Melanoma stage [TNM, 7th edition, 2010] [35]

Clark level	Description
I	Melanoma confined to the epidermis (melanoma in situ)
II	Invasion into the papillary dermis
III	Invasion to the junction of the papillary and reticular dermis
IV	Invasion into the reticular dermis
V	Invasion into the subcutaneous fat

13.2 Clinical Diagnosis

The diagnosis of a melanoma starts with a critical inspection of the patient. A popular mnemonic to remember signs and symptoms of melanoma is 'ABCDE' [3, 4]:

- *A*symmetrical skin lesion.
- *B*order of the lesion is irregular.

- *C*olour: melanomas usually have multiple colours.
- *D*iameter: moles greater than 6 mm are more likely to be melanomas than smaller moles.
- *E*volving, i.e. changing in shape, size or aspect.

Particularly for the identification of the aggressive nodular melanoma, the 'EFG' acronym may better apply [5]:

- *E*levated
- *F*irm to touch
- *G*rowing progressively for more than a month

13.3 Surgery

13.3.1 Surgery (Diagnosis)

Radical surgical excision is the cornerstone of both diagnosis and treatment. For a diagnostic excision, usually a 2 mm tumour-free margin is recommended. A wider excision is not advised for primary diagnosis, since in more than one third of cases, the histological diagnosis is not a melanoma. Furthermore, the prognosis is less dependent of radial extension and more from tumour depth, expressed by the Breslow thickness, which is difficult to assess by clinical observation.

If satellite or in transit metastases are present, a biopsy of one of these lesions should be taken for histological verification. If distant metastases are suspected, the diagnosis should be made by the most simple method, which usually is an incision biopsy or a fine-needle aspiration.

13.3.2 Re-excision

For a therapeutic (re-)excision, the following margins are recommended: 0.5 cm for in situ melanoma (pTis), 1 cm if the Breslow thickness ≤2 mm (pT1 and pT2) and 2 cm for Breslow thickness >2 mm (pT3 and pT4).

13.3.3 Sentinel Node Procedure and Lymph Node Dissection

The value of the sentinel node procedure in melanoma is not yet established and is not recommended beyond a clinical study.

Dissection of regional lymph node is not recommended as an elective procedure, but is indicated if regional lymph nodes are involved, i.e. inguinal, axillary or neck nodes. There is debate if such dissections should be radical or can be limited to superficial dissection or involved palpable nodes only.

13.4 Radiotherapy

The radiosensitivity of melanomas is heterogeneous, and the variation in radiation response amongst melanomas is almost as large as that reported for other human cancers differing in histological type [6]. However, based on very few clinical studies, it is mistakenly held that melanoma always is a radioresistant tumour and that the sensitivity is not much different from that of the normal skin [7, 8]. This suggests that there would only be a marginal advantage of fractionated irradiation, and the authors therefore recommended to use hypofractionated radiotherapy, i.e. the use of few but high fractions.

However, the assumption that there is only a minor fractionation effect of conventional schedules using 2.0–3.0 Gy per fraction was based on very few direct observations and was predominantly based on extrapolation of radiobiological modelling from melanoma patients that received high fraction doses (≥5 Gy) anyway and, moreover, an insufficient total doses (mostly ≤50 Gy). Further clinical studies that addressed the question of optimal fractionation, including a prospective clinical study, did not provide convincing evidence that hypofractionation is superior to conventional dose fractionation [9–14].

In hindsight, the shallow dose-response effect of melanoma radiotherapy may be biased on one hand by the fact that radiotherapy is usually reserved as palliation for patients with inoperable bulky tumours, with widespread metastases, and on the other hand by the large field sizes and inconvenient tumour sites frequently precluding the delivery of a biologically adequate dose (≥60 Gy).

13.4.1 Primary Curative Radiotherapy

Curative radiotherapy is an alternative for patients with a primary melanoma or lentigo maligna (M. Dubreuilh) unfit for surgery. This may also include patients with nodal metastasis. Many radiation schedules are being used, such as [9, 11, 14–16]:

- Conventional 2 Gy per day fractionation schedule of ≥60 Gy in microscopic disease and ≥70 Gy in macroscopic disease
- 45 Gy in 9 fractions of 5 Gy, 2 fractions per week
- 36 Gy in 6 fractions of 6 Gy, 2 fractions per week

13.4.2 Adjuvant Radiotherapy

Although the role of adjuvant radiotherapy, especially after dissection of nodal metastases, is debated, recent studies suggest an improvement of loco-regional control from ~60 % after surgery alone to ~80 % after surgery plus adjuvant radiotherapy, provided that a sufficient dose is being given (≥60 Gy, conventionally fractionated) [14, 17]. However, radiotherapy does not seem to improve survival in patients with N+ disease, since distant metastasis is the major cause of tumour relapse and death in this stage [18].

13.4.3 Recurrent Melanoma

Recurrent melanoma in the scar, or in previously resected in transit metastases or lymph node stations are dreaded for pain and the risk of ulceration. Usually, a second resection is technically not feasible. As argued above, tumour localisation, metastatic spread and a poor patient condition usually preclude high-dose curative radiotherapy. Palliative radiotherapy alone therefore results in few enduring complete remissions, but a partial response resulting in worthwhile palliation of pain, ulceration or obstruction is very common [19, 20].

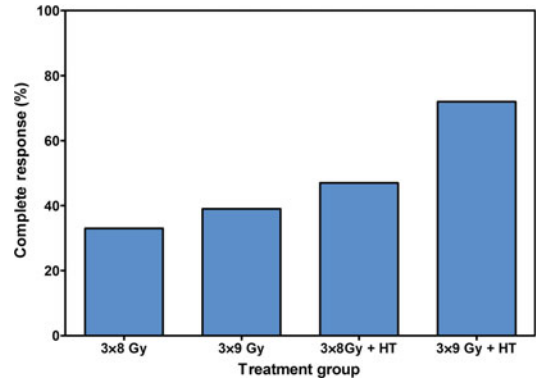

Fig. 13.2 Complete response in malignant melanoma treated with radiation alone or combined with hyperthermia as a function of radiation dose, yielding a 1.4- to 1.8-fold enhancement ratio of hyperthermia (Overgaard et al. [21])

Radiotherapy with hyperthermia improves local control. In the four-armed randomised trial by Overgaard et al. [21], patients received either 3×8 Gy or 3×9 Gy, 1 fraction per week, with or without hyperthermia [21]. Complete or partial response was 80 %. Complete response was >70 % in patients receiving 3×9 Gy plus hyperthermia, compared to <40 % in patients receiving radiotherapy alone. Hyperthermia was particularly more effective in smaller tumours (tumour size <4 cm, response >70 %) than in larger tumours. In larger tumours, one might consider to use a higher dose, i.e. 7–9×5 Gy, twice a week combined with weekly hyperthermia. Hyperthermia makes tumour cells more sensitive to irradiation; however, hyperthermia may induce the so-called thermal tolerance, which requires larger time intervals (>2 days) between each hyperthermia treatment (Fig. 13.2).

