4 Non-melanoma Skin Cancer and Cutaneous Melanoma from Radiotherapeutic Point of View

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4.1 Types of Skin Cancer (Basal Cell, Squamous Cell)

Each cell type of skin can lead to a different type of carcinoma. It is relatively easy to classify skin tumours into non-melanotic skin cancers (NMSC) and cutaneous melanomas (CM) (see Chaps. 1 and 6) [1].

In this chapter, we will discuss the role of radiotherapy in non-melanotic cancers, melanotic cancers and other, rare, tumours, such as subcutaneous lymphomas, Kaposi sarcomas, angiosarcoma and Merkel cell carcinomas, which originate in hair follicles.

The most common skin carcinomas are (Fig. 4.1a, b) basal cell carcinomas (BCCs) and squamous cell carcinomas (SCCs). BCCs are four times more common than SCCs. These tumours share many characteristics, such as similar origins, physical and age distribution. Cutaneous melanomas are malignant tumours that mainly affects Caucasians (Fig. 4.1c) [1, 2].

When seen in black, it is usually located on the limbs or on a giant congenital melanocytic nevus.

4.1.1 Causative Factors

The main factor in the development of skin cancer is ultraviolet (UV) radiation. Exposure to UV radiation has a direct correlation with the incidence of skin cancer.

Therefore, in areas with extensive sunshine, people with fair skin or working outdoors present an increased incidence of skin cancer, especially in areas of the body not covered by clothes [1].

The theory of sudden exposure to the sun (holiday season) has recently been gaining ground. Ultraviolet radiation excites electrons in the atoms and molecules that absorb it and causes harmful chemical reactions through changes in the DNA of cells, such as inhibition of DNA synthesis and cell division in the epidermis. Hairs, the existence of a thickened stratum corneum and melanin offer natural protection against UV radiation.

1. *Ultraviolet radiation* is divided arbitrarily into three (3) categories, according to wavelength: UVA from 320 to 400 nm, UVB from 290 to 320 nm and UVC from 200 to 290 nm. As UVC is filtered out by the ozone layer in the atmosphere, as this layer decreases, it may

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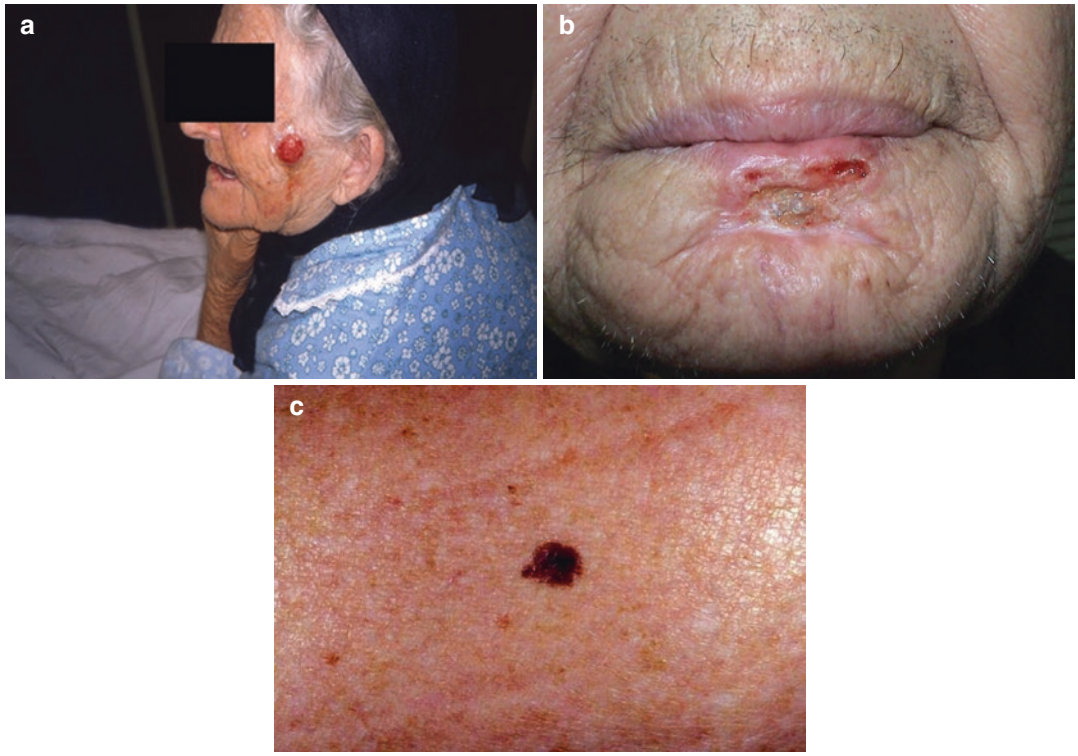

Fig. 4.1 (**a**) Basal cell carcinoma (BCC). (**b**) SCC. (**c**) Cutaneous melanoma

become an increased risk. UVB is the type of radiation primarily responsible for sunburns, skin lesions due to chronic sun exposure and skin cancer. UVA is less harmful but acts cumulatively with UVB.

2. *Ionising radiation* can cause skin cancer. Ionising radiation includes electromagnetic radiation, i.e. X-rays, gamma rays and radiation by electrons, protons, neutrons, particles and heavy nuclei.
3. The characteristic of ionising radiation is that a single exposure can cause cancer after a long latency period.

   The relative frequency of SCC in cutaneous cancers caused by radiation is relatively high (BCC/SCC about 2/1) and treatment outcomes are poorer.
4. *Due to chemicals*. Carcinogenesis is caused by bonds between substances, due to repeated exposure to chemical carcinogens and the bonds of these substances with various cellular macromolecules, RNA, DNA and proteins.
5. *Immunosuppression* is the most common induced form of skin carcinogenesis, with a distinct aetiology. Skin and lip cancer accounts for about 50% of tumours in immunosuppressed patients, with more than half being SCCs or mixed type.
6. *Viral carcinogenesis* has been implicated in several types of cancer, but its relationship with skin cancer has not been clarified.

Until now, no common mechanism has been documented for all aetiologies of carcinogenesis.

4.1.2 Skin Basal Cell Carcinoma

This originates in the cells of the basal layer of the epidermis and hair follicles. Its frequency is significantly increased in whites who have immigrated to tropical or subtropical countries and is fully associated with exposure to sunlight and ultraviolet radiation. It also occurs more frequently in areas with a high concentration of sebaceous glands. It differs from SCC in that it does not originate in differentiated skin cells.

Unlike other tumours, it almost never metastasises. Perineural and perilymphatic infiltration by cancer cells are of great importance in the histological examination.

This observation is crucial for the ***postoperative monitoring*** of the patient, because of the increased likelihood of tumour recurrence. ***Syndromes*** have also been reported in which basal cell carcinomas occur more frequently. These are (a) multiple basal cell carcinoma syndrome (Gorlin syndrome), (b) Basex syndrome, (c) albinism, (d) xeroderma pigmentosum (see Fig. 6.13) and (e) sebaceous nevus of Jadassohn (see Fig. 8.2). It can also develop into basal cell carcinoma in approximately 10–17% of cases.

BCCs are the most common type of skin cancer and occur mainly in surfaces exposed to sunlight, especially those with large numbers of sebaceous glands and hair.

They most frequently occur on the face and scalp (86%), the cervix (7%) and the rest of the body (7%). The most common sites of these tumours are the nose (25.5%), the cheeks (16%), the periorbital area (14%), the scalp (11%), the auricle and the preauricular region (11%) (see Chap. 6).

4.1.3 Clinical Forms of BCCs

Various types are distinguished based on clinical criteria:

(a) Nodular BCC, the most common.
(b) Sclerotic BCC.
(c) Pigmented BCC.
(d) Cystic BCC.
(e) Superficial BCC: unlike the previous types, it mostly occurs on the trunk)
(f) BCC syndrome (Gorlin). This is called a syndrome because of the coexistence of other findings, which, if observed or found by laboratory methods, lead to its diagnosis. Such is dyskeratosis of the palms and soles, mandibular cysts, agenesis of the corpus callosum, bifid ribs, hypertelorism, medulloblastomas and signs on the palms.
(g) Ulcerative BCC.
(h) Rarer forms: linear, precancerous epitheliomas, etc. (see Chaps. 1 and 6).

