The role of radiation therapy in the management of cutaneous malignancies. Part I: Diagnostic modalities and applications

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Learning objectives
After completing this learning activity, participants should be able to understand the indications, treatment modalities, clinical scenarios, purpose, and dosing regimen needed to treat a variety of skin cancers with radiation; and clinicians will be able to confidently recommend and incorporate radiation therapy in the treatment of skin cancers when indicated, thus improving patient care.

Disclosures
Editors
The editors involved with this CME activity and all content validation/peer reviewers of the journal-based CME activity have reported no relevant financial relationships with commercial interest(s).

Authors
The authors involved with this journal-based CME activity have reported no relevant financial relationships with commercial interest(s).

Planners
The planners involved with this journal-based CME activity have reported no relevant financial relationships with commercial interest(s). The editorial and education staff involved with this journal-based CME activity have reported no relevant financial relationships with commercial interest(s).

Radiation therapy offers distinct advantages over other currently available treatments for cutaneous malignancies in certain circumstances. Dermatologists and dermatologic surgeons should be familiar with the available radiation therapy techniques as well as their value and potential limitations in a variety of clinical scenarios. The first article in this 2-part continuing medical education series highlights the mechanisms, modalities, and applications of the most commonly used radiotherapy treatments as they relate to cutaneous oncology. We review the current indications for the use of radiation in the treatment of various cutaneous malignancies, the techniques commonly employed in modern radiotherapy, and the associated complications. (J Am Acad Dermatol 2021;85:539-48.)

Key words: adjuvant radiotherapy; definitive radiotherapy; electron beam radiotherapy; electronic brachytherapy; palliative radiotherapy; radiation therapy; radionuclide brachytherapy; superficial radiation.

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Dr MacFarlane is the principle author.
Funding sources: None.
IRB approval status: Reviewed and approved by MD Anderson Cancer Center IRB.
Accepted for publication May 24, 2021.
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0190-9622/$36.00

https://doi.org/10.1016/j.jaad.2021.05.058
Date of release: September 2021.
Expiration date: September 2024.

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INTRODUCTION

Radiation therapy (RT) was first utilized in 1900 to treat a patient with cutaneous squamous cell carcinoma (cSCC) of the nose. Following the advent of improved dermatologic and surgical techniques, such as Mohs micrographic surgery (MMS), the role of RT in the treatment of cutaneous malignancies gradually decreased.[1] There are certain circumstances, however, in which RT offers distinct advantages over other currently available treatment modalities. There are few sources of information addressing this topic within the dermatologic literature. We review the current indications for the use of radiation in the treatment of skin cancer, the techniques commonly employed in modern radiotherapy, the role of radiation in the treatment of specific cutaneous malignancies, and the associated complications.[1]

MECHANISM OF ACTION

Ionizing electromagnetic radiation in the form of high-energy photons (X rays or gamma rays) is absorbed by biologic tissue, which then produces double-stranded breaks in DNA.[2] Secondary effects include the induction of mitotic failure and cell death in rapidly dividing malignant cells in addition to the production of reactive oxygen species.[2] Cells with higher proliferation rates, such as epithelial cells, are more radiosensitive than more slowly dividing cells, such as those found in nerves.[2] Tumors with high proliferation rates respond more quickly to radiation than indolent tumors.[3] Normal adjacent tissues maintain repair mechanisms following sublethal doses of radiation, but complications may arise if the radiation dose is greater than that which the tissue can tolerate.[3]

The parameters of ionizing electromagnetic radiation are dose, number of fractions, and total time of a radiation course. The international unit of dosing is a Gray (Gy). Equal-sized doses are delivered in fractions over a specified time course. Although regimens that use a higher dose per fraction reach the same total dose more rapidly, they will ultimately lead to increased long-term toxicities and poor cosmesis. Dividing the total radiation dose into smaller fractions over a longer time period will have a maximal effect on malignant cells but a minimal effect on normal tissue. Consequently, a patient will experience fewer short-term complications and an improved ability to tolerate additional radiation should the disease recur.

