Update of Radiotherapy for Skin Cancer

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ABSTRACT
Skin cancer should be managed by a multidisciplinary team with close liaison among dermatologist, clinical oncologist and surgeon. Surgery remains the mainstay of treatment for most skin malignancies. However, there are a wide range of indications for radiotherapy, both as primary treatment modality and also in adjuvant and palliative setting. Where radiotherapy is used, the appropriate radiation modality must be selected. Superficial kilovoltage X-ray and electron beams are most commonly used. Dose and fractionation scheme vary and the choice of time-dose-fractionation depends on patient and tumour factors as well as required cosmetic result.

Keywords: *Radiotherapy, skin cancer, review*

INTRODUCTION

What is radiotherapy?

Radiotherapy is the treatment of disease, primarily malignant tumours, using electromagnetic and particle radiations. Radiotherapy has been used for skin cancers for nearly a century and in fact skin cancers were the first cancers to be treated and controlled with radiotherapy. During this protracted period, techniques of administering radiotherapy have developed continuously.

When radiotherapy is chosen to treat skin cancer, radiation is usually applied as beams from outside the body, a process known as external beam radiotherapy. In special circumstances, radioactive sources may be implanted directly into tissues to give interstitial radiotherapy or brachytherapy.

Ideally, a tumoricidal dose of radiation is delivered to a well-defined target volume whilst sparing the surrounding normal tissue, thereby achieving an optimum therapeutic ratio with the minimum level of morbidity. The SI unit of radiation absorbed dose is the gray (Gy) and one Gy equals 100 cGy.

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What are the aims of radiotherapy?

Radiotherapy is usually described according to the intention, radical or palliative, required for each patient.

For most skin cancers, radiotherapy treatment is intended to cure the patient of his malignancy and is known as radical radiotherapy. The area to be treated includes the known macroscopic tumour as well as any area where there is a known risk of microscopic disease being present. The radiation dose given is usually high and some side effects occur. These are kept to a minimum without compromising cure rate.

Palliative radiotherapy refers to the use of radiation in relieving distressing symptoms of relatively advanced disease that is beyond cure, for example in advanced metastatic melanoma. Palliative radiotherapy treatment is usually given over a shorter time and is kept to a lower total dose to minimize side effects and patient's discomfort.

How is radiotherapy administered?

Radiotherapy machines producing radiation have features which show where the radiation is emitted, thus allowing the patient to be aligned correctly for treatment. The commonest way to indicate where the radiation will be is a light beam mimicking the shape of the radiation beam used for external beam radiotherapy. Marks made directly on the skin surface to be treated or on a cobex cast laid on the skin surface are needed to indicate where the radiation beam should be applied to treat a tumour at the surface or deep in the body.

Radiotherapy is usually fractionated and each course of treatment consists of several doses or fractions. Typically, radiotherapy is delivered as one fraction on each weekday. Before treatment is commenced, the area to be treated is localised and the appropriate treatment schedule determined. This is referred to as radiotherapy planning and the procedures are summarized in Figure 1.

RESPONSE OF THE NORMAL SKIN TO RADIATION

The skin shows both early and late reactions to radiation as a result of combination of rapidly proliferating cells of the epidermis (contributing to early or acute reaction) and the connective tissues of the dermis and subcutaneous layer (late or chronic reaction). Factors affecting skin reactions to radiation include beam energy, total dose, dose per fraction and volume of skin irradiated.

Acute skin reaction usually starts with erythema, occurring in the first 7-14 days of a fractionated radiotherapy course, followed by dry, then moist desquamation if severe enough after 4-6 weeks. Acute skin reactions usually resolve at 6-8 weeks in the majority of patients.

Chronic effects of radiation develop slowly over a period of months to years. They are manifested as skin atrophy, fragility and pigmentary changes which could be hyperpigmentation or depigmention. Late vascular changes could lead to appearance of telangiectasia.

HOW DOES RADIATION WORK?