Deep infiltration can occur in the medial canthus, where the tumour can infiltrate along the median orbital lobe and the nasolabial fold to the nose, the tragus and the retroauricular areas. In this case, an MRI may be useful for determining extensive lesions (see Fig. 10.61).

4.1.4 Treatment

Treatment is usually done with superficial X-rays or electron beams. In low-risk small BCC with a well-contoured target tumour, we leave a margin of 3 mm around the tumour for clinical target volume (CTV) and further 2 mm will be added to CTV to define the planning target volume (PTV) in the treatment field with superficial radiation [2–5].

- Low-risk BCCs are generally small (<2 cm) well defined, without critical localisation and without aggressive histological types. Only 5% of well-defined BCCs under 2 cm indicate a subclinical extension beyond 5 mm.
- High-risk BCCs are generally large (>2 cm) with a critical localisation (eyes, ears, lips, nose and nasolabial folds) and present aggressive histology, as well as invasive, micronodular or perineural extension.

In many cases, they are treated equally well with radiotherapy or surgery (see Chap. 6)

4.1.5 Indications for Radiotherapy

1. Large superficial lesions, where a better cosmetic result can be achieved with radiotherapy.
2. Large lesions, where surgery would cause loss of function, such as paralysis, nystagmus or ectropion. It may also be used for:

(a) Extensive lesions over 5 cm, where surgery may require rhinectomy, ear amputation or eye enucleation.

(b) Elderly patients, in which radiotherapy-induced long-term skin atrophy may not have time to be manifest as a side effect.
(c) Multiple superficial lesions, where surgery is not indicated.
(d) Patients in poor general condition or refusing surgery.
(e) Selected tumours of the eyelids and eye canthus.
(f) Selected tumours in the nose, ears and lips. Larger lesions found in the cartilage are treated better with electrons.
(g) As adjuvant treatment after surgery (see Figs. 6.26 and 10.11).

4.1.6 Dose Fractionation

The daily dose and fractionation depends on the location, lesion size, age and general condition of the patient. The ease of implementing short-course treatments can counteract the risk of damaging healthy tissue.

There follow various effective widely used regimens.

1. Lesions <3 cm in diameter with Rö 80–140 kV
   (a) 36 Gy/8 Fr of 4.5 Gy in 17 days (Monday, Wednesday, Friday)
   (b) 30–32 Gy/4 Fr of 7.5–8 Gy in 2–4 weeks (1 or 2 sessions per week)
   (c) Single doses of 12–15 Gy may also be considered for tumours <3 cm maximum diameter.
2. Lesions >3 cm in diameter on skin on the nose or nose tip, with poor vascularisation (superficial radiation [electrons])
   (a) 45 Gy/9 sessions of 5 Gy in 21 days, every second week
3. Lesions >5 cm with electrons or high-potential radiation
   (a) 50–54 Gy/20 Fr of 2.5–2.7 Gy in 4 weeks
   (b) 40 Gy/15 Fr
   (c) 40.5 Gy/9 Fr
   (d) 32.5 Gy/5 Fr

Alternatively, in elderly patients, a weekly hypofractionated scheme of 6 Gy per fraction in 5 weeks would be also used in clinical routine practice [6].

4.1.7 Skin Squamous Cell Carcinomas (SCCs)

It is the second most common skin cancer after basal cell cancer. Treatments are very effective and can reach 90% cure rates. In the head and neck, 20% are subcutaneous. A common precancerous lesion is actinic keratosis (see Chaps. 1 and 6). Primary subcutaneous SCCs may develop slowly or quickly [1–4].

This may initially lead to metastases in the local lymph nodes and later in the viscera (see Fig. 6.17). Overall mortality is 3%. Head and neck subcutaneous SCCs may spread via the blood to the CNS or via the perineural space.

It usually appears as an ulcerated and painless hard nodule. It bleeds easily, has similar clinical features with BCCs, but usually progresses and ulcerates rapidly, does not display the characteristic rosette-shaped borders of BCCs and is foul and malodorous. An exception would be those tumours that recur and regrow from deeper tissue layers and falsely give the picture of a subcutaneous construct.

SCCs are divided into cauliflower-like and ulcerative (see Figs. 6.2 and 6.15), while according to their histological tissue separation by the clinician and the degree of their aggression they are classified as well, moderately and poorly differentiated or undifferentiated.

Overall, 25% of lesions recur. Risk factors for local or lymphatic recurrence include localisation (lip and ear SCCs have a higher recurrence rate), size (tumours >2 cm in diameter), infiltration depth (>4 mm), cell differentiation, perineural infiltration, the immune status of the patient and prior treatment [2].

Tumours located in non-sun-exposed sites and locations of previous exposure to radiation, thermal burns and chronic ulceration of old scars have a higher risk of recurrence and metastases.

Poorly differentiated and anaplastic SCCs metastasise more frequently than well-differentiated SCCs. Those located in the middle of the face and the lips are especially prone to neural infiltration. Patients with these characteristics require careful monitoring.

Tumours that grow on old scars or due to radiation necrosis are very aggressive and their rate of metastasis is as high as 25–30%. Lip cancers also present a significant metastasis rate (15%), particularly when located at the corner of the mouth (20%).

Mucosal SCCs have high rates of metastasis (40%). Radiotherapy in skin SCCs is applied in the existence of positive surgical margins and positive lymph nodes (see Fig. 10.11).

The treatment of SCCs is similar to that of basal cell carcinomas. Patients at high risk of SCCs and infiltrated lymph nodes should be examined by the oncology team (dermatologist, pathologist, plastic surgeon and oncologist).

Radiotherapy is applied for patients >45 years of age, because of the theoretical risk of additional malignancies. The tumour planning methods are similar to those of basal cell carcinomas. However, margin of 3 mm is added to the tumour to define the CTV and further 2 mm will be added to define the planning target volume (PTV) (Figs. 4.2 and 4.3) [2–4].

4.1.8 Dose Prescription

A range of dose prescription are in use. The gold standard is 60–66 Gy in 30–32 fractions over 6–$6^{1/2}$ weeks.

55 Gy in 20 fractions
40 Gy in 10 fractions
45 Gy in 9 fractions
32.5 Gy in 5 fractions

Single doses of 12 or 15 Gy have been used and equivalent results to fractionated schedules for tumours <3 cm maximum diameter are reported.

4.2 Mixed-Type Skin Carcinomas

This is a special category of tumours. They are often termed **basosquamous carcinomas (BSCs) or metatypical carcinomas** and are essentially differentiated from other types only based on the histological report.

In oncological terms, both, because of their degree of aggressiveness (same as squamous cell carcinomas) but also because of their usual history (due to relapse or incomplete treatment), are treated as squamous cell carcinomas (see Fig. 6.19).