INDICATIONS

Key points

- Definitive radiotherapy is an alternative treatment for skin cancers in nonsurgical candidates or those who refuse surgery.
- Adjuvant radiotherapy is performed postoperatively in aggressive tumors to decrease the risk of recurrence.
- Palliative radiotherapy provides local control and symptomatic relief for incurable or advanced disease.

The general advantages and disadvantages of RT in the management of cutaneous malignancies are summarized in Table I.

RT is a painless outpatient procedure that requires a longer time investment compared to surgery.[1] Definitive RT is an effective treatment for nonsurgical candidates due to medical comorbidities, particularly elderly patients (Fig 1).[4] Radiation allows for the preservation of uninvolved tissues adjacent to the tumor.[1] Its use is favored in large or locally advanced tumors where further surgery may result in significant morbidity, impaired function, or poor cosmesis.[1,4] This is especially important for large or locally advanced tumors of the head and neck, such as those near the eyelid, nose, ear, or lip.[4] RT allows for the inclusion of substantial margins around the clinically apparent lesion to account for subclinical tumor extension while avoiding the cosmetic and functional morbidity associated with surgery using standard oncologic excision margins.[5] Definitive RT also may be performed based on patient preference or resource availability.[4]

For most patients and most tumors, a total dose of 50-55 Gy can be divided into 20 daily fractions Monday through Friday at 2.5-2.75 Gy/fraction. The side effects of RT, such as alopecia or hypopigmentation, are usually limited to the irradiated field, but may persist or worsen over time.[1] For younger patients, lower doses of radiation per fraction are administered over a longer period of time in order to minimize late side effects while optimizing local control.[5] Alternative treatment options should be discussed with younger patients prior to initiating RT due to the possible risk of developing a secondary malignancy at a later time within the treated field.[3] For elderly or frail patients with significant comorbidities, a hypofractionated schedule may be used, in which a higher dose per fraction is delivered with decreased total fractions.

Adjuvant RT is a supplemental treatment for advanced disease to reduce the risk of local or regional recurrence following complete circumferential peripheral and deep-margin assessment or MMS. This option may be used for positive surgical margins and for tumors not amenable to further resection and is typically performed within 4 to 8 weeks postoperatively. Adjuvant RT also may be used when clear margins are obtained but there is evidence of perineural, parotid gland, bone,

Abbreviations used:

cSCC: cutaneous squamous cell carcinoma
EBRT: electron beam radiotherapy
Gy: gray
MMS: Mohs micrographic surgery
RT: radiation therapy
SRT: superficial radiation therapy

cartilage, or muscular invasion by the tumor (Figs 2 and 3). This is also beneficial if the tumor is multiply recurrent or involves the lymph nodes.

Palliative RT is used to provide local control or symptomatic relief in advanced or incurable disease, including cutaneous metastases, to improve a patient's quality of life. These tumors are often debilitating due to pain, infection, or bleeding. The dosing regimen and fractionation schedule depends on the tumor size, location, patient life expectancy, and expected toxicities of the treatment.[1] The likelihood of local control is decreased by aggressive features of the tumor, such as perineural spread or bone involvement.[6] Commonly used regimens for patients with nonmelanoma skin cancers are 30 Gy in 10 fractions over 2 weeks or 45-50 Gy in 18 to 25 fractions over 4 to 5 weeks.[1] A large dose of 20 Gy in a single fraction may be given to patients in poorer health and when long-term cosmesis is not a concern.[1]

PRE-RADIATION WORK UP

In order to determine which therapeutic option is ideal for a patient, several questions should be addressed. Table II lists the factors to consider prior to the initiation of RT. Biopsy for confirmation of the diagnosis is necessary, as the histology dictates subsequent decisions about the applicability and technique of RT. The appropriate RT modality ultimately will be determined after careful consideration of these patient-specific factors.