13.4.4 Brain Metastasis of Melanoma

Brain metastasis is a common and usual fatal complication of melanoma, sometimes as the only manifestation occurring many years after first diagnosis.

Surgical resection is usually performed for operable single metastasis, both for diagnosis and swift palliation [22]. Post-operative whole brain radiotherapy (30 Gy in 10 fractions of 3 Gy) is usually recommended for patients with a single metastasis, without extraneous disease and in a fair or good general condition (Karnofsky performance status ≥70).

For patients without extracranial disease, with one to three brain metastases, stereotactic radiotherapy alone gives comparable control rates as surgery, with a median survival up to 9 months [23].

For patients with multiple brain metastases (>3), with extracranial disease and in a poor condition, a short fractionation schedule (20 Gy in 5 fractions of 4 Gy) is probably as effective as more prolonged schedules. The median survival is less than 3 months.

13.4.5 Extracutaneous Melanoma

Extracutaneous melanomas are rare tumours, between 8 and 11 new cases per million citizens, compared to 120–160 cases of cutaneous melanoma per year [24]. Melanoma of the eye is the most common extracutaneous localisation. The prognosis of extracutaneous melanoma is worse than that of cutaneous melanoma.

13.4.6 Melanoma of the Eye

Choroidal melanoma is the most common primary malignant tumour of the eye. Until the introduction of plaque brachytherapy in the 1960s, enucleation was the standard treatment. From that time on, various eye-conserving treatment modalities such as ruthenium-106 (Ru-106) or iodine-125 plaque brachytherapy, proton beam radiotherapy, stereotactic radiotherapy, transscleral or transretinal local resection and phototherapy (photocoagulation or transpupillary thermotherapy, TTT) have been developed with the aim of preserving useful vision without increasing the risk of metastatic spread [25]. A randomised trial comparing iodine-125 brachytherapy with enucleation did not find a difference in survival, but vision could be saved in 40 % of patients [26]. In a recent study of patients treated by Ru-106 brachytherapy, the 5-year local tumour control was 96 %, a functional vision could be retained in 50 % of patients, and 4.4 % required enucleation for tumour recurrence or radiation complications [27]. The dose to the scleral surface was 600–800 Gy in 6–8 days.

Conjunctival melanoma is a rare melanoma localisation, which, unfortunately, is frequently treated with mutilating surgery alone, harbouring a high recurrence rate, and with meagrely effective treatments for palliation [28]. The recommended treatment is local excision followed by brachytherapy, with either a high dose rate strontium-90 (Sr-90) or a low dose rate Ru-106 plaque applicator [29, 30]. Recommended doses vary between 60 Gy in 6 fractions of 10 Gy high dose rate Sr-89 to 100 Gy and continuous low dose rate Ru-106 at 1 mm depth. Tumour control is well over 90 % in tumours of the lateral conjunctiva, but both local recurrences and distant metastasis are high (>50 %) when the medial eye and caruncula are involved. For larger tumours, surgery plus interstitial brachytherapy can be considered [31].

13.4.7 Melanoma of Squamous Epithelium

Melanoma of the squamous epithelium usually presents as multiple superficially extended disease of the mucosa, for instance, of the oral or vaginal mucosa. The tumour is usually not amenable for radical surgical resection. If palliative radiotherapy is indicated, we recommend combination with hyperthermia, which may yield durable local control [20].

13.5 Recent Developments in Melanoma Treatment

13.5.1 Activation of the Immune System

For metastatic melanoma, alkylating cytostatic drugs, such as DTIC and temozolomide, were the only demonstrated effective chemotherapy. Immunotherapy, although promising, is

usually reserved for patients in clinical studies. Ipilimumab is an antibody that activates the body's immune system by inhibiting the cytotoxic T-cell lymphocyte antigen-4 molecule. In a randomised study in patients with stage III or IV melanoma, the median survival was improved to 10 months for patients treated with ipilimumab compared to 6.4 months in the control groups [32]. Treatment-related mortality was about 2 %. These findings fuel further research for targeted therapy and combination with chemotherapy and radiotherapy.

13.5.2 PARP Inhibition and Hyperthermia

Radiotherapy works by causing DNA breaks. These DNA breaks are less well repaired by tumour cells than by normal cells. Hyperthermia is a tumour-selective sensitiser of radiotherapy by selectively inhibiting the DNA repair in (hypoxic) tumour cells and not so much in healthy (normoxic) cells. The molecular mechanism of hyperthermia was, until recently, poorly understood.

For some time, it is known that the BRCA2-protein is an essential DNA-repair molecule involved in the repair of DNA double-strand breaks by homologous recombination. Fong et al. [33] found that patients with congenital BRCA2 deficiency and with metastasised breast cancer respond well by additionally inhibiting DNA single-strand break repair by inhibition of PARP [33]. Recently, we found that hyperthermia blocks the production of the BRCA2 protein. Next, hyperthermia did sensitise tumour cells proficient in BRCA, but not in BRCA-deficient cells [34]. Next, we found, both in vitro and in vivo, that the inhibition of PARP sensitises tumour cells for hyperthermia and delays tumour growth. These results are presently translated in to early clinical studies.

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Side Effects of Radiation Treatment

14

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14.1 Introduction

Cutaneous side effects of radiation treatment have been studied for more than a century [1]. The knowledge of these side effects is still very important because patients have to be carefully informed prior to therapy. In the last 20 years, we have gained more insight into the molecular basis of these changes (Sect. 14.5), and reliable data on the very low carcinogenic risk of therapeutic radiation have been obtained by long-term follow-up studies of thousands of individuals (Sect. 14.7).