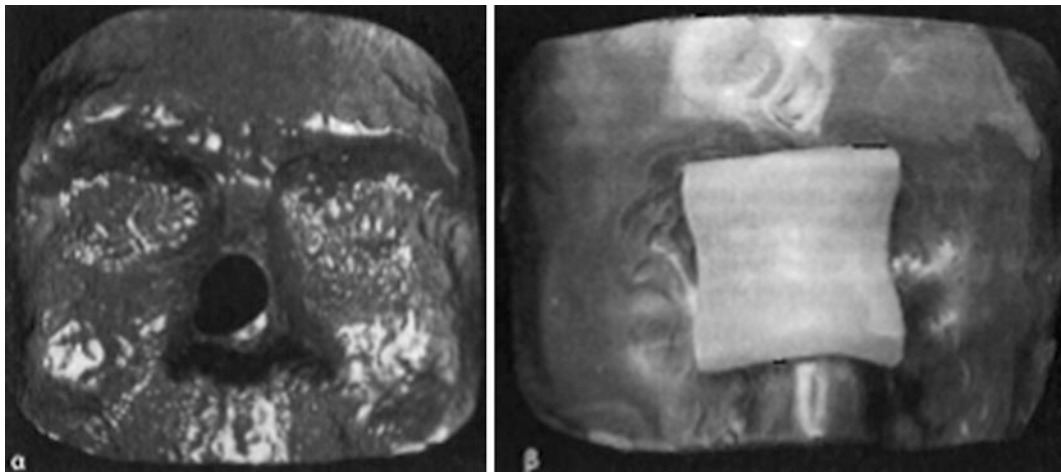

Fig. 4.2 Lead mask for lower lip electron treatment

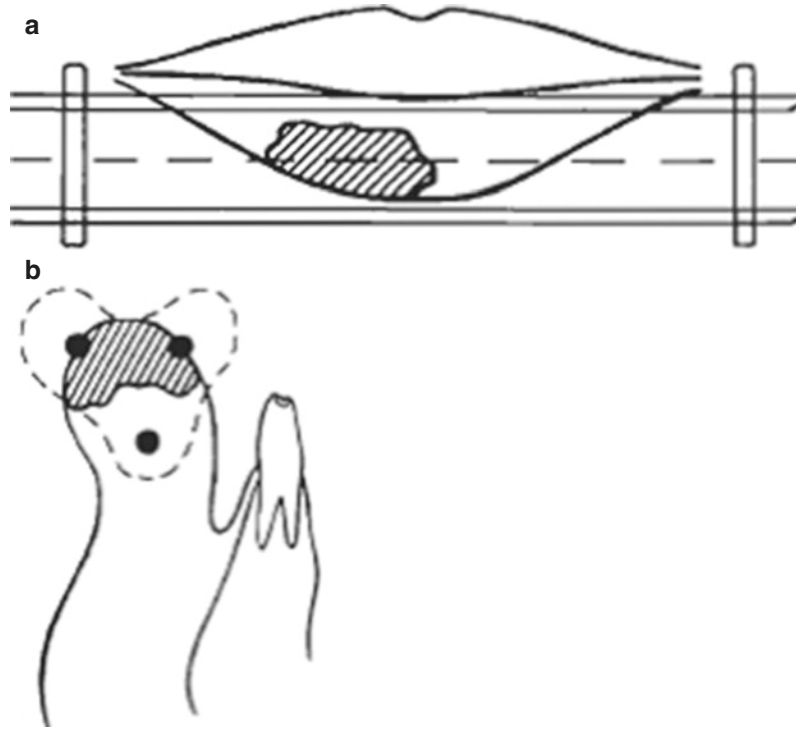

Fig. 4.3 Implantation of three sources in lower lip cancer. (**a**) Frontal section. (**b**) Transverse

4.2.1 Adnexal Carcinomas of the Skin

This is a special category of extremely rare, highly malignant and metastatic invasive carcinomas. They derive from the malignant behaviour of the cells of hair follicles and sweat glands (see Fig. 6.4).

Merkel cell carcinomas have a frequency of 0.23 per 100,000 in the Caucasian population. Merkel cells were first described in 1875 by Merkel and are known to date for their action as "slow-acting mechanoreceptors" that exist in the basal layer of the skin and provide information on touch and hair motion. These cells, which have a neuroendocrine origin and are transformed, cause a highly malignant carcinoma, known as Merkel cell carcinoma [5].

This was first described by Toker in 1972.

Causative factors are (a) the sun, (b) exposure to arsenic, (c) congenital ectodermal defect, (d) Cowden's disease, (e) Hodgkin's disease, (f) immunosuppression, (j) HIV and (h) CLL.

Macroscopically, it resembles a basal cell carcinoma. It is a rare tumour with high recurrence rates, frequent lymphatic infiltration and a high risk of metastasis. Three-year survival is 31–62%. Postoperative findings, radiotherapy in the tumour bed and the section with electrons and 3–5 cm margins should be considered, as should primary treatment without surgery (see Figs. 1.21 and 10.21).

Radiotherapy is also indicated in local lymph nodes with extensive nodal disease.

Radical radiotherapy	Dose 60 Gy/30 Fr over 6 weeks
Radical chemotherapy, radiotherapy	Dose 50 Gy/25 Fr over 5 weeks
Adjuvant radiotherapy	50 Gy/20 Fr of 2.5 Gy/4 weeks
and the tumour	or 45 Gy/15 Fr of 3 Gy over 3 weeks
Lymph node radiotherapy	50 Gy/25 Fr/5 weeks

4.3 Kaposi Sarcoma

These were first described by the Professor of Dermatology at the University of Vienna Moritz Kaposi in 1872 as "idiopathic" multiple pigmented sarcomas of the skin. The emergence and spread of HIV infections resulted in a significant increase in the incidence of Kaposi sarcomas, mainly in male homosexual HIV (+) patients (Fig. 4.4). Indeed, the description of Kaposi sarcomas in young homosexual males was one of the two reports that led to the acceptance of a new syndrome, later termed AIDS.

Based on their epidemiological data, Kaposi sarcomas are distinguished today into four types:

1. "Classic" or "Mediterranean-type".
2. "African" or "endemic".
3. AIDS-associated or "epidemic".
4. Iatrogenic (associated with iatrogenic immunosuppression), in the event of transplants, chemotherapy, etc.

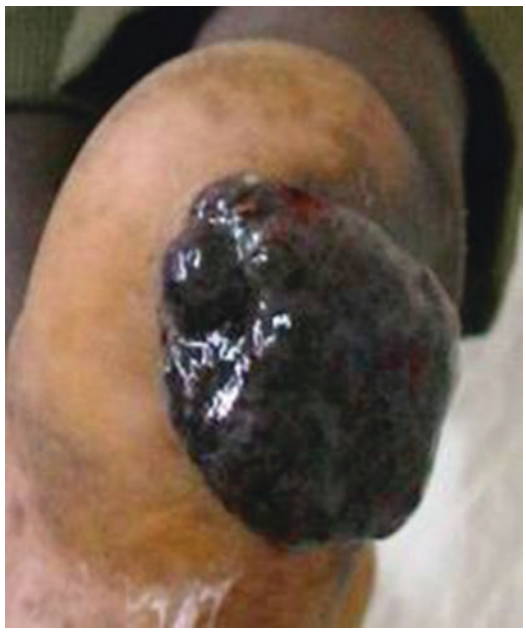

Fig. 4.4 Kaposi sarcoma in a 36-year-old female

The fact that all clinical forms of Kaposi sarcomas constitute a single disease is underlined by the finding of the DNA of a new herpes virus, human herpesvirus 8 (HHV8), in all types.

4.3.1 Pathogenetic Mechanisms

(a) Genetic factors.
(b) Cytomegalovirus (CMV), human papilloma virus (HPV), mycoplasma, etc.
(c) Nitrite formulations.
(d) Hormonal factors.
(e) Immune disorders (cytokine secretion, angiogenesis).

4.3.2 Clinical Image of Kaposi Skin Sarcomas

It develops in three successive stages in the skin:

1. Stage of patches.
2. Stage of papules/infiltrated plaques.
3. Tumours.

4.3.3 Clinical Image of Mucosal Kaposi Sarcomas

It coexists with skin lesions and appears in the tooth sockets, the mucosa of the tongue sides and the soft palate.

4.3.4 Visceral Kaposi Sarcomas

Localisations other than the skin are very common and visceral expansion affects up to 75% of patients. It most frequently affects the lungs and gastrointestinal tract, as well as the liver, spleen, pancreas, gonads, kidneys and bone marrow.

4.3.5 Coexistence of Kaposi Sarcomas with Other Malignancies

It usually coexists with B-cell lymphomas but also with leukaemias, epithelial cancers or other tumours.

