Basal Cell and Squamous Cell Carcinoma – Radiotherapeutic Approaches

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Radiotherapeutic Approaches to Basal Cell and Squamous Cell Carcinomas and Some Other Skin Tumors

Carcinomas of the skin are the most accessible cancers, the diagnosis is readily made and the limits of the lesion are usually easy to define. No single treatment method is best for all cancers of the skin. If the sole criterion of success is eradication of the lesion, surgery and radiotherapy yield similar results. Most cutaneous cancers are sufficiently sensitive to radiation to be eradicated by doses that are well tolerated by the surrounding normal tissue. If appropriate principles are followed and precautions are taken, X-irradiation is a safe and effective method of therapy [1, 2]. Our discussion is deliberately limited to radiotherapy of cutaneous cancers of moderate size that can be effectively treated with Grenz rays, superficial X-rays or contact therapy units. Larger and more complicated skin cancers should be referred to Mohs’ surgery and/or radiation oncologists for treatment with higher kilovoltage, megavoltage, or electron beam techniques or for implants with radioactive isotopes.

In the first section, we want to stress the advantages of soft or superficial X-ray therapy:

- Possible on an outpatient basis
- Painless
- Possible for physically or psychologically handicapped patients (also patients over 90 years old) [3]
- Possible for anticoagulated patients
- In patients where there exists a contraindication for a surgical intervention
- Healthy tissue or certain organs can be protected
• The margin of normal appearing skin is usually wide (more than in surgical excisions)
• The intervention is not traumatic
  The patient has to be informed that there are also disadvantages of radiation therapy:
• The treatment cannot be done in one single session
• If the patient has already received full tumor doses in a radiation field, this particular field cannot be irradiated a second time
• Radiation treatment is followed by alopecia (except if treated by Grenz rays)
• Chronic radiation dermatitis tends to be accentuated with time

What Is Then the Ideal Indication for Radiotherapy?
Radiotherapy is particularly valuable for medium-sized tumors of 1–4 cm in diameter in the face of elderly people, since smaller tumors are mostly treated by surgery and larger lesions are mostly treated either by Mohs’ surgery or by a combination of surgery and megavoltage treatment.

What Are the Best Areas to Be Treated by Radiation Therapy?
The real superiority of irradiation over excision lies in its greater preservation of uninvolved tissue. In certain anatomic regions this may pose a problem for the surgeon but not for the radiotherapist who can easily adjust the size of the field to the required area of treatment. Therefore radiation is often the treatment of choice in areas where tissue cannot be readily sacrificed for cosmetic and/or functional reasons. There is general agreement that ionizing radiation is often preferable to other methods of treatment for cutaneous tumors of the following areas [1]: eyelids, medial or lateral canthi of the eyes, nose, ears and lips.

Excellent areas for radiotherapy are also the nasolabial fold and preauricular areas as well as larger tumors of the cheek. On the other hand, the skin of the trunk and extremities has a greater tendency to develop radiation sequelae, particularly telangiectasias and changes in pigmentation [4].

Before radiation therapy of a lesion is begun, the diagnosis must be confirmed by biopsy.

Why a Biopsy?
The histological examination determines the type of the tumor, the radiosensitivity of the tumor, the exact extension of the tumor, the depth of the tumor and the exclusion of an error.

Concerning the radiosensitivity of skin tumors we can distinguish four categories (see table 1), i.e. (1) highly indicated and unique advantage: Kaposi’s sarcoma (KS), mycosis fungoides and other lymphomas of the skin, (2) good indication: basal cell (BCC) and squamous cell carcinomas (SCC), keratoacan-
We also distinguish between curative radiotherapy in tumor’s such as BCC, SCC, keratoacanthomas, precancerous lesions and melanomas of the lentigo maligna (LM) type, whereas radiation therapy is palliative in tumors such as Merkel cell carcinoma, KS and most lymphomas.