14.2 Acute Radiodermatitis

Acute changes in the irradiated field by definition occur during radiotherapy or up to 90 days after its initiation. With increasing total dose, the following symptoms may develop [2, 3]: (1) dry skin by functional impairment of sebaceous and sweat glands; (2) epilation; (3) erythema, the clinical correlate of inflammation and vascular dilatation due to vasoactive substances; (4) dry desquamation, which indicates an increased cell turnover and death rate in the epidermal layer; (5) hyperpigmentation by increased activity of

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melanocytes; (6) moist desquamation because the epidermal barrier function has been partially lost; and (7) erosion or ulceration due to partial or complete loss of the epidermal layer. The more severe reactions moist desquamation, erosion, and ulceration have not to be expected after total doses below 45 Gy [3, 4]. However, these acute reactions may at least partially be caused by the tumor itself. Malignant epithelial and melanocytic tumors relatively often invade the epidermis. With the regression of the tumor, the remaining epidermal layer may be destroyed. The beginning erosion or ulceration together with the disappearance of a palpable nodule may indicate the destruction of the tumor [5].

Fractionation has only a minor influence on acute reactions of the skin compared to late changes [3, 6]. This is indicated by the α/β value which is high for acute reactions compared to late ones [3]. After the end of radiotherapy, the erosions and ulcerations in the irradiated field are reepithelized from the margins and from surviving epithelial cells.

14.3 Chronic Radiodermatitis

14.3.1 Macroscopic Appearance

Months to years after superficial radiation therapy, characteristic changes may appear in irradiated skin that have been termed roentgenoderm or chronic radiodermatitis: depigmentation and telangiectases occur relatively often; hyperpigmentation, depressed scars, and diffuse erythema less often; and induration and keratoses rarely [7]. My colleagues and I have assessed hypopigmentation, hyperpigmentation, telangiectases, erythema, depressed scar, keratosis, and induration in 1,149 fields after irradiation of skin tumors more than 90 days after therapy. Visible changes were already found in the irradiated field within the first year after treatment. The frequency of most changes increases for at least 4 years. Erythema was more often observed in the first year after therapy compared to the following years, while keratosis and induration were almost constant [7].

Permanent hair loss in the irradiated field usually occurs after treatment of a malignant tumor of the skin: single doses exceeding 10 Gy are sufficient to cause permanent alopecia [8]. In the past, three types of chronic radiodermatitis have been described that are rare today: (1) after repeated treatments for benign dermatoses with high cumulative total doses [9]; (2) after occupational overexposures in an era when radiation protection measures were less strict than today: this chronic radiodermatitis was seen in dentists, veterinarians, and workers in industry. The affected reddish gray skin – often on the hands – thickened and developed premalignant keratoses. The nails became friable and exhibited longitudinal striations. Ulcers and radiogenic neoplasms sometimes developed [8, 10]; (3) after intentional epilation with excessive single doses of X-rays, sometimes by lay persons [11].

14.3.2 Cosmetic Considerations

Visible radiation sequelae do not appear below a threshold dose. This is typical for non-stochastic effects. (Stochastic effects have no threshold dose. The probability of their occurrence is strictly dose related.) The threshold dose for visible radiation sequelae is lower than the dose usually required for the treatment of malignant tumors, with the exception of some malignant lymphomas. Sulzberger et al. [12] concluded from a survey of 1,000 patients treated 5–23 years previously that fractionated doses of 0.75–0.85 Gy or less were not likely to be followed by any visible cutaneous sequelae if the total cumulative dose did not exceed 10 Gy. After total doses of 10.0–26.3 Gy, only 1.5 % of the patients experienced changes of cosmetic importance in the irradiated field, such as atrophy, hypopigmentation, hyperpigmentation, telangiectases, or keratoses. After radiotherapy of malignant cutaneous tumors, one should therefore expect visible changes with cosmetic relevance, even if total doses and doses per fraction were relatively low. After total doses of not more than 45 Gy, we observed hypopigmentation in 84.2 % of 19 fields more than 4 years after therapy and telangiectases in 83.3 % of 18 fields [7].

Turesson et al. [6] reported that only 21 % of their patients were completely free from telangiectases 5 and 8 years after treatment with doses per fraction of 2.62 Gy and total doses of 55 Gy. Locke et al. [13] have observed poor cosmetic results after doses per fraction of ≤2.0 Gy and total doses not exceeding 40 Gy.

Evaluation of visible radiation sequelae might be important with the aim to learn how treatment parameters like total dose, dose per fraction, hardness of the X-rays, and field size influence the cosmetic long-term results. Unfortunately this intention has several problems which impede the interpretation of the final results: (1) the evaluation is relatively free from bias if only the presence or absence of particular visible changes, i.e., hypopigmentation, hyperpigmentation, telangiectases, erythema, or depressed scar is documented [7]. However, this evaluation does not take into account that the different symptoms are more or less pronounced, a factor which contributes a lot to the overall cosmetic results. To grade either particular symptoms or the entire cosmetic outcome is subjective, even if one tries to define the grades as most authors have done [7, 13–21]. Standardized criteria for cosmetic outcome do not exist and may be difficult to establish. Turesson et al. [6] have overcome this problem by comparing fields treated with different doses per fraction in the same patient who had received postoperative radiotherapy for breast cancer. Each patient was her own control. They found that telangiectasia was less pronounced if the same total dose was applied in fractions of 2.62 Gy five times per week compared to 5 Gy twice a week. A similar approach is not possible for the evaluation of visible radiation sequelae after radiotherapy of cutaneous malignancies. (2) Radiotherapy with the aim to cure malignant tumors is not designed for a later evaluation of long-term radiation sequelae. Particular treatment parameters, for instance, relatively low total doses or doses per fraction, may be underrepresented with the consequence that the final evaluation of results is limited [7]. Although these problems demand a cautious interpretation, some results are interesting: A worse cosmetic outcome has been observed after irradiation of larger [13, 18–20] and thicker [19] tumors. Several groups reported that total dose [13, 14, 19] and dose per fraction [13] do not significantly influence the cosmetic result. Later than 90 days after therapy incidence rates of visible changes, i.e., hyperpigmentation, hypopigmentation, telangiectases, erythema, keratosis, and depressed scar did not differ by more than 15 % (of the overall treated fields) if low and high total doses, ≤45 Gy versus >60 Gy, or low and high time-dose-fractionation factors (TDF) [22], ≤105 versus >140, were compared [7]. Low doses per fraction seem to have some cosmetic benefit although results are controversial [6, 13]. However, the usefulness of doses per fraction of ≤2 Gy is debatable since Locke et al. [13] have found a significantly reduced control rate of basal cell carcinomas after these low doses per fraction.