4.3.6 Staging and Treatment of HIV Aids–Kaposi Sarcomas (Fig. 4.4)

The choice of treatment requires a comprehensive assessment of multiple components, such as:

1. The general condition of the patient.
2. The degree of underlying immunodeficiency.
3. The clinical appearance and distribution of the tumour, including:
   (a) The number, form, extent of distribution of skin lesions
   (b) The speed of their development
   (c) The possible involvement of the mucosa
   (d) Whether lymph nodes are affected
   (e) The existence of lymphoedema
   (f) The possible extension to the viscera

4.3.6.1 Systemic Treatment

(a) Antiretroviral therapy
(b) Antiretrovirals and interfirm
(c) Chemotherapy

4.3.6.2 Topical Treatment

The most important element in the use of topical treatment methods is that they can in no case substitute systemic therapy.

Generally, however, Kaposi sarcomas are not a "classic" type of cancer, where the removal or destruction of the primary focus leads to the reduction or elimination of the possibility of metastasis. They are in fact a multisystemic disease and thus topical treatment methods treat the lesion and not the disease.

Topical treatment methods:

(a) Cryotherapy (cryoablation with liquid nitrogen)
(b) Laser
(c) Radiotherapy

It has been used extensively to treat both "classic" Mediterranean Kaposi sarcomas and HIV-associated sarcomas, as its vascular sarcomatous lesions are quite sensitive to radiation. In several studies, >2/3 of cases allows partial or complete response, regardless of stage.

Radiotherapy helps in pain management, as in cases of extensive Kaposi sarcomas in the lower extremities and oedemas. It also helps in the treatment of lesions in difficult anatomical regions, such as the oral mucosa, face, eyelids or soles.

4.3.7 Skin Radiotherapy

The doses used are from a single dose of 800 Gy to 15 Gy/3 sessions of 5 Gy over 1 week.

4.3.7.1 Radiotherapy in the Mucosa

Doses of 20 Gy/10 sessions over 2 weeks in conjunction with:

- Local infusion of interferon
- Local infusion of chemotherapeutic agents
- Surgical methods

Radiotherapy is a very effective monotherapy for the treatment of **mycosis fungoides** (50% of cutaneous lymphomas), as shown in details in section 4.6. It is used:

- In early stage Ia–IIb **mycosis fungoides**, skin radiotherapy is like ultraviolet A radiation (PUVA).
- In stage Ilb–IVb, radiotherapy is used alone or with systemic therapies to treat skin lesions, lymph node and visceral metastases.

A problem later occurs in superficial lymph nodes. In a few cases, the liver, spleen, lung and bone marrow are affected.

4.3.8 Total Skin Electron Beam Therapy

This is used in the entire skin at every stage of mycosis fungoides.

4.4 Cutaneous Melanoma

This is a malignancy of melanocytes (Fig. 4.5). This is a highly malignant tumour that metastasises to lymph nodes and, via the blood, to the brain, bones and lungs (see Chaps. 1 and 6). Melanomas account for 1–3% of all malignant tumours and their incidence is increasing by 7.4% per year worldwide. The mortality of patients with melanomas has doubled in the last 35 years. The incidence of the disease increases with age, but one in four (1/4) people with melanomas are younger than 40 years. It usually occurs in adults with white skin or after the transformation of a melanocytic nevus [7–13] (see also Chaps. 1 and 6).

4.4.1 Development

Most melanomas develop from skin melanocytes and present two phases of development, which may overlap in some cases: **phase 1, horizontal development**, where atypical melanocytes spread radially, occupying a greater area, and **phase 2**, **vertical development**, where the lesion invades the skin layers in depth and becomes a pure malignant melanoma (see Chap. 3).

Often, the first indication of a melanoma is a change in the size, shape or colour of a nevus (wart). Normally, a nevus is a brown, dark or black mark on the skin. It may be flat or raised and round or oval in shape. Nevi are usually small, less than 0.5 cm. A nevus may be present since birth or may appear later, usually in the first 10 years of life. Many nevi disappear with age. Most people have 10–30 nevi on their skin. The vast majority of these are completely harmless. A change in a nevus, however, is an indication for a visit to a dermatologist. Of course, melanomas can occur as new nevi.

4.4.2 Early Diagnosis

In men, melanomas usually occur on the trunk, head and neck. In women, they usually occur in the arms and the legs. They are more common in fair skins. In the black race and in very dark people, they are more likely to occur on the palms and soles.

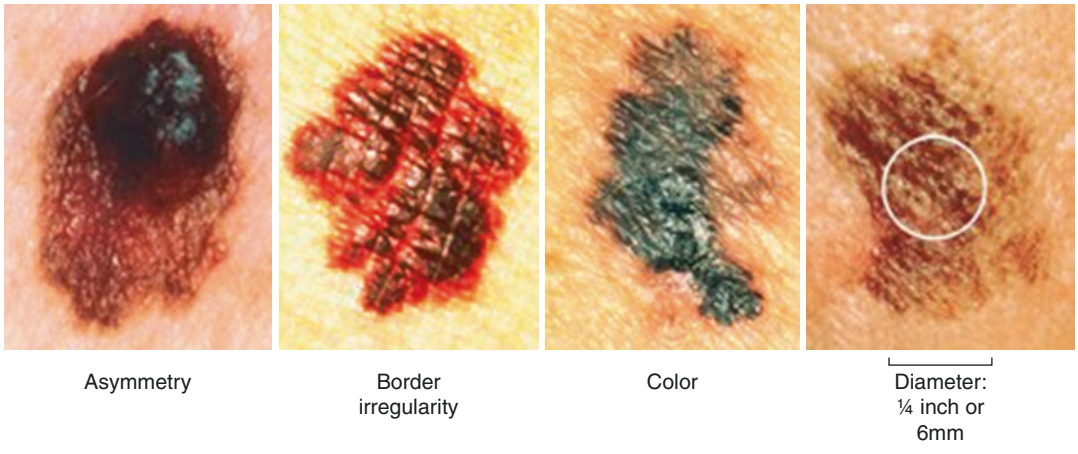

Fig. 4.5 Cutaneous melanomas

Early diagnosis and treatment are a golden rule in medicine and this is especially true for melanomas: The earlier they are diagnosed, the more likely it is that they will be completely cured. Patients should regularly examine their skin and should visit a dermatologist in the event of any change in the appearance of existing nevi or the emergence of a new one. Especially those with a history of melanomas should regularly be examined for the possibility of relapse (every 3–6 months).

Some families have a certain category of nevi, called dysplastic nevi. These are more frequently transformed to melanomas. They are found in large numbers (>50) and some have a diameter of >0.5 cm (see Chap. 1).

4.4.3 Diagnosis

As melanomas can lead to metastases, early diagnosis by a dermatologist is crucial. A biopsy will determine the final diagnosis. The tumour is removed and examined under a microscope by a pathologist. The next step is to determine the extent or stage of the tumour by measuring its thickness, the depth of invasion in the skin and whether there are metastases in adjacent lymph nodes or other organs. Treatment is planned accordingly upon determining the stage, taking into account the age and general health of the patient [7–13] (see Chap. 6).

4.4.4 Types of Melanoma

Malignant melanomas are divided into the following types:

1. **Superficial spreading melanomas**. This type of melanoma starts as a hyperchromatic spot, which subsequently becomes a palpable papule. It extends laterally and horizontally and has a rough contour. Its colour varies between different shades of brown, black or red. Prognosis is considered good during horizontal development but worsens as the lesion invades the skin in depth. Superficial spreading melanomas affect young and middle-aged people and are more common in women (see Figs. 1.24 and 6.29).
2. **Nodular malignant melanomas**. Nodular malignant melanomas are the most clinically aggressive type of melanomas. They account for 15–30% of the total number of melanomas. They appear at the age of 50–60 years and are twice as common in men than women. The lesion appears as a dark brown or black invaded nodule. The raised lump eventually becomes ulcerative and bleeds. The most common sites are the head, neck and chest (see Figs. 1.25 and 6.30).
3. **Amelanotic melanomas**. It is characterised by an achromatic hard lump, which often becomes ulcerative (see Figs. 1.26, 1.31 and 6.33).
4. **Lentigo maligna melanomas**. This appears on the face, usually on the cheeks, forehead or nose, in older people. It appears as a flat pigmented lesion, which grows gradually. The colours in the lesion vary from grey to sepia and sometimes may also have red, blue, grey or white spots. It has uneven limits. At later stages, after penetration from the basement membrane to the dermis, a part of the lesion thickens and becomes nodular. It is then called a lentigo maligna melanoma (see Figs. 1.27, 6.31 and 6.43).
5. **Malignant melanoma of the limbs**. Melanomas of the limbs are a special form of cutaneous melanoma, which develops on the palms and soles or in the bed of the nails and toes. It accounts for about 7% of melanoma cases. It is more common in men and in older people. It appears and evolves over several years (see Figs. 1.28 and 6.32).