Are there contraindications for radiotherapy with soft X-rays? These are:
- Tumors penetrating into cartilage or bone
- Intraoral tumors
- Tumors penetrating into the nostrils
- Tumors in scars of osteomyelitis, burns, chronic ulcers or in chronic radiodermatitis
- No re-treatment of previously irradiated skin carcinomas
- Genodermatoses which are prone to neoplasms, such as basal cell nevus syndrome or xeroderma pigmentosum

Which Radiation Quality?
Since the work done in England, Germany and the United States and with the introduction of the beryllium-windowed X-ray units, i.e. soft X-ray therapy
in dermatologic radiotherapy, as a rule of thumb, radiation qualities with a half-value depth (HVD = D1/2) corresponding to the depth of the tumor were proposed. Most of the radiation will then be absorbed in the pathological tissue and the possibility of undesirable radiation effects on underlying uninvolved tissue will be markedly reduced. The depth of the tumor can either be reasonably estimated by inspection and palpation or by an exact histopathological description of the tumor depth, preferably by an experienced dermatopathologist. Several papers could show that 50% of all BCC and SCC infiltrate to a depth of only 2 mm or less, and 75% of these tumors to 5 mm or less [1].

With Grenz and superficial X-ray machines, the kilovoltage is in a fixed combination with filters in order to avoid filter mistakes and thus application of faulty dosages. These X-ray machines have a kilovoltage between 10 and 50 kV, sometimes up to 100 or even 150 kV. With filter combinations, an HVD (D1/2) from 1 to 20 mm can be reached. For dermatologic purposes, it is rarely necessary to irradiate tumors thicker than 20 mm.

**Why Fractionated Doses?**

Fractionation of radiation dosage is based on the assumptions that tissues recover at different rates from the effects of radiation and that tumor tissue recovers more slowly than normal tissue. When a given dose of radiation is divided into several increments and delivered over a period of several days, the biological effect is usually less pronounced than that of the same radiation administered in a single dose. This lesser damage with fractionation appears to be related to cell recovery between increments and to the capabilities of recovering cells to adapt to radiation-induced alterations of the surrounding tissues. Small tumors and radiations fields, therefore, support higher single doses than large tumors with large irradiation fields which have to be irradiated with smaller single doses. In addition, in large irradiation fields, we have to consider an additional backscatter factor.

Much work has been done in an attempt to define optimum time-dose-volume relationships for carcinomas of the skin. There is no consensus as to the total dose needed to eradicate a cutaneous cancer and when to terminate radiotherapy. Different authors have recommended different dosages [1]. The tendency is to use standardized schedules (see table 2).

It is still worthwhile to observe the patient’s reaction during radiation therapy and to look for an exudative or erosive reaction in the irradiated margin. When larger individual doses are administered, the recommended total dose is usually smaller than in cases where smaller individual doses were used.

In the following we will discuss the different types of cutaneous cancers.
Disseminated Actinic Keratoses

Usually, there is agreement that small actinic keratoses are best treated by surgical excision or other equivalent methods. The problem arises in extensive and disseminated actinic keratoses such as on the scalp. Here again, there are possibilities with topical treatments such as 5-fluorouracil or imiquimod cream, but usually recurrence rates are higher or recurrences appear sooner than after treatment with radiotherapy. Since these lesions are intraepidermally and often in an atrophic epidermis, the ideal treatment is with Grenz rays. The treatment consists of 6 sessions of 6 Gy twice weekly applied on one or several divided fields [5]. At the end of the treatment, an erythema or an exudative reaction will occur. If there is marked pruritus topical corticosteroid cream may be of excellent help to the patient. One month after the end of treatment, the erythema has mostly gone. The patient has to be told to continue sun protection with a hat and application of a sunscreen. Rarely, it is necessary to perform a second treatment years later.

The dose schedule is shown in table 2, treatment results in figure 1.
Bowen’s Disease/Queyrat’s Erythroplasia

This carcinoma in situ is to be treated similarly to actinic keratosis, but histopathologically these lesions are more acanthotic, i.e. these are thicker lesions. Even in elderly patients, it is possible to apply Grenz rays with a D1/2 of 1 mm. If the lesions are more infiltrated, soft X rays with the quality of 20 kV or more are necessary. The dose schedule can be adapted (see table 2): again fractions of single doses of 6 Gy up to a total dose which may be a little higher than for actinic keratoses, i.e. around 40 Gy. Single doses with soft X rays would be 4 Gy. Exudative reactions have to be expected a little earlier the genitoanal area. Treatment results are excellent [5].

The dose schedule is shown in table 2.