RADIATION THERAPEUTIC MODALITIES

Key points

- Electron beam radiotherapy is the treatment of choice for radiation oncologists treating skin cancers because it treats tumors that are broad, deep, or found within a complex topography
- Radionuclide brachytherapy involves the application of radioactive source followed by radiation, but it is often not used because it has little advantage over electron beam radiotherapy
- Electronic brachytherapy does not require the application of radioactive source, thus safety is less of a concern compared to radionuclide brachytherapy; however, it is a newer treatment without long-term safety and efficacy data
- Superficial radiation therapy has been the preferred method for dermatologic office-based radiotherapy of skin cancers for over 100 years

Table I. Advantages and disadvantages of radiation therapy

Advantages	Disadvantages
Outpatient procedure	Extended treatment course of 3-6 weeks
Painless, well-tolerated treatment	Long-term cosmetic sequelae (eg, dermatitis and telangiectases) may worsen over the decades following treatment
Can be used in patients who are medically inoperable, particularly the elderly	Risk of secondary malignancy within the treated field, particularly in younger patients
Allows for preservation of uninvolved structures and is tissue preserving	Limited pathologic data to detect subclinical spread

Adapted from Garner et al[1] with permission from Springer Nature.

Electron beam radiotherapy

Electron beam radiotherapy (EBRT) treats broad tumors, deep tumors, or tumors within a complex topography. It is also an ideal treatment for cutaneous malignancies < 5 mm in thickness. In contrast to X rays, the energy source is an electron that is delivered through a device called a linear accelerator. The energy of an electron beam determines the depth of the tissue it will adequately treat because the dosage of the electron beam declines linearly past its targeted treatment depth.[5] For example, a 6 megaelectron volt (MeV) beam delivers 80% of its dose at a depth of approximately 2 cm, while a 20-MeV beam delivers 80% of its dose at a depth of approximately 6 cm.[1] In order to deliver 100% of the designated dose at the skin surface, a bolus of gelatin-like material is added to the skin surface, thus minimizing tissue damage to deeper structures like bone and cartilage (Fig 4).[1,5] Due to the linear decline in dosage outside of the treatment field, tumors treated with EBRT must be treated with an additional margin of 1 to 2 cm.[5] The dose depth behavior of electron beams is illustrated in Fig 5.[1] In cases in which there is perineural invasion of a large or named nerve of the head or neck, the nerve should be tracked and radiated