4.4.5 Staging

Various staging systems are used for cutaneous melanomas [8–13]. The ***four main ones are the Clark Level, Breslow Thickness, TNM and AJCC***.

The depth of invasion is the ***best predictor*** of the outcome. According to one classification sys-

tem **(Clark)**, primary melanomas are divided into ***five levels of invasion***, which the pathologist determines easily depending on the skin element this reaches:

- **Stage I (in situ):** The melanoma is in situ, in the basal membrane of the epidermis, in the dermo-epidermal junction, where the outer layers of the skin meet the internal.
- **Stage II:** Extension to the upper third of the dermis, the papillary dermis.
- **Stage III:** The melanoma extends to the boundary between the papillary and the reticular dermis.
- **Stage IV:** Invasion of the reticular layer.
- **Stage V:** Invasion of the subcutaneous tissue, such as adipose tissue (see Chaps. 1 and 6).

Stage I melanomas are almost always curable by surgical removal of the lesion. Stage II melanomas relapse in about 60% of cases. Stage III and IV melanomas relapse in 85% of cases.

According to **another classification system (Breslow thickness)**, the exact depth of penetration as measured microscopically is taken into account and used together with the previous system. Melanomas with a thickness less than 0.75 mm are usually considered highly curable by surgery alone, although some cases with such "thin" lesions may relapse. Tumours with thicknesses from 0.76 to 1.5 mm are considered to have caused moderate invasion and have a worse prognosis than thin lesions. *Melanomas with a thickness of 1.6 mm* or larger are very deep, in particular *those with a thickness of more than 4 mm*.

Although there is no precise correlation between the two classifications, ***some interdependence between the levels and thickness of invasion*** may be noted. It is advisable to consider that any lesion with an invasion depth greater than 1.5 mm can potentially relapse and is thus high risk (see Chap. 3). Frequent contact with the surgeon or oncologist is required in such cases, to perform the appropriate examinations (see Chaps. 2 and 6).

Another sign indicating ***poor prognosis***, except the advanced stage, is the ***invasion of local lymph nodes***. Usually, lymph nodes form an immunological barrier against the tumour. When these are invaded by the tumour, the cancer cells eventually pass into the blood, from which they migrate to distant organs. At least 80% of patients with affected lymph nodes present a tumour relapse elsewhere in their body. Other prognostic factors are the *presence of bleeding or ulceration* and the general health of the patient (see Chap. 21).

4.4.6 Treatment

After the lesion is identified as a malignant melanoma, the disease should be staged. Clinical and imaging examinations, mainly radiological, investigate whether there is evidence of lymph node or systemic metastases. Systemic or distant metastases may occur in organs such as **the lungs, liver, bones, brain or others**. The appropriate treatment is selected depending on the stage the disease appears to be in [7].

The therapeutic approach is essentially divided into three parts:

1. Treatment of the primary lesion, which covers the wide, treatment and supplementary local excision.
2. Management of the local lymph nodes.
3. The possible administration of systemic therapy for any metastatic disease (see Chaps. 2 and 6).

The treatment of melanomas starts with their local excision. As melanomas often present microscopic metastases in the skin near the primary melanoma, the so-called ***satellite metastases***, an extra 1 or 2 cm of macroscopically normal skin surrounding the scar of the diagnostic biopsy or around the melanoma itself should be removed. This excision should reach the *underlying muscle fascia*. This reduces the potential for a local recurrence of the disease in the future. Depending on the size and position of the gap created by the wide excision of the melanoma, plastic surgery with a skin graft or flap may be necessary (see Chap. 6).

The second part of the therapy concerns the management of regional or local lymph nodes. When the melanoma is located in the upper or lower limbs, the usual local lymph node group is in *the axillary or inguinal region, respectively*. However, when it is located in the trunk or in the neck and head region, the location of its lymph node metastases is unpredictable. Lymph node scintigraphy contributes to the accurate identification of the position of the local lymph nodes in each patient, by revealing even those that are in atypical or unexpected lymph node groups (see Chap. 5). The imaging of lymph nodes in this scan shows the position of the local lymph nodes but not the possible existence of invasion. The existence of local distended lymph nodes is evaluated in a clinical setting, sometimes with an ultrasound. If the cytologic or histologic examination of a palpable lymph node documents the existence of metastasis, there is an indication for radical therapeutic lymphadenectomy. Previously, many patients with clinically identified melanoma, i.e. with no metastases in the clinical examination and imaging studies, used to undergo prophylactic lymphadenectomy. However, in about 80% of patients who underwent this operation, the lymph nodes removed were free of disease, meaning that a major surgery with potential complications was performed without benefit to the patient. Today, we can identify 20% of patients with metastases in lymph nodes through a small operation, ***sentinel lymph node biopsy***. The sentinel lymph node is the lymph node of the regional group that first receives the lymphatic drainage from the area of the melanoma and therefore, in the case of lymph node metastases, is the first to be invaded. The intraoperative detection and biopsy of the sentinel node determines the state of the regional lymph nodes and only when this presents metastatic cells do we proceed to the removal of all remaining regional lymph nodes (selective radical lymph node ablation). Thus, only patients who actually need it undergo this major operation. Sentinel node biopsy is usually combined with wide (supplementary) excision of the melanoma and is usually performed under general anaesthesia. Sometimes, it can be done under local or regional (dorsal) anaesthesia. However, lymph node ablation always requires general anaesthesia (see Chaps. 6 and 22).

Systemic chemotherapy is recommended in the event of distant metastases, i.e. in organs such as the lungs, liver and bones (see Chap. 2).

4.4.7 Radiotherapy

Although traditionally considered a radiation-resistant tumour, this does not seem to apply in all cases. Clinical and laboratory studies suggest that melanomas have particular radiobiological characteristics. These are:

1. High reconstructive repair capacity of the non-fatal radiation lesion. In the LQ model, this is expressed as a low value of the *a/b* ratio (0.5–2 Gy).
2. Therapeutic result independent of the overall treatment time, perhaps due to limited repopulation.
3. Significant effect of tumour size (number of cells) on the therapeutic result.

The clinical implication of the aforementioned texts is the use of large doses per fraction (usually 4–6 Gy) in radiotherapy for melanomas.

Lentigo melanoma: Using a relatively low dose of 20 × 2.5 Gy with a margin of 1–2 cm and superficial radiation X (KV) or electron beams, we observe a complete response rate of 80–85% [7].

Furthermore, after lymph node ablation, the indications for radiotherapy are:

(a) Cervical localisation.
(b) Extracapsular extension.
(c) More than three invaded lymph nodes.
(d) Palpable lymph nodes initially.