Lentigo Maligna

This is another precancerous lesion which is an excellent indication for radiation treatment, since extensive lesions in the face of elderly people are not

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Fig. 1. Disseminated actinic keratoses of the scalp in a 78-year-old male patient, before (a) and 6 months after (b) Grenz ray treatment, 6 times 6 Gy (36 Gy), twice per week.
seldom. This treatment modality is not known too well because it has always been thought that this is not a curative treatment. Recent reports have shown that it is at least as good as surgical procedures [6–8]. As we mentioned above, the inclusion of a wide enough margin is not a problem for the radiation therapist and, therefore, large LM are an excellent indication for radiotherapy. The classical treatment schedule is called after Miescher who proposed 5–6 times 20 Gy Grenz rays for medium-sized lesions (around 2.5 cm in diameter); for larger lesions we would prefer 10–12 times 10 Gy Grenz rays (see table 2). Here again, we want to stress that the epidermis in the elderly is atrophic and with an HVD of 1 mm we even reach atypical melanocytes in the hair follicles!

**Basal Cell Carcinoma, Squamous Cell Carcinoma, Keratoacanthoma**

These tumors represent the classical indications for radiotherapy with soft X-rays or superficial X-rays, since most of them are well circumscribed and rarely larger than 2.5 cm, and as we described above, 75% of these tumors are less than 5 mm thick. Some treatment centers use the same treatment schedules for BCC and SCC, though one could imagine that SCC should be treated with a higher total dose, since they represent more aggressive tumors. Elderly patients prefer not to come every day for their treatment sessions. Therefore, medium-sized lesions may well be treated with e.g. a 4 Gy single dose in 3 fractions per week. There is the possibility for small lesions which cannot be excised for certain reasons, to apply an even higher single dose, e.g. 6–8 Gy per fraction twice a week. We absolutely agree that large lesions, i.e. lesions over 4 cm, are best treated with daily fractions of 2 or 3 Gy (see table 2). Treatment results are shown in figures 2 and 3.

We want to stress the importance of the histopathology of BCC or SCC for the outcome of the treatment result. We have seen in a large study that if the histopathology does not show a nodular type of BCC or SCC, but rather a sclerosing type the recurrence rate rises immediately. Therefore, these latter histological types are not well suited for the treatment with soft X-rays. There are two possibilities: (1) if the patient is operable, Mohs’ surgery is the preferred method, or (2) if surgery is contraindicated megavoltage therapy should be chosen.

Metatypical carcinomas are considered as SCCs. For keratoacanthomas the same dose schedule is used as for SCCs [9, 10]. Carcinomas of skin appendages and, as we mentioned above, carcinomas penetrating into cartilage or bone, or localized in the mucous membranes or arising in chronic scars are not an indication for a soft X-ray therapy.
Radiation treatment is possible for BCCs, SCC’s or keratoacanthomas, which were not completely excised or incompletely treated by electrodissection or cryotherapy. The techniques are the same as for primary tumors. The functional and the cosmetic results after irradiation of such treated tumors are usually satisfactory [1].

**Fig. 2.** BCC in a 70-year-old woman on the right nasolabial fold before (a) and 12 months after (b) soft X-ray treatment (40 kV), 6 times 8 Gy (48 Gy), once a week.

**Fig. 3.** BCC in a 64-year-old man on the left inner canthus before (a) and 6 months after (b) soft X-ray treatment (40 kV), 12 times 4 Gy (48 Gy), twice per week.

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**Melanoma of the LM Type**

Since the time of Miescher, it has been well known that not only LM, but also lentigo maligna melanomas (LMM) respond well to radiation treatment and are thus considered curative indications [6–8]. In contrast to LMs, LMMs penetrate into the dermal tissues and, therefore, Grenz ray treatment is not recommended but rather soft or superficial X-rays, i.e. radiation qualities of at
least 20 kV or more. We want to stress that LM and LMM are not to be consid-
ered radioresistant, but are maybe tumors with a reduced radiosensitivity; the
reasons discussed are [11]: a high percentage of nonproliferating cells, a high
percentage of hypoxic cells, a high probability of potentially lethal repair, sub-
populations of cells with different radiosensitivity in the ‘shoulder’ region of
the survival curve, synthesis of the prostaglandins (radioprotectors) in the
tumor cells, and melanin as a scavenger of ‘radicals’.

Therefore, higher doses per fractions are recommended, mostly around
6 Gy per fraction. The proposed dose schedule is shown in table 2.

Our results of 64 patients show a similar outcome for radiation treatment
and for surgical treatment with a cure rate of around 90% [7]. This is for LM,
but also for LMM, especially large lesions in the face of elderly persons, and
thus avoiding major surgical procedures and scarring. From a cosmetic and
functional point of view the outcome is excellent.