If a tumour is exposed to enough radiation, exponential cell killing will result in tumour eradication. The biologic effects of radiation result principally from

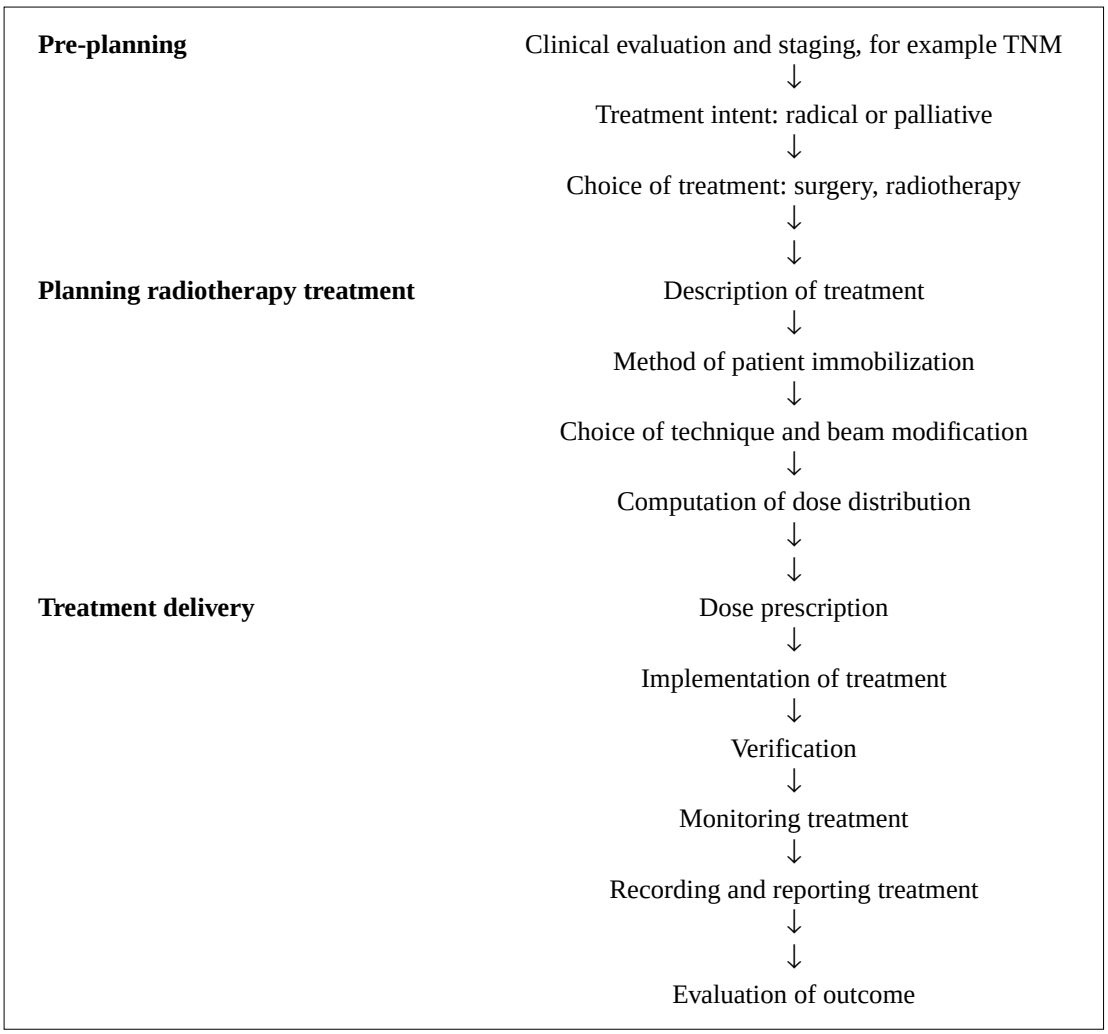

Figure 1: Radiotherapy planning processes

damage to tumour DNA, which is the critical target. Some skin tumours are killed by relatively low radiation doses, for example mycosis fungoides and Kaposi's sarcoma which are radiosensitive. Some require higher doses and are radioresistant, for example melanoma.

Adjacent normal tissue cells will also be killed especially for those which divide frequently. Treatment is carefully planned so that the tumour receives a higher dose than the surrounding normal tissue, and the dose is fractionated so that normal tissue can recover and tumour can be locally eradicated without serious normal tissue damage.