Local/regional adjuvant radiotherapy increases the disease-free interval and survival. Many radiotherapy regimens have been implemented, with a daily dose ranging from 2 to 8 Gy as a single dose. Correspondingly, the total dose

Table 4.1 Randomised studies in radiation therapy for melanoma cancer [14]

Authors	Total dose	Daily dose	Fractions	Regional control
Ballo (2006)	30 Gy	Over 2.5 weeks	5 fractions	93%
Bonnen (2004)	30 Gy	Over 2.5 weeks	5 fractions	89%
Chang (2006)	30 Gy 60 Gy 74.4	Over 2.5 weeks 2 Gy Twice daily	5 fractions 30 fractions 62 fractions	87%
Creagan (1978)	50 Gy	3–4 week split	28 fractions	11% OS: $P = 0.09$
Trans-Tasman Radiation Oncology Group (Burmeister, 2006)	45–50 Gy	2.25–2.38 Gy	20–21 fractions	91%
Fenig (1999)		≤300 cGy		87%
Seegenschmicat (1999) (skin)	50–60 Gy	2 Gy	25–20 fractions	
Seegenschmicat (1999) (bone metastases)	35–36 Gy 8 Gy 45 Gy	2.5–3 Gy 8 Gy 2.5 Gy	14–12 fractions Single fraction 18 fractions	
Patcell (2003) (brain metastases)	20 Gy 30 Gy 40 Gy	4 Gy 3 Gy 2 Gy	5 fractions 10 fractions 20 fractions	
RTOG (metastatic melanoma)	32 Gy 50 Gy	8 Gy 2.5 Gy	4 fractions 20 fractions	23.8%
Overgard	9 Gy 5 Gy	3 Gy	3 fractions 8 fractions/twice weekly	69%

applied is 20–60 Gy. Table 4.1 presents the doses that have been applied in various studies.

Studies where radiotherapy combined with hyperthermia has been applied clearly exhibit an increased probability of local tumour control compared to radiotherapy alone [14].

4.4.8 Prognosis

The prognosis of the disease is generally mainly determined *by the thickness of the melanoma*, the presence of ulcerations in the histologic examination, the number of lymph nodes invaded by the disease, the size of the infiltrated lymph nodes and the presence or absence of distant metastases.

Thus, in situ melanomas have a 5-year and a 10-year survival rate of 100%, melanomas with a thickness *less than or equal to one millimetre have* a 5-year survival rate of 91–95% and a 10-year rate of 83–88%, melanomas with a thickness of 1.01–2 mm have a 5-year survival rate of 77–89% and 64–79% at 10 years, melanomas with a thickness of 2.01–4 mm have a 5-year survival rate of 63–79% and 51–64% at 10 years, melanomas thicker than 4 mm have a 5-year survival rate of 45–67% and 32–54% at 10 years and melanomas with distant hematogenous metastases have a 5-year survival rate of 9–19% and a 10-year survival rate of 6–16%.

The difference in survival rates demonstrates the importance of the early diagnosis of melanomas. The earlier the diagnosis and appropriate treatment are made, the better the prognosis.

However, melanomas are unpredictable tumours, which may relapse and lead to metastases even after many years. That is why, based on the protocol, melanoma patients should be monitored regularly for their entire lives.

4.5 Subcutaneous Angiosarcoma

Subcutaneous angiosarcomas of the scalp and face are a rare condition that primarily affects elderly patients. It is often multifocal and therefore complete surgical removal is difficult. It is biologically aggressive, with a high risk of metastases, while 5-year survival is 15%, with 50% mortality at 15 months.

The treatment of choice is surgical removal. Postoperative radiotherapy is recommended in infiltrated excision borders. In cases of unresectable disease, high-dose electron radiotherapy and large margins around the tumour allow local control and palliation.

Dose:

- ***Adjuvant:*** 50 Gy/25 sessions.
- ***Palliative:*** 44 Gy/11 sessions of 4 Gy or 60 Gy/30 sessions over 6 weeks.

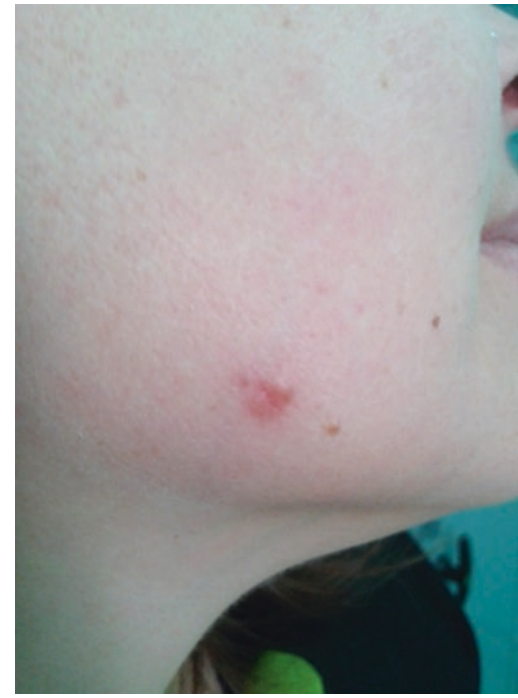

Fig. 4.6 Primary cutaneous anaplastic lymphoma of the face

4.6 Cutaneous Lymphomas

4.6.1 General

Although rare, cutaneous lymphomas (Figs. 4.6 and 4.7) represent a separate entity in hematologic oncology. Accounting for about 4% of non-Hodgkin lymphomas (NHL), cutaneous T- and B-cell lymphomas (CTCLs and CBCLs) are a group of disorders characterised by their epidermotropic behaviour, primarily affecting the skin. T-cell origin lymphomas are most common, representing 70% of CL, with MF accounting for about 50–70% of cases. Sézary syndrome (SS) accounts for 3% of CTCL (Table 4.2) [15].

The most common type of CTCL is MF which represents a low-grade NHL of skin homing T-helper lymphocytes within epidermis and dermis. The course of the disease is initially indolent with limited skin lesions but most patients progressively develop patches, plaques or tumours and finally nodal and visceral disease.

Staging and classification of MF is based on TNMB system where T describes skin lesions, N refers to nodal status while M refers to visceral

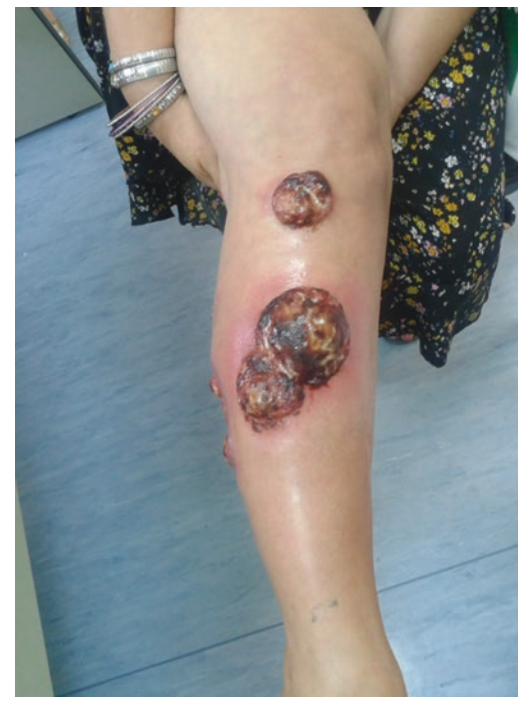

Fig. 4.7 Mycosis fungoides in the tibia

Table 4.2 World Health Organization–European Organization for Research and Treatment of Cancer classification of cutaneous lymphomas with primary cutaneous manifestations

Cutaneous T-cell and NK-cell lymphomas
Mycosis fungoides
Mycosis fungoides variants and subtypes
Folliculotropic mycosis fungoides
Pagetoid reticulosis
Granulomatous slack skin
Sezary syndrome
Adult T-cell leukaemia/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 c/d T-cell lymphoma (provisional)
Primary cutaneous pleomorphic CD4+ small/medium T-cell lymphoma (provisional)
Cutaneous B-cell lymphomas
Primary cutaneous marginal zone B-cell lymphoma
Primary cutaneous follicle centre B-cell lymphoma
Primary cutaneous diffuse large B-cell lymphoma, leg type
Primary cutaneous diffuse large B-cell lymphoma, other intravascular large B-cell lymphoma
Precursor haematologic neoplasm
CD4+/CD56+ haematodermic neoplasm (blastic NK-cell lymphoma)