Recently, a prospective randomized trial compared the outcome of surgery to radiotherapy for basal cell carcinomas of the face [23, 24]. The evaluation of the cosmetic results was based on subjective judgments of the patient, a dermatologist, and three independent persons. Significantly better cosmetic results after surgery were found by the dermatologist and by two of the three independent judges 24, 36, and 48 months after treatment and by the patients 48 months after therapy. The cosmetic results of surgery were not found to be superior to those of radiotherapy for tumors of the nose. Some authors prefer radiotherapy for tumors of particular anatomic sites: Huynh et al. [25] recommend radiotherapy of the lips, especially when functional and cosmetic concerns are an issue. By choosing radiotherapy for a carcinoma of the pinna of the ear, a cosmetic defect can sometimes be avoided that would result from excision [26].

Most patients tolerate the visible changes after radiotherapy for cutaneous malignancies [7, 27–31]. Cosmetic changes may be accepted more readily if patients are carefully instructed prior to treatment. If one has the impression that the cosmetic result is relatively important for the patient, a colleague who is experienced in surgical techniques should be asked for advice. The final choice of either radiotherapy or surgery depends mainly on the size and the localization of the tumor.

14.3.3 Pruritus and Burning

Occasional pruritus and burning have been relatively often reported by our patients [32]. Permanent pruritus or burning was rare: more than one interview had been performed for 677 irradiated fields with respect to pruritus and for 666 fields with respect to burning. For four fields (0.6 %), pruritus more than once per week and for one field (0.1 %) burning more than once per week was stated in all interviews. Pruritus and burning later than 90 days after therapy were significantly less frequently reported after irradiation with lower total doses or lower TDF, by men and by patients older than 70 years of age. The largest diameter of the irradiated field had a significant influence on pruritus and the hardness of the X-rays (half value depth) on burning [32].

14.3.4 Epiphora

Epiphora (watery eyes) as a late consequence of radiotherapy has been reported in 9.2 % [33], 10 % [34], 11.5 % [35], and 31 % [36] of cases. Our patients [32] stated epiphora at any time later than 90 days after irradiation for 53.7 % of 354 fields (for 22.4 % of fields never more frequently than once per week). Permanent epiphora was relatively rare: more than one interview was performed for 94 fields after irradiation around the eye. Epiphora more than once per week was stated in all interviews for six fields (6.4 %) only. Epiphora was significantly less frequently stated after lower total doses, lower TDF, after treatment of thinner tumors, and by men [32].

Occlusion of the nasolacrimal drainage system is not the only cause of epiphora. Our patients have reported epiphora after radiotherapy around the eye although the medial canthus was not in the field [32]. Hypersecretion caused for instance by wind and inflammation is enhanced due to radiation-induced damage to secretory (goblet) cells of the conjunctiva, meibomian, and accessory glands [37]. This explains why epiphora usually does not permanently trouble the patient.

Intubation of the nasolacrimal drainage system prior to radiotherapy has been suggested as a prophylaxis for epiphora [36, 37]. A significantly lower incidence of epiphora after radiotherapy [36] as well as unsatisfactory results of this prophylactic treatment [35, 37] has been reported.

14.3.5 Insufficient Occlusion of the Mouth

After treatment of lip carcinomas fluid may run out of the mouth when eating and drinking as a consequence of insufficient occlusion. This has been reported for 11.1 % [38], respectively 0 % [39, 40] of irradiated patients. Our patients have stated insufficient occlusion of the mouth for 14.6 % of 55 irradiated fields. Patients were not permanently troubled by these sequelae: 30 individuals were interviewed more than once during the follow-up period. No one reported symptoms of insufficient occlusion more than once per week in every interview [32].

Destructive growth of the tumor before radiotherapy may contribute to insufficient lip function after treatment. In a small group of 18 irradiated and 15 surgically treated patients with lip carcinomas, oral incontinence has been more frequently found after surgery [38].

14.3.6 Microscopic Appearance

The epidermis is often atrophic with loss of the rete ridge pattern [41] (Fig. 14.1). Epidermal hyperplasia and hyperkeratosis may be found in foci [42]. The dermo-epidermal junction shows vacuolar alteration with a few scattered lymphocytes [42]. Dyskeratotic cells [41] and in late lesions crowded keratinocytes with abnormal nuclei [42] may be found. Subepidermal fibrin is frequently observed [42].

The dermis is sclerotic, especially in late lesions [42]. Fibrocytes may have abnormal nuclei and stellate cytoplasm. Giant multinucleate fibrocytes are often observed [42].

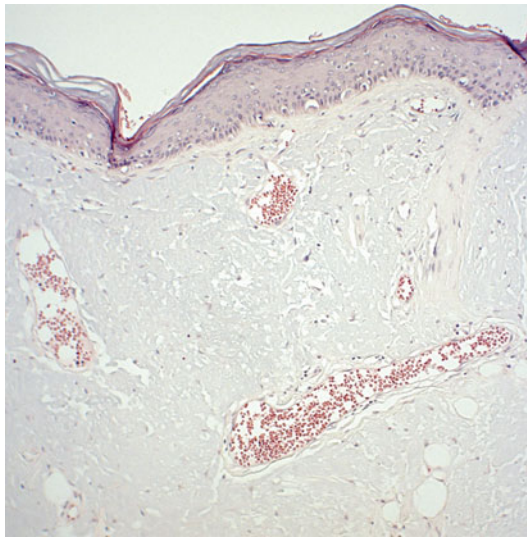

Fig. 14.1 Histopathology of chronic radiodermatitis (hematoxilin and eosin). Hair follicles and sebaceous glands are missing. The connective tissue is relatively homogeneous; many blood vessels are dilated (40×)

Hair follicles and sebaceous glands are absent [41] (Fig. 14.1) unless relatively low doses were applied. Erector pili muscles often remain. There is usually some atrophy of eccrine sweat glands; they may be completely destroyed [41].

Blood vessels are often occluded by thromboses [42]. Telangiectases may be observed in the upper dermis, especially in late lesions [42]. The number of capillaries is often diminished [41]. Endothelial cells may be hyperchromatic [42].

14.4 Radiogenic Ulcers

14.4.1 Definition

The most serious dermatologic complication of radiation therapy is ulceration. This may develop months to years after apparent complete healing of the primary radiation reaction or ulceration can persist after the end of radiotherapy. My colleagues and I have used the term "radiogenic ulcer" for any defect in the irradiated field, which is present at any time more than 8 weeks after the end of radiotherapy and which is not caused by a recurrence of a malignant tumor [5].