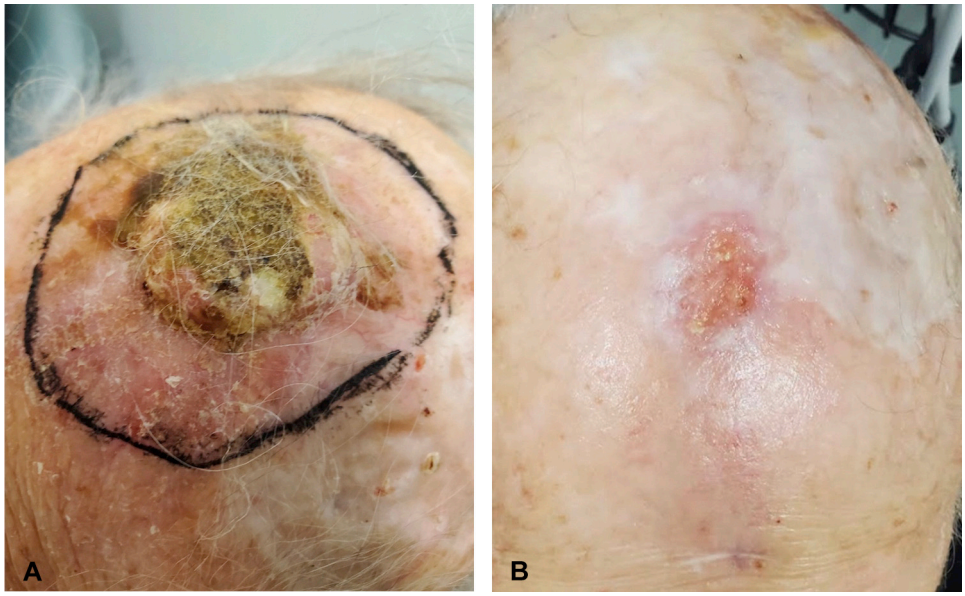

Fig 1. Radiotherapy of cSCC. **A,** a 95-year-old man with a 5-cm cSCC of the frontal scalp (radiation field outlined in *black*). **B,** Four weeks following radiation at a dose of 50 Gy in 20 fractions. *cSCC,* Cutaneous squamous cell carcinoma.

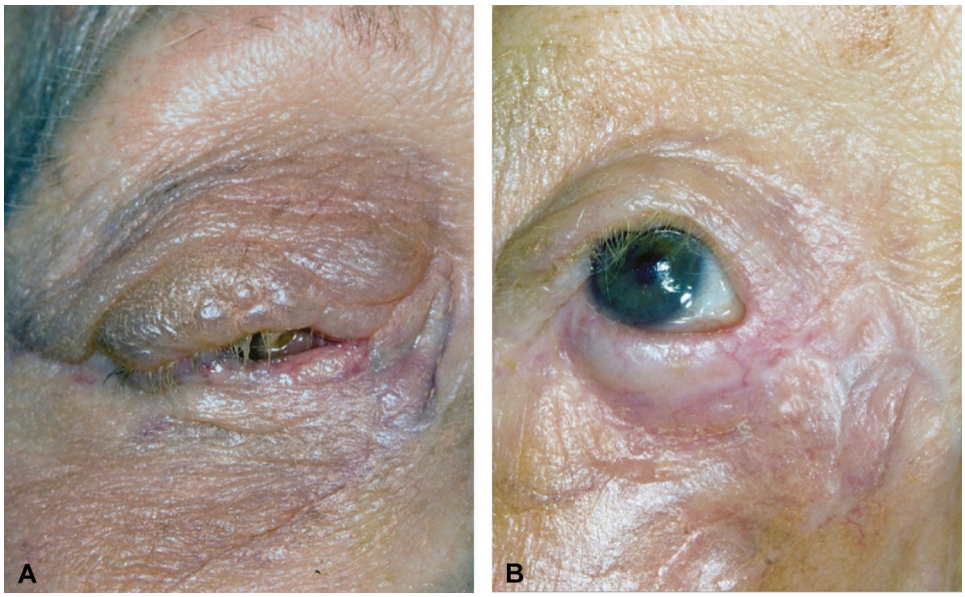

Fig 2. Adjuvant radiotherapy for cSCC. **A,** a 77-year-old woman with a multiply recurrent cSCC of the right lower eyelid with significant perineural invasion previously treated with surgical resection with MMS, right partial maxillectomy, right infraorbital nerve resection, and dissection of the pterygopalatine fossa to the skull base. **B,** Two months following adjuvant radiation at a dose of 60 Gy in 30 fractions to the operative site, proximal course of the infraorbital nerve to the skull base, and ipsilateral neck lymph nodes without evidence of recurrence. *cSCC,* Cutaneous squamous cell carcinoma; *MMS,* Mohs micrographic surgery. Adapted from Garner et al[1] with permission from Springer Nature.

proximally to the skull or intracranially to the brainstem.[7] For eyelid tumors, shielding with lead or tungsten shields is often required to protect the eye as radiation can expose the lens to more than 5-10 Gy, which is the threshold dose at which cataracts form.[8]