Table 4.3 Staging of mycosis fungoides/Sezary syndrome

	TNMB	TNMB classification and staging of mycosis fungoides and Sezary syndrome
Skin	T1	Limited patches, papules and/or plaques covering <10% of the skin surface
	T2	Patches, papules and/or plaques covering ≥10% of the skin surface
	T3	One or more tumours (≥1 cm in diameter)
	T4	Confluence of erythema ≥80% body surface area
Node	N0	No abnormal lymph nodes; biopsy not required
	N1	Abnormal lymph nodes; histopathology Dutch Gr1 or NCI LN 0-2
	N2	Abnormal lymph nodes; histopathology Dutch Gr2 or NCI LN 3
	N3	Abnormal lymph nodes; histopathology Dutch Gr3 or NCI LN 4
	Nx	Abnormal lymph nodes; no histologic confirmation
Visceral	M0	No visceral organ involvement
	M1	Visceral involvement (must have pathology confirmation)
	M2	Abnormal visceral site; no histologic confirmation
Blood	B0	Absence of significant blood involvement: ≤5% peripheral blood lymphocytes are atypical (Sézary) cells
	B1	Low blood tumour burden: >5% of peripheral blood lymphocytes are atypical (Sézary) cells but do not meet criteria of B2
	B2	High blood tumour burden: ≥ 1000/mcL Sézary cells or CD4/CD8 ≥10 or ≥40% CD4+/CD7− or ≥30% CD4+/CD26− cells

involvement. B describes blood status by means of atypical cells (Sézary cells) in peripheral blood (Tables 4.3 and 4.4). Median age at diagnosis is 56 years and 70% of patients are male. Most patients are diagnosed in early stages I and II with patches or plaques limited to skin. The disease has an indolent course with excellent prognosis in these stages with only 5–10% disease progression in 10 years and median survival between 15 and 30 years. Advanced stages of disease with diffuse erythroderma or tumours have poor prognosis with a median survival of less than 10 years [16].

Nearly all patients with MF experience relapse(s) after treatment and are at risk of disease progression or even transformation to a more aggressive T-cell malignancy. Goal of treatment is disease remission and prolongation of time to relapse.

Treatment of MF and CTCL in general is either skin directed or systemic, depending mainly on stage and course of disease. Initial treatment approaches in patients with patch or

Table 4.4 Clinical staging of MF and SS

	T	N	M	B
IA	1	0	0	0,1
IB	2	0	0	0,1
IIA	1–2	1,2	0	0,1
IIB	3	0–2	0	0,1
IIIA	4	0–2	0	0
IIIB	4	0–2	0	1
IVA	1–4	0–2	0	2
IVA	1–4	3	0	0–2
IVB	1–4	0–3	1	0–2

plaques include skin directed therapies which are topical corticosteroids, topical chemotherapy, retinoids, phototherapy (mainly PUVA) and electron beam radiation.

1. Topical, skin-directed treatments
   (a) Corticosteroids
   (b) Local chemotherapy
   (c) Retinoids
   (d) Phototherapy—photochemotherapy
   (e) Radiation therapy
2. Systemic treatments
   (a) Extracorporeal photopheresis
   (b) Immunotherapy
   (c) Monoclonal antibodies
   (d) Denileukin diftitox
   (e) Vorinostat
   (f) Systemic chemotherapy
   (g) Transplantation of progenitor cells

4.6.2 Total Skin Electron Beam Radiation Therapy

Total skin electron beam therapy (TSEB) is one of the many different skin-directed treatment options for CTCL. It takes advantage of special characteristics of particle radiation by electrons that can deliver therapeutic dose to patient's skin without damaging subjacent healthy organs.

During TSEB, ionisation radiation can be safely applied to skin with prescribed dose depending on clinical guidelines. Radiation penetrates only the skin without affecting and harming internal organs and critical structures.

Table 4.5 Objectives of total skin electron radiation

• Align dose distribution to target volume
• Sufficient dose within target volume
• Patient compliance
• Cutaneous remission
• Long-term clinical results
• Minimal toxicity
• Accommodate repeated administration as required

According to the consensus of the European Organisation for Research and Treatment of Cancer (EORTC) the principal objectives of any method of TSEB are listed in Table 4.5 [15]. Various TSEB treatment techniques have been introduced over past several decades with six field "Stanford" technique being the most widely accepted technique worldwide (Figs. 4.8 and 4.9).

The primary target volume is the epidermis, adnexal structures and the dermis. Human body has a complex surface form, which results in difficult dose homogeneity. In order to achieve optimum dose distribution and homogeneity the source skin distance (SSD) from linear accelerator must be at least 2.5 m. So the main prerequisites for TSEB are a linear accelerator that can produces large electron fields at an extended SSD and a large treatment room.

All current techniques require a linear accelerator that can generate a homogeneous electron field. For optimum dose distribution, the eighty percent isodose line should be more or equal to 4 mm deep to skin surface to ensure that epidermis and dermis fall within high dose region while 20% isodose line should be less than 20 mm from the skin surface to minimise dose to underlying structures, mainly bone marrow. Total prescribed dose is 30–36 Gy in 1.5–2 Gy per fraction with 1 week break mid treatment in cases of significant acute toxicity, like erythema. Thicker lesions or tumours may be boosted with extra dose to ensure surface dose more or equal to 50% of prescribed TSEB dose [16, 17]. TSEB is administered in 2-day treatment cycles, 4 days per week for 9 weeks. During first day of each