14.4.2 Mechanism of Development

Radiogenic ulcers are usually combined injuries [43]. The profound changes in connective tissues and blood vessels caused by ionizing radiation [44] result in a reduced supply of nutrients and oxygen in chronic radiodermatitis. Coexisting diseases, like diabetes mellitus and hypertension, may further reduce this supply. If the demand for nutrients and oxygen is then increased – for example, by inflammation due to excessive sunlight exposure, infection, allergic reaction, or an insect sting – the supply may not be sufficient any longer. Tissue necrosis may then develop.

14.4.3 Incidence

Fortunately radiogenic ulcers after irradiation for a malignant cutaneous tumor are relatively uncommon. This complication has been observed in 3.0 % [31], 5.0 % [24], 5.5 % [20], 6.3 % [5], and 9.4 % [45] of fields in selected series. Radiogenic ulcers were more frequently observed after larger total doses [1, 45]; in larger treatment fields [5, 20]; in older patients [45]; on the scalp [5], lip [5], ear [5, 46], forehead, and temples [5]; and after treatment with harder X-rays (higher half-dose depths) [5]. Slower healing of irradiated fields should be expected on the trunk and limbs [47]. A radionecrosis rate of 9.2 % has been observed on the lower limbs [48]. Large individual doses increase the risk of developing a radiogenic ulcer: Traenkle et al. [49] compared 322 patients who were irradiated with 4×10 Gy in 8–10 days with 816 patients treated with either 9×5 Gy in 12 days or 13×4 Gy in 18 days or 18×3 Gy in 25 days. Patients who had received 10 Gy fractions developed radiogenic ulcers in 13.9 % of fields (cumulative probability), while radiogenic ulcers were observed in only 2.9 % of fields following 3–5 Gy fractions. Radiogenic ulcers sometimes develop many years after therapy (Table 14.1). Long follow-up periods are therefore necessary to assess the true incidence of these radiation sequelae.

Table 14.1 Ulcers in the irradiated field after radiotherapy of 1,267 basal and squamous cell carcinomas [5]

Time after irradiation	Ulcers
2 months to 3 years	50 (63 %)
>3–6 years	20 (25 %)
>6–9 years	7 (9 %)
>9–15 years	3 (3 %)
Total	80 (100 %)

14.4.4 Treatment

Sixty two of the 80 (77.5 %) ulcerations in our series healed permanently with conservative management based on ointments and moist compresses [5]; two lesions (2.5 %) were cured by surgery under local anesthesia. The conservative therapy takes into account the pathogenesis of radiogenic ulcers: moist compresses have an anti-inflammatory effect but do not reduce proliferative activity as corticosteroids do. In addition, local infection has to be controlled by appropriate antibacterial or, if necessary, antifungal ointments. My colleagues and I have used ointments containing gentamycin in most cases. If need be, allergic reactions should be excluded by epicutaneous testing. Traenkle and Dattatreya [49] reported that 90 % of 55 cases of radionecrosis healed with simple topical applications, 80 % of them within 3 months. Spontaneous involution was observed as long as 7 and 8 months after the onset of breakdown. Problematic radiogenic ulcers that require surgery under general anesthesia, that recur, or that cannot be cured at all are rare. In our series, they developed in only 0.9 % of the originally treated fields [5].

14.5 Molecular Basis of the Observed Changes

14.5.1 Biochemical Changes Indicate Cellular Activities

Radiation-induced skin alterations are not solely caused by cell damage with the consequence that the cell dies immediately or later when it tries to divide. Active biochemical processes are involved in these changes [50].

14.5.2 Ceramide

Ionizing radiation increases intracellular ceramide which by several pathways can induce apoptosis of endothelial cells. This mechanism is active after single doses of >5–10 Gy, while after doses of 3 Gy, the release of ceramide is inhibited and anti-apoptotic signaling systems predominate [51].

14.5.3 Collagen Synthesis

Connective tissue changes are mainly caused by an overproduction and deposition of extracellular matrix. An increase of newly synthesized collagen, one of the substances of the extracellular matrix, was found in the skin of irradiated mice as early as 1 week after irradiation [52]. This increase was observed for almost 1 year. Cultured fibroblasts from the skin of irradiated mice produced more collagen as well [52].

14.5.4 Transforming Growth Factor-β1 (TGF-β1)

The increased production of extracellular matrix is mediated by cytokines, particularly TGF-β1 [53, 54]. This cytokine, one of three mammalian isoforms of TGF-β [51, 53, 55], is a homodimeric peptide with a molecular mass of 25 kDa, first purified from human platelets [56], that produces its effects by activating plasma membrane serine/threonine kinase receptors [53]. Cells usually secrete TGF-β1 as a latent complex consisting of the TGF-β1 homodimer, a latency associated peptide, and another high-molecular-weight protein, the latent TGF-β1 binding protein, which binds to the extracellular matrix by disulfide bonds [51, 53]. Ionizing radiation induces enhanced synthesis of TGF-β1. The initial step may be activation of matrix bound latent TGF-β1 by proteolytic enzymes in the presence of reactive oxygen species. Activated TGF-β1 binds to the TGF-β1 receptor type 2 on the membrane of fibroblasts, platelets, macrophages, lymphocytes, epithelial, or endothelial cells. The receptor complex is formed by binding the receptor type 1. The receptor complex starts the TGF-β

signaling pathway by activation of kinases [51]. This results in enhanced gene expression and production of TGF-β1 in an autocrine fashion [51]. TGF-β1 signaling is mediated by SMAD proteins, especially SMAD3 [57]. The name "SMAD" genes has been created by combining the abbreviations for related genes in invertebrates [58]: the "small" mutant (SMA) of a gene essential for the male tail ray development of Caenorhabditis elegans and the "mothers against decapentaplegic" gene (MAD) of Drosophila. The activities of TGF-β1 and the importance of the SMAD signaling pathway have been shown in SMAD3-deficient knockout mice: 6 weeks after irradiation less fibrosis, a lower incidence of ulceration and fewer dermal inflammatory cells were observed in irradiated fields of these mice compared to normal controls. Irradiated sites contained less TGF-β1 in cells and extracellular matrix [55]. TGFβ-1 does not only enhance the synthesis of extracellular matrix, but it also induces inhibitors of matrix degrading enzymes [51]. Some SMAD proteins, for instance, SMAD7, can inhibit the TGF-β1 signaling.