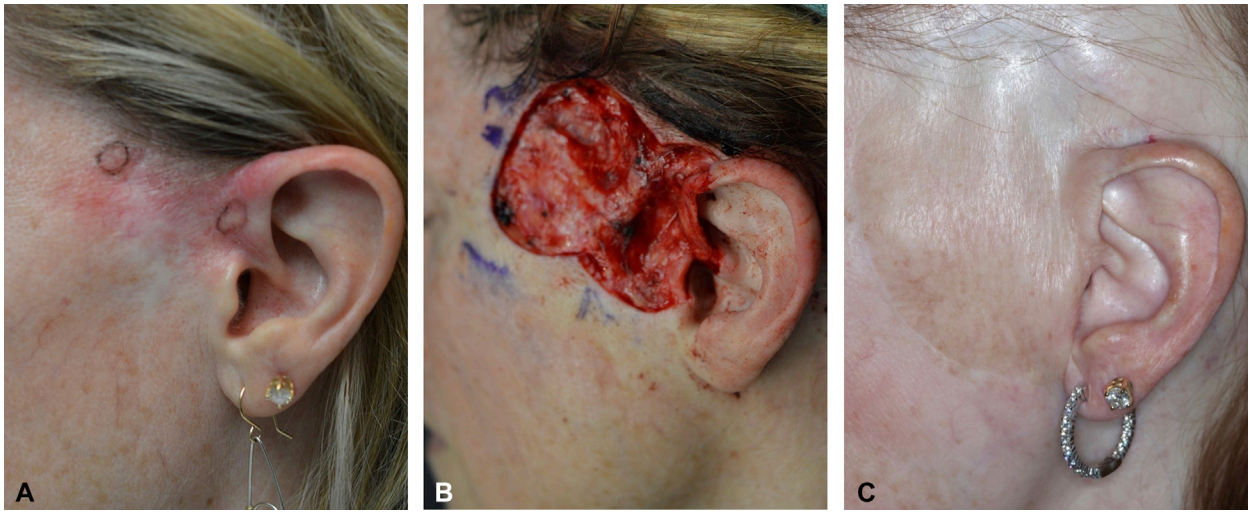

Fig 3. Adjuvant radiotherapy for microcystic adnexal carcinoma. **A,** A 55-year-old woman with recurrent microcystic adnexal carcinoma with significant perineural invasion of the left side of the face and left ear. **B,** Immediately following surgical resection with MMS, including dissection of left parotidectomy and left side of the neck with clear margins obtained. **C,** Two years following reconstruction with radial forearm free flap and adjuvant radiation at a dose of 60 Gy in 30 fractions to the left side of the face and ipsilateral neck lymph nodes. *MMS,* Mohs micrographic surgery.

Table II. Clinical questions to address prior to radiation therapy

Where is the tumor located? Is it in a higher-risk anatomic area (near the eyelids, nose, ears, and lips)?
Has the histologic diagnosis been adequately established?
Has appropriate staging been completed?
Is this lesion recurrent?
Has the patient had any treatment for this lesion? If so, what? Have these treatments helped or not?
What treatments, if any, are planned?
What are the anticipated goals of radiation treatment — primary or adjuvant therapy? Definitive or palliative?
Has the patient undergone any previous radiation? If so, what site was treated? What was the duration — or, more ideally, dose of the treatment? What facility performed the treatment? How long ago was treatment completed?
Does the patient have any other cancer diagnoses? If so, how were those conditions treated?
What is the patient's overall medical condition?
What are the patient's comorbidities?
Does the patient have a history of any conditions that may be exacerbated by radiation, such as CREST syndrome, dermatofibrosis, lupus erythematosus, or scleroderma?
What are the patient's expectations regarding radiation?

Adapted from Garner et al[1] with permission from Springer Nature.

Radionuclide brachytherapy

Radionuclide brachytherapy involves the application of a radioactive source such as iridium-192 or cobalt into or onto the target tissue followed by high-dose radiation of gamma photons.[5,8] Interstitial brachytherapy involves the insertion of a radioactive catheter within a tumor. It is used for areas that are difficult to treat due to concerns for poor cosmetic or functional outcome.[8] This enables the delivery of high-dose radiation to the tumor while sparing much of the surrounding normal tissues; however, it requires general anesthesia for the placement of the radiation catheters in addition to extra time for the delivery of treatment.[1] A dose of 50-55 Gy is typically delivered over 4-6 days to an area that encompasses 7 to 10 mm around the implanted sources. For elderly patients or those with significant comorbidities, a hypofractionated schedule may be used (5-10 fractions of 4-6 Gy per fraction).