Direct and indirect action of radiation

When any form of radiation is absorbed in biological material, there is a possibility that it will interact directly with the critical targets in the cells. The atoms of the target may be ionized or excited, thus initiating a chain of events that leads to a biological change, which is called the direct action of radiation.

Alternatively, the radiation may interact with other atoms or molecules in the cell (especially water) to produce free radicals that are able to diffuse far enough to reach and damage the critical targets. This is known as the indirect action of radiation. In mammalian cells, it is estimated that about two-thirds of the X-ray damage is due to the hydroxyl free radical.[1]

The chain of events from the absorption of incident photon to the final observed biological damage for the indirect action of X-ray are summarized as follows:

Incoming X-ray photon → Fast electron → Free radical→
Chemical change from breakage of DNA bonds → Biological effects

RADIATION MODALITIES USED IN TREATMENT OF SKIN CANCER

Low energy superficial kilovoltage (KV) X-ray

These are X-rays with energies ranging from 50 KV to 150 KV and are applied at short source to skin distance. Beam qualities of kilovoltage X-rays are measured in terms of half value layers (HVL). This is the thickness of stated material required to reduce the intensity of the X-rays beams to half of the original value. For example, for an 80 KV beam, the HVL may be approximately 2.5 mm of aluminium.

The maximum dose of superficial X-ray is at the skin surface and most of the remaining energy is deposited in the superficial tissues. This lack of skin-sparing effect is ideal to treat tumours on skin surface. An energy should be selected such that the 90% depth-dose (which is defined as 90% isodose of maximum dose achieved) would encompass the target volume. Most small, superficial skin lesions are adequately treated with 80 KV to 150 KV X-ray.

Advantages of superficial X-ray include simplicity both in design and operation, which is less expensive and simpler to maintain than megavoltage X-ray machine. Its disadvantages include high bone absorption and limited penetration - over the range of energies in common use, the 80% depth varies from only 6 to 16mm. Thus thick or deep seated lesions require treatment by more penetrating radiation like electron beam. As the range of applications is rather limited for superficial X-ray, it is not widely available in local clinical oncology department where only a small number of skin cancers are treated.

Orthovoltage X-ray

The energy range of orthovoltage X-ray is from 200 KV to 500 KV. Most oncology centres no longer have this equipment. Similar to superficial X-ray, it has limited penetration and has no skin-sparing effect. In the old days when it was used suboptimally to treat deep-seated tumours, the lack of skin-sparing resulted in considerable skin damage to patient, which gave radiotherapy its image of "burning" the skin.

Electrons

Electrons are the commonest particulate radiation used in radiotherapy. As electrons are produced by megavoltage linear accelerators which are used to treat various internal malignancies in radiation oncology, electron beam therapy is available in every local clinical oncology department.

Electrons lose their energy over a finite range dependent on their energy. Skin bolus is required to build up the skin surface dose to near 100% when electron is used to treat skin cancers. The energy of electron therapy is chosen so that the target volume is encompassed by the 90% depth dose with a sharp fall in dose beyond. Thus, by selecting an appropriate beam energy, a uniform dose may be delivered from the

surface to the desired depth, with relative sparing of deep normal structures. Unlike superficial X-rays, electron beam is used to give a greater depth dose with appropriate energy to treat large or thick lesions or those with a high risk of deep penetration.

High energy megavoltage (MV) photons

Megavoltage photons are not routinely used in the treatment of skin cancer because of deep penetration. However in treating neglected cases of skin cancers with extensive and advanced disease with deep invasion, multiple beam arrangement with megavoltage X-ray may be required in order to achieve homogeneous coverage of the large target volume.

Brachytherapy

This refers to implanting radioactive sources directly into tumour tissues under general anaesthesia for tumour irradiation. Single plane implants using iridium wire as radioactive source is usually used. However, in practice, there are very few situations in dermatologic radiotherapy where brachytherapy has an overall advantage over external beam treatment. Where tumours are situated in a curved plane, brachytherapy may give a more homogeneous distribution than external beam.