The activity of TGF-β1 is similar in normal wound healing and in radiation induced fibrosis. However, in normal wound healing, TGF-β1-related cellular activities are later downregulated, while in irradiated tissue extracellular matrix proteins and TGF-β1 are continuously produced at high level [53].

Blood vessels may be altered by ionizing radiation through a mechanism resembling that for connective tissue changes: irradiation causes the production of TGF-β1 in endothelial cells. TGF-β1 induces the fibrogenic phenotype of vascular smooth muscle cells. Radiation-induced vascular hypertrophy and thickening of the intima are associated with elevated levels of TGF-β1 and SMAD proteins [59].

TGF-β1 inhibits the growth of epithelial, endothelial, and hematopoetic cells [53] and therefore appears at least partially responsible for the epidermal atrophy often found in chronic radiodermatitis.

The effects of TGF-β1 can be mediated by SMAD-independent signaling pathways as well [60–66]. One of these, the Rho/ROCK pathway is predominantly active in radiation-induced enteropathy [62].

14.5.5 Other Cytokines

The chronic radiation reaction is not mediated by TGF-β1 alone. Other cytokines are involved including platelet-derived growth factor, interleukin 1, insulin-like growth factor, connective tissue growth factor, and tumor necrosis factor alpha. However, TGF-β1 plays the key role in the fibrotic process because it can modify the activity and expression of most genes coding for growth factors and their receptors [53].

14.6 Standardized Evaluation of Late Radiation Sequelae

To evaluate a specific treatment for a malignant tumor, one has to consider both the percentage of cases cured and the side effects. Results from different studies cannot be compared appropriately if uniform criteria are not used for the assessment of acute and late side effects. In 1995, the Radiation Therapy Oncology Group and the European Organization for Research and Treatment of Cancer have published the LENT-SOMA scoring system [67–72]. The name comprises two acronyms: LENT = late effects normal tissue and SOMA = *s*ubjective, *o*bjective, *m*anagement, and *a*nalytic. "Late" in this context means more than 90 days after the onset of therapy. The four SOMA criteria are defined as follows: subjective, these are perceptions and problems reported by the patients like pain and pruritus; objective, this is evaluated by the physician through physical examination including conventional radiographs or images and/or results of laboratory procedures; management, this describes the measures necessary to treat the side effects, i.e., medical or surgical intervention; and analytic, this documents the potential deficits that can only be evaluated by more sophisticated methods like computer tomographs or special laboratory tests. LENT SOMA scales were devised for 38 anatomic sites [67], including skin/subcutaneous tissue. The LENT SOMA system is suitable for the documentation of late side effects after radiotherapy for malignant tumors of the skin. Late side effects after treatment(s) can be caused by the tumor and/or its involution.

They are not exclusively due to the irradiation of normal tissue. The LENT SOMA system was used in recently published studies [73, 74] for the documentation of late adverse effects in different organs including the skin.

14.7 Radiogenic Skin Cancer

14.7.1 Cancer Risk After Radiotherapy for Benign Dermatoses

A significantly increased risk to develop a basal cell carcinoma of the head and neck could be assessed in two studies, one from Israel and one from New York, after radiotherapy for tinea capitis (ringworm of the scalp) at age <1–15 years [75–80]. The relatively small incidence rates of basal cell carcinomas differed between both studies, but the relative increase was similar (Table 14.2). Follow-up periods and number of patients were large in both studies. No significantly increased risk of other skin cancers or melanoma was found.

Several co-factors influence the carcinogenic risk: (1) the cumulative risk of radiation-induced skin cancer increases with time from exposure [77, 79]. The results of the tinea capitis study from New York [79] with very long follow-up support the belief that an increased skin cancer risk from irradiation continues for a lifetime. (2) The carcinogenic risk of radiotherapy depends on the applied total dose [77]. (3) Ultraviolet light is an important cofactor for the development of X-ray-induced skin cancer in humans. In the study from New York [79], 25 % of both the irradiated and the control patients were African-Americans who are protected by their black skin color against the carcinogenic potential of ultraviolet light: only three basal cell carcinomas occurred in the irradiated patients from this ethnic group, compared to 124 among the irradiated Caucasians. No skin cancer was found among the African-Americans of the control group. The incidence of skin cancer among the Caucasians was significantly lower on the relatively ultraviolet-shielded scalp compared to the margins of the scalp. Significant predictors of skin cancer risk were North European ethnicity, a history of painful sunburns with blisters, and light skin color. In the Israeli study [81], sunbathing in summer was found to be a cofactor for the development of skin cancer.

More neural tumors were found at the head and neck in the Israeli study [76] and intracranial in the New York study (Table 14.2) [80]. An increased frequency of thyroid cancers was observed in the Israeli study only [78]. This is probably due to genetic differences between the patients of both studies [78].

The two large studies after radiotherapy of children and adolescents for tinea capitis unequivocally demonstrate the carcinogenic potential of therapeutic ionizing radiation, but they presently do not have any practical importance because ringworm of the scalp is no longer treated by X-rays. The carcinogenic risk of modern radiotherapy with small doses as used for benign dermatoses is low: Most studies have failed to assess a significant increase of skin cancer [82–86]. Two groups report a significantly elevated likelihood only for individuals irradiated below 20 years [87] or 40 years of age [88] respectively. Patients with basal cell nevus syndrome [85, 89] have a higher risk. Usually only small doses of radiation reach internal organs during radiotherapy of dermatoses with modern techniques [9, 90]. That this treatment induces a malignant tumor in internal organs is therefore highly unlikely [91].