Brachytherapy also can be combined with EBRT to deliver a sufficient dose to both the tumor and the surrounding tissue at risk, as seen in Fig 6.[1] Surface-conforming brachytherapy involves the insertion of a radioactive source into a mold that fits onto the

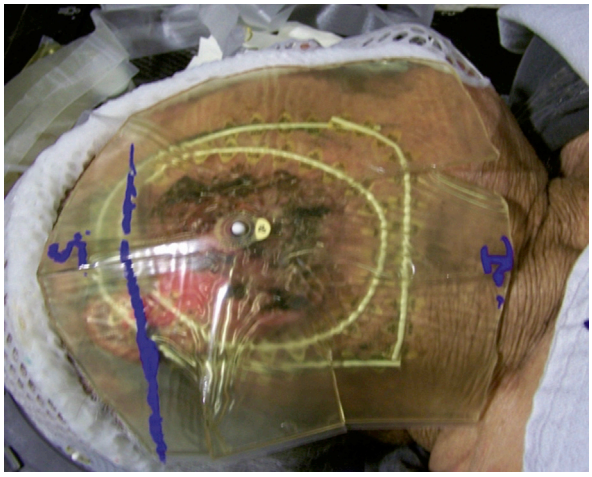

Fig 4. Electron beam radiotherapy setup. The head and neck of a 93-year-old man with a cSCC of the right preauricular cheek is immobilized (seen in right profile) with a custom-made mask. The desired treatment field is outlined with radiopaque wire visualized on computed tomography scan. The radiation field and margins are covered homogenously with a 3-mm bolus in order to evenly distribute treatment dosage. *cSCC,* Cutaneous squamous cell carcinoma. Adapted from Garner et al[1] with permission from Springer Nature.

tumor surface, which confines the radiation field to a superficial area.[8] There is a higher rate of treatment failure for recurrent tumors, tumors > 2 cm, or tumors > 2 mm in depth due to a decline in radiation dose at increased depths.[5,8] This method may be used in areas with poor wound healing or decreased vascularity, such as on the anterior lower portion of the legs or dorsal hands.[5,8]

Electronic brachytherapy

Electronic surface brachytherapy is a newer and safer form of brachytherapy utilizing an X-ray photon radiation source that does not require a radioisotope or dedicated treatment vault.[5,8,9] Best used in small, well-defined lesions < 3-4 mm in depth, this modality is not currently recommended for treating cutaneous malignancies because there is a lack of long-term safety and efficacy data.[5] A dose of 40-50 Gy is typically delivered in 8-10 fractions twice weekly to a depth of 2-3 mm.

Superficial radiation therapy

Superficial radiation therapy (SRT) has been used for more than a century to treat cutaneous malignancies; however, its use has decreased over time as more sophisticated surgical methods have developed.[10] The emergence of newer SRT machines has renewed interest in office-based radiotherapy.[5] SRT uses low-energy photons produced by a 10-30 kilovolt (kV) X-ray machine.[11] Radiation is absorbed within the first 2 mm of tissue. The machinery for SRT is smaller and procedures are less expensive than those of EBRT, because X rays are used instead of a linear accelerator.[11] Furthermore, a bolus is not required because the dosage decrease outside the radiation field is less than with EBRT.[10]

Table III presents a comparison of the common modalities of RT in the treatment of most basal and squamous cell skin cancers.[12,13] The American Society for Radiation Oncology Clinical Practice Guidelines for RT in the treatment of basal and squamous cell skin cancers suggest similar cosmetic outcome and local control rates among these radiotherapeutic modalities, with many large case series reporting local control rates of over 90%.[12,14-19] Randomized trials comparing the efficacy of different radiotherapeutic modalities would be difficult to undertake due to an increased risk of recurrence, morbidity, and possible mortality in patients randomized to receive RT alone compared to surgery. The cost of RT depends on multiple factors, including modality, outpatient versus hospital location, and fractionation schedule.[20,21] Increased costs are associated with the hospital setting, greater number of fractions delivered, and EBRT.[20,21] Superficial RT is associated with the lowest costs.[20,21]