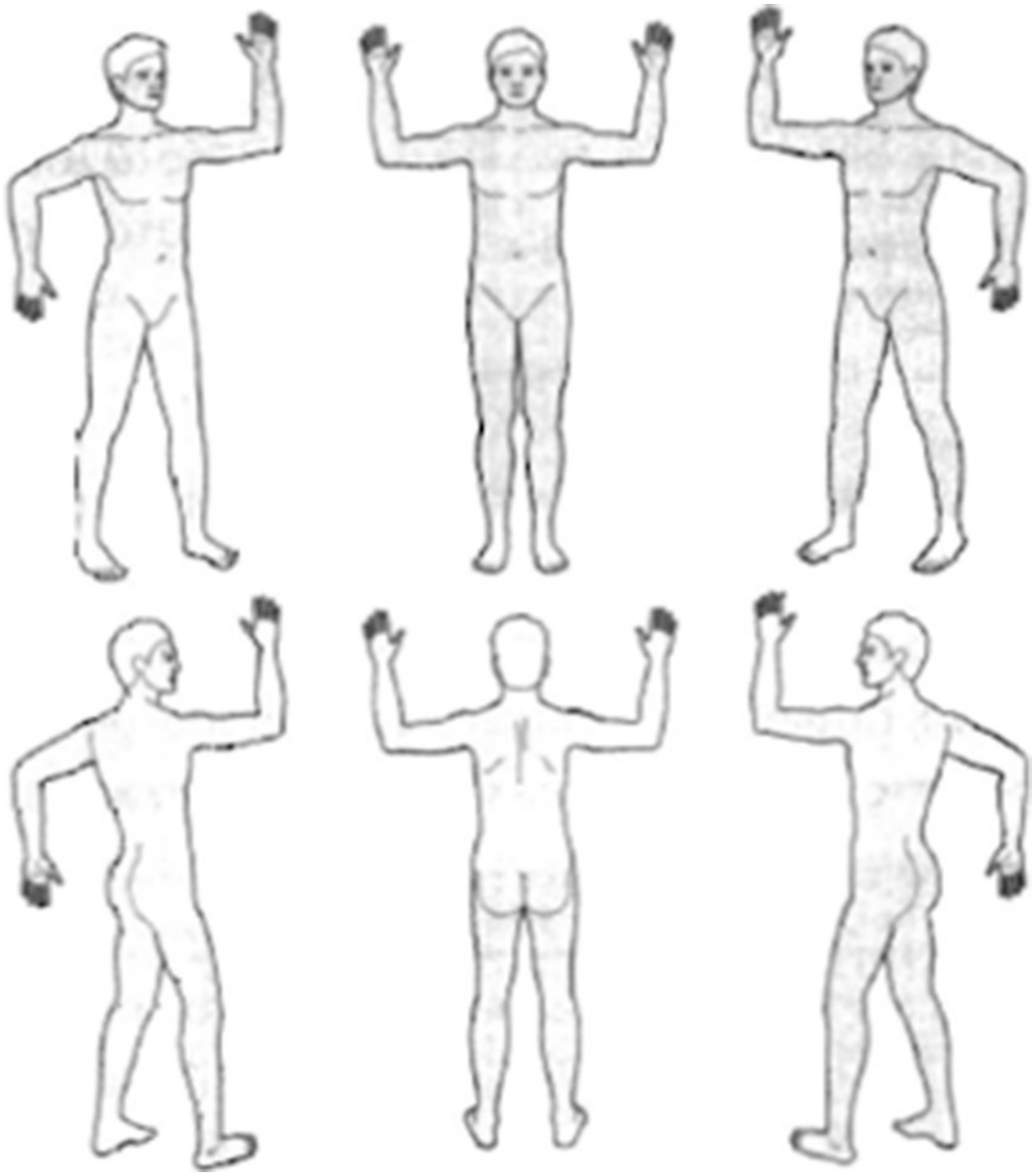

Fig. 4.8 Total skin electron beam therapy (TSEB). Whole-skin electron beam therapy technique. Six (6) treatment positions

cycle patient is treated in three positions, anterior and two posterior obliques with the rest three positions, posterior and two anterior obliques being treated during the second day [18–22]. During treatment, care is taken to protect the eyes. Areas that cannot be directly exposed to the electron beam (feet, perineum, upper inner thigh area, retroauricular area, inner part of the skull and skin folds) are treated with separate electron fields.

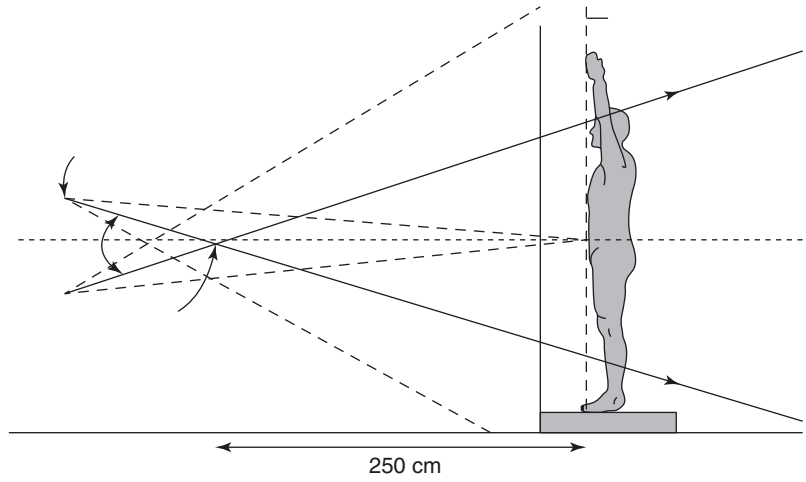

Fig. 4.9 Total skin electron beam therapy (TSEB). Whole-skin electron beam therapy technique. Management of fields

4.6.3 Clinical Implementation

4.6.3.1 TSEB as Initial Treatment

TSEB is often prescribed in cases of disease recurrence or progression after other curative treatment and rarely is administered as an initial therapy. CTCLs are highly radiosensitive like other lymphomas so almost in all cases the expected treatment result is full clinical response. Goal of treatment is prolongation of disease relapse by means of long-term progression free survival [19, 20].

In stage IA, TSEB as initial treatment achieves excellent results with 95% clinical and pathologic remission. According to many studies, the 10-year cause specific survival is almost 100% even though most patients experience relapse and 50% progression-free survival in 10 years. Same excellent results by means of response to treatment can be seen in patients with stages IB and IIA (T2N1) MF where TSEB achieves 90% cutaneous remissions. Nearly two-thirds of patients will experience relapse and other adjuvant therapies may be needed. Many studies suggest that combination of treatments can achieve excellent cause specific survival in 10 years.

In most advanced stages of disease with the presence of skin tumours, treatment is often individualised with additional boost treatment with electrons given to thick tumorous sites. In cases of limited patch—plaque and tumour disease—TSEB can offer good results with 50% progression-free survival in 5 years. In patients with more extensive disease, TSEB can be administered with palliative intent as nearly all patients experience disease progression despite any treatment.

TSEB is an effective treatment option in cases of diffuse erythema without blood involvement where nearly 75% of patients can show remission with full relief of symptoms. In contrast, patients with B1 or B2 stage of disease can be offered TSEB for palliation of symptoms often in combination with other treatment approaches.

4.6.3.2 Toxicity of Treatment

TSEB acute toxicity is usually mild in severity and self-limiting in nature. Late toxicity is rare but tends to be more severe and permanent, affecting quality of life. Most common acute adverse effects include erythema, scalp alopecia and anhydrosis. Late toxicity includes nail dystrophy, telangiectasias, skin atrophy, fingertip anaesthesia and infertility in male patients.

Minor erythema is the usual acute toxicity during TSEB. Greater or more severe reactions are sometimes seen on areas previous exposed to UV phototherapy. Fractionation significantly minimises skin toxicity and different fraction sizes ranging from 1.2 to 2 Gy have been employed without compromising effectiveness.

Shielding of highly sensitive structures like eye lenses is of great importance so special shields are used to ensure no radiation exposure to eyes. Protection is sometimes taken also for nails and testes to avoid chronic nail dystrophy and infertility, respectively.

4.6.3.3 TSEB as Second-Line Therapy

TSEB is very effective in cases of relapse—disease progression after other treatments. It can achieve skin remission and relief of symptoms and can be administered in all patients despite the initial treatment with minimal or no cumulative toxicity. New treatment strategies like targeted therapies are an interesting field of research, and combination of TSEB with novel agents is yet to be defined.

4.6.3.4 Repeating TSEB

As mentioned above, even though TSEB achieves excellent treatment results, many patients will experience relapse. For these cases, investigators from many centres worldwide have reported successful administration of repeated TSEB regimens to a total dose of usually 8–12 Gy with minimal toxicity. According to the EORTC consensus guidelines, additional courses of TSEB should only be offered in patients that other appropriate therapies have failed. Main late toxicity after repeated TSEB therapy is skin atrophy and necrosis.

4.6.4 Novel Treatment Regimens: Defining the Appropriate Dose

Given the facts that MF is a highly radiosensitive disease with excellent response after TSEB therapy and that nearly all patients will sometime during the course of disease will progress or relapse so repeating of radiation may be needed, many investigators worldwide have studied the role of low-dose TSEB. Treatment protocols of 10–12 Gy instead of 36 Gy have been administered with excellent partial and in some cases complete response rates and minimal toxicity according to relative literature.

4.6.5 Primary Cutaneous B-Cell Lymphoma

Primary cutaneous B cell lymphomas (CBCL) are rare entities, representing an uncommon form of extranodal non-Hodgkin's lymphomas. They are typically characterised by malignant B-cells limited to the skin at initial diagnosis. Two major pathologic classification systems for CBCLs exist: the European Organisation for Research and Treatment of Cancer (EORTC) system and the World Health Organization (WHO) system. According to the EORTC system, most CBCLs are classified either as follicle centre cell or marginal zone indolent lymphomas. According to the WHO system, most primary CBCLs are classified as diffuse large B-cell lymphomas [15].

Like T-cutaneous lymphomas, CBCLs are radiosensitive so radiotherapy with electrons, orthovoltage or high-energy photons is often employed during the course of the disease. Regional fields of radiation are usually the treatment of choice for localised skin lesions while sometimes TSEB is employed for generalised skin disease. Minimum total dose of 36–40 Gy is prescribed as doses less than 36 Gy in CBCL are often correlated with increased local recurrence rates.

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