TREATMENT PLANNING OF RADIOTHERAPY FOR SKIN CANCER

As most readers of this article would be practising dermatologists rather than clinical oncologists, the technical details of radiotherapy treatment planning would not be described here. Suffice it to say that the main steps in planning irradiation for skin cancer are as follows:

1. Define the extent and size of cancer.
2. Delineate the surface area and depth to be encompassed in the target volume. A safety margin must be allowed around the gross tumour to encompass subclinical extension into surrounding tissues. This depends on tumour size, morphology, histology and aggressiveness. For small superficial lesions less than 5 mm in diameter and with a well-defined edge, margins of 5-10 mm are satisfactory. For larger lesions or those with indistinct margins, margins of 1 cm or more may be needed.
3. Select the beam type, energy, quality, daily fraction size and total dose.
4. Tailor the field-defining device.
5. Tailor the device for blocking exit beam when appropriate.
6. Tailor the bolus when appropriate.
7. Tailor the technique for patient immobilisation and for reproducing the precise placement of the field-defining device each day.
8. Determine the machine position and setting for the irradiation.
9. Document the setup with photographs.

PRINCIPLES OF MANAGEMENT OF SKIN CANCER

Skin cancer should be managed by a multi-disciplinary team with close liaison among dermatologist, clinical oncologist and surgeon in determining the best form of treatment.

Surgery remains the mainstay of treatment for most skin malignancies. However, in most instances, skin cancer can be equally effectively managed by surgery or radiotherapy and with high cure rate achieved. Thus, in selecting the most appropriate treatment, factors such as age and general health of patient, cure and complications rate, cosmetic and functional results, patient preference and convenience and the cost and availability of local expertise and facilities may tend to affect the choice of treatment.[2]

Malignant skin conditions for which radiotherapy is indicated is summarized in Table 1.

ROLE OF RADIOTHERAPY IN THE MANAGEMENT OF SPECIFIC SKIN CANCERS

Basal cell carcinoma (BCC) and squamous cell carcinoma (SCC): surgery or radiotherapy?

Studies using retrospective series have suggested comparable control rate after surgery or radiotherapy. Cure rates with surgery or radiotherapy are particularly high for BCC, but these treatments have never been compared prospectively.

An exception to the above is a prospective, randomized trial by a French group[3] comparing surgery

Table 1. Malignant conditions of skin for which radiotherapy is indicated

Highly indicated and of unique advantage	Often indicated and competitive with other treatment methods	Rarely indicated
Kaposi's sarcoma	Basal and Squamous cell carcinoma of head and trunk	Fibrosarcoma
Mycosis fungoides	Bowen's disease	Basal and Squamous cell carcinoma of scrotum, soles and palms
Lymphoma cutis	Erythroplasia Angiosarcoma Keratoacanthoma Melanoma Merkel cell carcinoma	

and radiotherapy for facial basal cell carcinoma less than 4 cm size. A total of 347 patients were treated, 174 in surgery group and 173 in radiotherapy group. The 4-year actuarial failure rate with surgery was 0.7% compared with 7.5% in radiotherapy group ($p=0.003$). Besides 87% of surgery-treated patients were judged to have better cosmetic results versus 69% in radiotherapy arm ($p<0.01$). Thus the authors concluded that in treatment of facial BCC of less than 4 cm diameter, surgery should be preferred to radiotherapy. However, a major criticism of this study is that most patients in the radiotherapy arm were treated with either brachytherapy (55%) or contact therapy (33%) and only 12% with conventional radiotherapy. Thus the results of this study may not reflect the usual results obtained with conventional external beam treatment. Besides, the failure rate with surgery in this study (0.7%) was considerably lower than that reported in other series and may not be generally reproducible.[4]

In general, surgery is indicated for BCC/SCC in the following situations :

1) Small lesions in which simple excision and direct closure is quick, safe and usually gives a good cosmetic result and high cure rate.
2) Surgery is preferred to radiotherapy in younger patients (<50 years old) because surgical scar is often less noticeable than the coin-shaped area of pale skin with overlying telangiectasia which characterises the late effects of radiotherapy, and which could gradually worsen with time. Besides, there is a very small risk of a second cancer developing in radiation field and the risk of which increases with time.[5,6]
3) Larger lesions involving cartilage, tendon, joint or bone, where the risk of necrosis of bone or cartilage after radiotherapy is higher; and bulky lesions that are still amenable to surgery without significant loss of function, and which would have a lower cure rate with radiotherapy.
4) Lesions where there is uncertainty about disease extent even after biopsy or where the margins are difficult to assess clinically, for example morphoea basal cell carcinoma.
5) Lesions that recur after radiotherapy should not be retreated with radiation therapy because of suboptimal salvage rate, poor long-term cosmetic results and increased risk of complications. These are best managed with Mohs' micrographic surgery.[7]
6) Sites tolerating radiotherapy poorly such as abdominal wall, perineum, shin and sole of foot.