14.7.2 Cancer Risk After Higher-Dose Radiotherapy for a Malignant Cutaneous Neoplasm

The risk of developing a radiation-induced cutaneous malignant tumor following radiotherapy of a malignant neoplasm of the skin has not been evaluated in a controlled study. We assume that this risk is very low in part because (1) radiation fields are usually small [92] and the amount of irradiated skin is an important factor for risk [85]; (2) most patients who are irradiated for a cutaneous malignancy are relatively old and may therefore not experience a radiation-induced skin tumor because their life expectancy is shorter than

Table 14.2 Tumors after radiotherapy for tinea capitis (ringworm of the scalp)

	Israeli study [75–78]	New York study [79, 80]
Number of irradiated patients	10,834	2,224
Number of controls	16,226	1,380
Age at exposure	<1–15 years	<1–15 years
Average total dose	6.8 Gy	4.8 Gy
Follow-up	Mean: 24.5 years	Median: 39 years
Basal cell carcinomas[a]		
Number in irradiated patients	41 (0.4 %) *s*[b]	127 (5.7 %) *s*[b]
Number in controls	13 (0.1 %)	21 (1.5 %)
Increase in irradiated patients	4.7-fold	3.8-fold
Excess relative risk per Gy	0.7	0.6
Other skin cancers[a]		
Number in irradiated patients	1 (0.009 %)	11 (0.5 %)
Number in controls	2 (0.01 %)	0
Melanomas[a]		
Number in irradiated patients	2 (0.02 %)	0
Number in controls	1 (0.006 %)	0
Thyroid cancer		
Number in irradiated patients	103 (1.0 %) *s*[b]	2 (0.09 %)
Number in controls	56 (0.3 %)	0
	Neural tumors[a]	*Intracranial tumors*
Number in irradiated patients	56 (0.5 %) *s*[b]	16 (0.7 %) *s*[b]
Number in controls	10 (0.1 %)	1 (0.07 %)
Leukemia		
Number in irradiated patients	Not evaluated	8 (0.4 %)
Number in controls	Not evaluated	1 (0.07 %)

[a]Head and neck tumors only
[b]*s* significant increase

the long latency period [77, 93–96] for the induction of a neoplasm, and (3) benign dermatoses have often been treated in the past – not in published controlled studies [12, 77, 79, 97] – with repeated courses of fractionated radiotherapy resulting in high cumulative total doses. These treatments cause mutations and thereby more radiation induced skin tumors. Malignant tumors, most importantly, are irradiated with higher dose, single courses in a short time interval resulting in cell death [8, 85]. Dead cells clearly cannot become neoplastic. In animal experiments, the incidence of radiation-induced skin tumors was higher if the same total dose was applied in 64 fractions (a biologically smaller dose), as compared to 16 fractions (a biologically greater dose) [98]. Ehring and Honda [99] described 106 patients with a basal cell carcinoma arising on previously irradiated skin. Only two of the basal cell carcinomas developed following radiotherapy of a malignant tumor. The results of Landthaler et al. [45] showed that the incidence of radiation-induced skin tumors following radiotherapy of a cutaneous neoplasm is indeed relatively low: 12 basal cell carcinomas (2 %) and 9 squamous cell carcinomas (1.5 %) were found in 612 radiation fields more than 10 years following radiotherapy. Moreover, these tumors developed exclusively in sun-exposed areas.

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Diagnosis and Treatment of Cutaneous Radiation Injuries

15

Ralf U. Peter

Contents

15.1 Epidemiology

Individuals are exposed to ionizing radiation either intentionally during radiation therapy, most often for systemic or cutaneous malignancies, through industrial exposure, or following a major accident such as at Chernobyl, Lilos [4–8], or, recently, Fukushima. In the past, hospital workers were at risk, as the dangers of ionizing radiation were not fully appreciated; recently, new diagnostic procedures in cardiology pose a new risk pattern [9].

However, while accidents are still the most common source, the concern is about the intentional misuse of nuclear materials in the realm of international terrorism or organized crime. Possible scenarios include:

- Detonation of a small nuclear explosive in a densely populated area
- Adding radioactive nuclides, usually with a short range, to a conventional explosive
- Hiding radioactive substances in objects of daily use such as chairs or car seats for the elimination of a single individual

15.2 Aetiology and Pathogenesis

In all these scenarios, there will be an inhomogeneous exposure to particles of varying injuries with a surface skin dose of 60–100 Gy or more. Depending on the nature of the nuclides, there may be a sharp drop in dosage after several cm so

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that lethal dosages are unlikely to reach the bone marrow. Thus, the skin is likely to be the organ most severely affected. This is true not only for α- and β-rays but also for sources dominated by γ-rays, such as ^{137}Cs and ^{60}Co. Characteristic for such exposure is that initially inadequate attention is paid to ionizing radiation so that early or abortive signs and symptoms are often overlooked. The physician is paradoxically faced with patients who present with acute damage days or weeks after exposure. A thorough understanding of the course of the pathophysiologic reaction is essential for prompt diagnosis and appropriate therapy.

Ionizing radiation is best known for inhibiting proliferation of stem cells in tissues which are otherwise capable of regeneration, such as the skin, mucosa, and bone marrow. In addition, it elicits transcription of a cascade of proinflammatory cytokines (IL-1, IL-3, IL-5, IL-6, TNF-α), chemokines (IL-8, eotaxin, CCR-3 receptor), receptor tyrosine kinases (EGF-R), and adhesion molecules (ICAM-1, VCAM, E-selectin) in keratinocytes, fibroblasts, and endothelial cells. These factors combine to create a local inflammatory reaction rich in neutrophils and eosinophils, which is self-perpetuating, leading to marked tissue damage [2, 3].

The pathophysiology of early and late damage from ionizing radiation is quite different. The early reaction in the first few days reflects the immune activation and inflammation, while the late reaction after weeks underscores the damage to the epidermal stem cells and resultant loss of protective covering. Later, the main change is the expression of TGF-beta1 in dermal and subcutaneous fibroblasts with overproduction of collagen. Thus, the late radiation changes represent a lymphocytic fibrotic inflammation.

15.3 Clinical Findings

The term cutaneous radiation syndrome (CRS) was proposed by the Second Consensus Development Conference for the Diagnosis and Treatment of Radiation Injuries in 1993 to compass the complex series of events that follow exposure to ionizing radiation and has in the meantime received general international acceptance (recent query in Google: more than 68,000 hits) The following clinical stages can be identified:

- *Prodromal erythema*. In this brief phase, lasting minutes to hours, there is erythema and pruritus, which resolves and is followed by a latent period.
- *Acute or manifest*. This is equivalent to the old term of *acute radiation dermatitis*. Patients may have erythemas, bullae, or ulcers, depending on the degree of exposure. Acute dermatitis may develop 6–12 days after exposure to radiation. Generally, a dose of more than 7 Gy (it may be less than 3 Gy on specific areas such as the eyelids) is required for radiation erythema and subsequent dermatitis. Depending on the interval between exposures, smaller but repeated doses have a cumulative effect. In most instances today, cutaneous radiation syndrome is intentional, either because an area of skin is being treated or because the nature of the underlying lesion is such that the portals cannot be arranged for sparing the skin.