**Paget’s Disease**

We want to discuss Paget’s disease in the context of carcinomas and not
precancerous lesions, because at least Paget’s disease of the nipple mostly
shows an underlying carcinoma. We also agree that in extramammary Paget’s
disease, an underlying carcinoma is seldom found. In such situations, we deal
with a superficial lesion and thus Grenz rays maybe used. The dose schedule is
similar to that used for Bowen’s disease.

**Merkel Cell Tumor**

Merkel cell tumor is a rare primary skin tumor and occurs most frequently
in the 7th and the 8th decades. Tumors occur with greatest frequency in the head
and neck region (50%). Tumors are characterized by a high rate of local recur-
rence after surgical excision (25–60%) and by frequent involvement of regional
lymph nodes (45–79%); distant metastatic failure is common (22–48%) [12].
Several series have shown promising results when radiation therapy is added to
the initial surgical management of Merkel cell carcinoma. At the MD Anderson
Cancer Center, they found that 83% of patients showed disease control when
they were treated with surgery and radiation therapy for palpable neck disease
[13]. Doses of 50 Gy at conventional fractionation appear adequate for the treat-
ment of subclinical disease, but when microscopic or gross residual disease
exists, boost doses of 60–70 Gy are indicated [12, 14].
Cutaneous Lymphomas

In general, the lesions of cutaneous lymphomas, i.e. T cell or B cell lymphomas, are very radiosensitive [15, 16]. With the exception of certain circumscribed B cell lymphomas or localized CD30-positive lymphomas where radiotherapy is curative, the radiation treatment for lymphomas is palliative. Total doses in the range of 20–30 Gy have been commonly used and offer excellent palliation. Doses in this range may result in a relapse rate of up to 30%. Single doses of 2 Gy, either daily or 3 times per week, seem to offer the best local control (see also table 2).

Because of the possible need for subsequent treatment in adjacent areas, it is important to document the treated areas with Polaroid photographs, accurate drawings, and, if feasible, tattooing of the corners of the fields with India ink. In most patients, the lesions will not clear during or at the completion of irradiation and it may take up to 6–8 weeks for a complete response. For individual skin lesions, energies may be orthovoltage or electron beam. The depth of infiltration defines the energy of the beam required. Larger, bulkier lesions such as deep ulcers or lymph nodes may be treated with either cobalt or 4–6 MeV photons [for the total skin electron beam therapy, see 17–19].

Kaposi’s Sarcoma

Here we distinguish between non-AIDS-associated and AIDS-associated KS.

Non-AIDS-Associated KS

Local irradiation of KS includes the lesion plus a normal tissue border of approximately 1–2 cm. Thin, cutaneous lesions can be effectively treated either by superficial X-ray therapy (e.g. 20–150 kV) or relatively low-energy electron beams, e.g. 4–6 MeV. Thick nodules are best treated by electron beams that encompass the entire lesion homogeneously but spare underlying normal tissues. Lesions on the eyelids are treated most easily by superficial X-rays and protective shields over the optic lens.

Based on the available evidence, both local therapy and elective regional therapy are effective techniques for the treatment of classical KS. The literature supports the use of a wide range of doses and fractionation patterns. As long as a sufficiently high dose is delivered, e.g. 20–30 Gy in ten fractions or even for small lesions 8 Gy in one fraction, a salutary outcome is likely. The treatment schedule is shown in table 2.
**AIDS-Associated KS**

Usually, the same dose schedules are used (see above) and apparently no difference was evident, apart from the fact that it may take 3–4 months in these patients for the tumors to resolve and that radiation-induced edema of the feet or face, as well as symptomatic mucositis are more severe in patients with AIDS than in other patients [20].

Radiation therapy may be reserved for specific indications such as pain, ulceration, bleeding, functional impairment (e.g. on the legs), or improvement of the appearance of cosmetically disfiguring lesions (e.g. the eyelids). Palliative radiation therapy for AIDS-associated KS are: (1) a sufficiently high dose should be delivered to accomplish the desired goal and maintain this state for as long as possible, (2) the treatment should be delivered as rapidly as possible, and (3) the treatment should not induce distressing side effects.

In conclusion, we would just like to stress that there are two possibilities of radiation therapy: (1) curative therapy for: precancerous lesions, BCC and SCC, LM and LMM, isolated B lymphomas, and Merkel cell carcinoma, and (2) palliative therapy for: lymphomas (T and B), KS, angiosarcoma, melanomas, leukemic infiltrates of the skin, and metastatic nodules of various carcinomas.

**References**