Relative indications for radiotherapy for BCC/SCC include the following :

1) Radiotherapy is generally recommended for skin cancer located in the central face and is particularly useful for sites such as eyelids, tip or ala of nose or commissure of lips since these areas can be difficult to reconstruct surgically. Advantages of radiotherapy are that treatment is relatively painless, and, for sites mentioned above, it may be less expensive than excision followed by reconstrutive surgery.
2) Older patients, especially if long-term atrophy caused by radiotherapy may not be considered relevant.
3) Large superficial lesions where extensive surgical repair is required and might give a poorer cosmetic result than radiotherapy.
4) Patients who refuse surgery, are unfit or are on anti-coagulation therapy.
5) Larger lesions where surgery might cause major

functional loss such as numbness, paralysis, mouth dribbling or eye ectropion.

6) Skin cancers with perineural invasion detected on histology of excision specimen should receive post-operative radiotherapy.[8]

Radiotherapy fractionation schedules

A wide spectrum of fractionation schedules and total doses for irradiation of skin cancer have been used. In general, a more fractionated course (i.e. smaller daily dose, but larger number of fractions) would minimise late side effects such as fibrosis, telangiectasia and necrosis and thus achieve better cosmetic results. Such schedules are especially useful for large lesions and for lesions of canthi, eyelids, nose and ears. Schedules using higher daily doses and fewer fractions can be used for smaller lesions or when patients' visits must be limited. Commonly used fractionation scheme is summarized in Table 2.[9]

Results of radiotherapy for BCC/SCC

In one recent large series of skin cancers treated in an academic radiation oncology department using modern treatment techniques, 339 cases managed over a 20-year period were reviewed: 242 were BCC, 97 were SCC. Superficial X-ray were used in 187 cases, electron in 57, megavoltage X-ray in 15 and a combination of beams in others.[10] For the majority of lesions, control rate after radiotherapy is in the order of 90% or more. Recurrent cancers carry a worse prognosis for local control. A downward trend is seen for local tumour especially in larger SCC. A lower control rate for larger tumours treated with electrons are observed. However, electron treatment techniques were not standardized and technical variations may account for this observation.

Significance of a positive margin after surgical excision for BCC/SCC

A frequently asked question is whether further treatment is required if resection margin is involved.

Studies with minimum follow-up period of 5 years show that only about one-third of BCC that extend to resection margin ultimately recur.[11-13] Thus, management of a positive margin is still controversial. Since it may be difficult to detect early recurrence (especially if the area is fibrotic or where a graft was used to close the defect, or if patient is unreliable for follow-up), immediate re-treatment with further surgery or radiation therapy should be considered.[14-16] In cases involving a graft, radiotherapy should not be started until a good "take" has occurred, which may need 3-4 weeks. The entire graft should be included in the target volume. Wilder and colleagues[17] showed that all 21 cases of BCC that extended to surgical margins were controlled with addition of post-operative radiotherapy.

Unlike BCC, immediate retreatment should be considered when SCC extended to surgical margin since this type of cancer is more likely to recur locoregionally than BCC, and studies showed that fewer than one-half of patients developing lymph node metastases are salvaged.[15,16]

Malignant melanoma

The primary treatment of melanoma is surgical excision. Historically, melanoma is regarded as radioresistant. However radiobiological data suggests that this is true only at small doses per fraction. With higher doses per fraction, radioresistance might be overcome.[18] There are a number of indications for radiotherapy in its management.[19]