The cutaneous radiation syndrome can be graded, just as burns are, even though this subdivision is not included in the newer grading systems:

1. The mildest form of CRS consists of an erythema usually followed by patchy hyperpigmentation. Depending on the dose (about 4 Gy) and the half-value depth, there may be blocked sebum secretion and hair loss. Dryness and hair loss appear after about 3 weeks; regrowth usually starts after about 1–3 months.
2. Larger doses, in the range of 8–10 Gy, lead to more intense erythema, edema, blisters, and weeping wounds. Here, the loss of hair, sebaceous glands, sweat glands, and even nails may be permanent. The skin heals with telangiectases and pigmentary changes.
3. An acute radiation ulcer is typically painful, heals slowly, and always evolves into chronic radiation dermatitis. A radiation ulcer can be a disaster, especially over cartilage or bone. Today, severe damage usually

reflects a mistake in dosimetry. Doses in the range of 12 Gy or higher are required.

- *Subacute*. In this phase, there may be persistent erythema and ulcerations. The erythema and subsequent ulcerations are caused by radiation-induced vasculitis affecting the deep cutaneous and muscular vessels.
- *Chronic*. This stage is the prototype of poikiloderma; there are telangiectases, hypo- and hyperpigmentation, and atrophy. The skin may have a yellow hue (radiation elastosis) and is usually sclerotic. It is dry and appendages are lacking. While 2nd degree acute changes heal with varying degrees of atrophy and pigmentary changes, 3rd degree acute changes always lead to chronic stage of CRS. Additionally, subcutaneous fibrosis leads to subsequent hypoxemia and secondary ulceration.

There are additional concerns in special sites:

- *Facial exposure*. Here one must be alert to eye involvement and the risk of radiation-induced cataracts. Acute mucositis of the oral and nasal mucosa may also develop.
- *Male genitalia exposure*. Damage to the testes with temporary or permanent infertility is likely. A rising FSH level is a good sign for testicular damage. After occupational accidents with ionizing radiation, FSH levels should be determined immediately and after several weeks for documentation. Immediately after exposure, there are still viable sperm in the epididymis which can be harvested and cryopreserved for use should permanent infertility develop.

15.4 Diagnostic Approach

Everything should be documented as carefully as possible for later compensation. The extent of the prodromal erythema helps define what areas have been exposed, although it does not correlate to the intensity of the acute stage or the degree of problems in the chronic stage. In the acute stage, the time interval between exposition and dermatitis suggests the severity of the reaction. Imaging studies are helpful to document the extent of soft tissue damage and necrosis.

15.5 Course and Prognosis

The damage of chronic CRS is famous for not improving with age, but worsening. There are many considerations:

- *Radiation fibrosis*. Some patients who receive high dosages of radiation develop extensive cutaneous fibrosis, in contrast to the atrophy usually seen with lower dosages. This feature has been particularly noticed in victims of the Chernobyl accident, in whom low-dose interferon has ameliorated the problem [7]. The fibrosis is chronic and progressive.
- *Radiation ulcer*. Skin with chronic radiation damage lacks adequate vascularization and is easily injured, even by quite minor trauma. When ulcers develop in such areas, the lesions heal very poorly and rarely form sufficient granulation tissue. The ulcers are usually sharply bordered and have an adherent, fatty yellow base.
- *Radiation-induced tumors*. Secondary tumors occur in CRS but the distribution and incidence of the tumors is misunderstood. In areas of marked damage, tumors are rare. Instead, they develop in the transitional zone between normal and irradiated skin, arising in about 10 % of individuals with a latency period of 30 years. Tumors also arise in areas with documented exposition but no changes; a single dose of <2 Gy suffices.
  - The most common tumors are basal cell carcinoma and squamous cell carcinoma; the former is fivefold as common [1]. Sarcomas are rare and malignant melanoma has never been described following accidental exposure to radiation.
  - When evaluating patients, it is important to consider the likelihood of combined damage with both UV-induced and radiation-induced changes. Here the risk of malignant melanoma is considerable and increased over UV damage alone.

15.6 Therapy

The first step is decontamination, if there has been exposure to radioactive nuclides. The clothing should be completely removed; it may contain

up to 80 % of the superficial dose. As trivial as this simple step sounds, it is often forgotten. Then the skin should be cleaned with lukewarm water and a syndet. Depending on the nature of the contamination, topical ion exchange materials and chelating agents can be employed. Occlusive ointments and medications that improve circulation should be avoided, as they increase uptake of radioactive materials [2–4, 7].

NSAIDS may account for symptomatic relief, but, in contrast to glucocorticosteroids, do not change the pathophysiological process of inflammation.

In the prodromal stage, low-potency topical corticosteroids and systemic antihistamines can be used. If the prodromal erythema covers more than 10 % of the body surface (rule of nines), high-dose topical and systemic corticosteroids (prednisolone 1–10 mg/kg daily) should be administered during the latency period to reduce the severity of the acute stage.

Acute stage of CRS is treated like a thermal burn with regard to fluid balance, pain control, and careful monitoring for infection. Unlikely organisms may be found, reflecting a degree of immunosuppression. The hemorrhagic necrotic areas are particularly likely to be infected.

Once areas of necrosis are demarcated, the appropriate approach is debridement followed be moist wound care. The previously recommended generous excision of necrotic areas can often be avoided by the prompt institution of anti-inflammatory measures during the latency period. Defects can be covered with split- or full-thickness grafts following accidental exposure to nuclides with limited penetration, as one can be sure that the deep cutaneous and muscular vessels are intact. This is not the case with ulcers following radiation therapy where deep damage is likely, and re-coverage a problem.

The treatment of the chronic stage has seen much progress. The fibrosis can be addressed with a combination of pentoxifylline 400 mg t.i.d. and vitamin E 500 mg daily or the subcutaneous injection of INF-γ (3–6 million IU s.q. 3× weekly) for 3–12 months. IFN-γ functions more rapidly with benefits seen after 2–3 months, while the vitamin E/pentoxifylline is much cheaper and logistically easier but first shows benefit after 5–6 months.

The skin should be kept well hydrated with a non-sensitizing emollient, perhaps containing urea or linoleic acid. This will help reduce water loss through the damaged epidermis. Radiation keratoses can be treated with topical retinoids. It is possible that this may reduce development of squamous cell carcinomas but not well proven. The telangiectases can be treated with laser therapy, if they are cosmetically disturbing or associated with a burning or warm sensation, which is often the case.

All patients with cutaneous radiation syndrome require life-long follow-up.

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