Table 2. Recommended radiotherapy dose and fractionation schedule for BCC/SCC

Total dose (Gy)	Number of fractions	Duration of treatment	Comments
40	10	2 weeks	Less satisfactory cosmetic results but used when Rx must be short or for small (<1.0 cm) away from nose, ear or eyelids
30	5	1 week	Same as above
20	1	1 day	Same as above
45	15	3 weeks	Moderate size (5x5 cm^2) away from nose, ear or lids
50	20	4 weeks	<1.5 cm size, thin lesion of nose, ear, canthi or eyelid
55	30	6 weeks	Moderate size (5x5 cm^2) lesion of nose, ear, canthi or eyelid
60	33	7 weeks	Large lesion with minimal or suspected bone or cartilage involvement
65	36	7 weeks	Large recurrent lesion or with cartilage or bone involved

Adjuvant radiotherapy (radiotherapy given after apparently complete surgically resection) improves the local control of head and neck melanoma.[20] It has also been shown to improve control rates after therapeutic lymph node dissection especially for those with extracapsular spread or multiple node involvement.[21]

Un-resectable lentigo maligna melanoma has been successfully treated with radiotherapy. Reported control rates are in the order of 70-80%.[22] As these lesions tend to occur on face, radiotherapy may be cosmetically more acceptable than surgery and could be equally effective.

Sadly, radiotherapy is most frequently used in the setting of advanced metastatic disease to palliate distressing symptoms. Radiotherapy is effective in relieving pain of bony metastases in most patients. For brain metastases, whole brain irradiation was shown to achieve reasonable palliation with neurological improvement and with acceptable toxicity.[23] Cutaneous metastases with symptoms like pain, bleeding and impending ulceration can be palliated by local radiotherapy.

Cutaneous T cell lymphoma (CTCL)

CTCL cells are very radiosensitive. Individual focal plaque or nodular lesions causing symptoms can be treated with localised superficial X-ray or electron beam. Total dose in the range of about 30 Gy at 2 Gy per day achieve more durable local control compared with lower total dose of 10-20 Gy.[24] This treatment is useful in controlling local aggressive disease as well as recurrent lesions in covered areas in patients treated with PUVA.

Total skin electron beam (TSEB) therapy has been shown to be an effective treatment. The most favourable responses are seen in the early stage of disease, especially plaque phase. Several series reported complete response rates of 72-98%.[25-27] In the Stanford series by Hoppe,[26] complete response rates were: limited plaque 98%, generalized plaque 71%, tumour 35% and erythroderma 64%.

Unfortunately, despite high complete response rate, most patients relapse subsequently. In the Stanford series, 5-year freedom from relapse rate was 50% for limited plaque and only 20% for extensive plaque. They can be treated by other modalities or further small-volume X-ray treatment.

TSEB is a very complicated and sophisticated treatment. Therefore, before it is selected to use, it is essential to have superb medical physics and radiation dosimetry support and an experienced clinical oncolgist who has enough experience in it.

Acute side effects of TSEB include generalised erythema and focal oedema. Alopecia and loss of nails are usually transient. Long term side effects include inability to sweat for the first 6-12 months and chronic skin dryness. Areas of telangiectasia may be observed.

Kaposi's sarcoma (KS)

Classical KS occurs in elderly males of Mediterranean or Jewish descent with lesions confined mainly to the lower leg. It is radioresponsive and may be treated with radiotherapy although reports are based on small number of patients.[28]

AIDS-related KS is now the commonest form of disease in the developed world. Lesions occur anywhere in the skin, mucous membranes, gastro-intestinal tract or viscera. Radiotherapy is effective to palliative cutaneous KS to relieve pain, reduce oedema and improve cosmesis of visible lesions, notably those on the face and arm. A single dose of about 8 Gy using kilovoltage X-ray or electron gives good local results and may be more acceptable to patient than protracted courses.[29] Acute radiation-induced oropharyngeal mucosal reactions are usually very severe when treating AIDS-related KS at these sites and here fractionated regimes are appropriate.

CONCLUSIONS

While surgery is still the mainstay of treatment for skin cancer, radiotherapy remains an important modality in primary, adjuvant and palliative management of a wide range of skin malignancies. The physical properties of superficial kilovoltage X-ray and electron beams are particularly usefult to treat superficial lesions. Clinical oncologist should work as part of a multidisciplinary team in achieving the best results in terms of tumour control, cosmesis and cost-effectiveness.

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