COMPLICATIONS

Key points

- Early reactions include erythema, epilation, desquamation, and ulceration
- Late reactions include telangiectasia, fibrosis, ulceration, necrosis, and radiation-induced secondary malignancy

The potential adverse effects of RT should be discussed with patients prior to the initiation of treatment as both acute and late reactions may occur. One of the earliest acute reactions is erythema within the radiation field, followed by dry desquamation and then moist desquamation.[1] Daily washing may reduce bacterial load within the irradiated area and the application of a mid-potency topical corticosteroid may reduce discomfort and pruritus.[1,22] The irradiated field should be protected from sunlight, excessive heat, cold, or friction during and after RT in order to prevent further injury.[23] Pain, desquamation, and hemorrhagic crusting may occur and persist for 3 weeks after the conclusion of RT, which is then followed by re-epithelialization.[5] Petrolatum-based emollients with or without hydrogel dressings can be used to maintain a moist environment to enhance

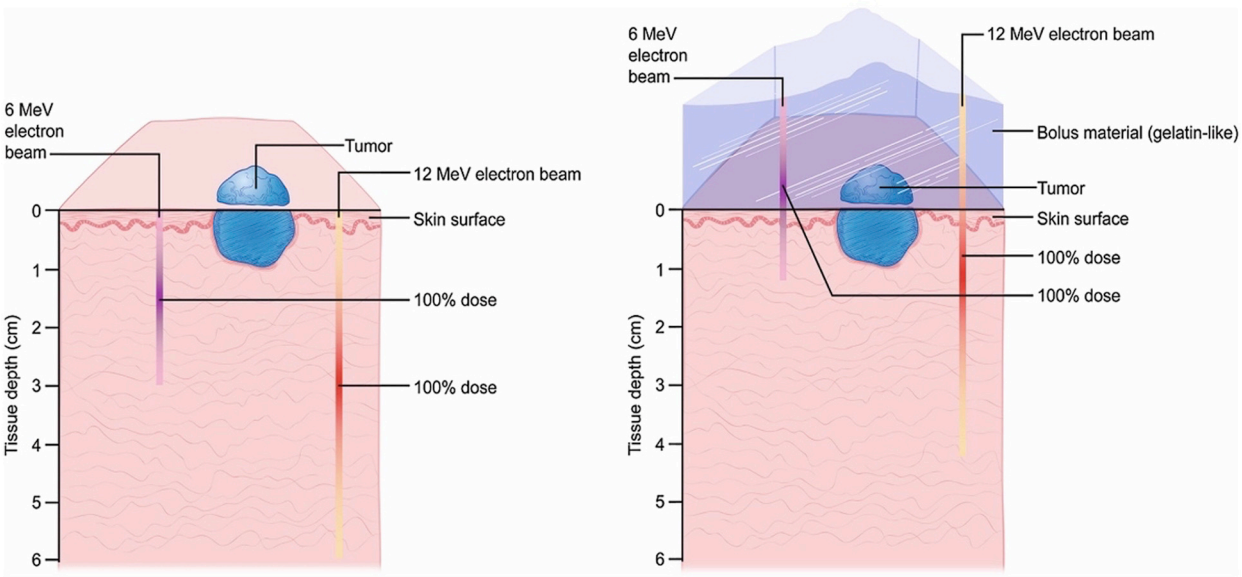

Fig 5. Dose depth of electron beams. Dose depth of 6-MeV and 12-MeV electron beams without bolus (left) and with bolus (right). The bolus improves dosage amount that covers the tumor while sparing underlying tissue. Illustration by Alice Y. Chen. Adapted from Garner et al[1] with permission from Springer Nature.

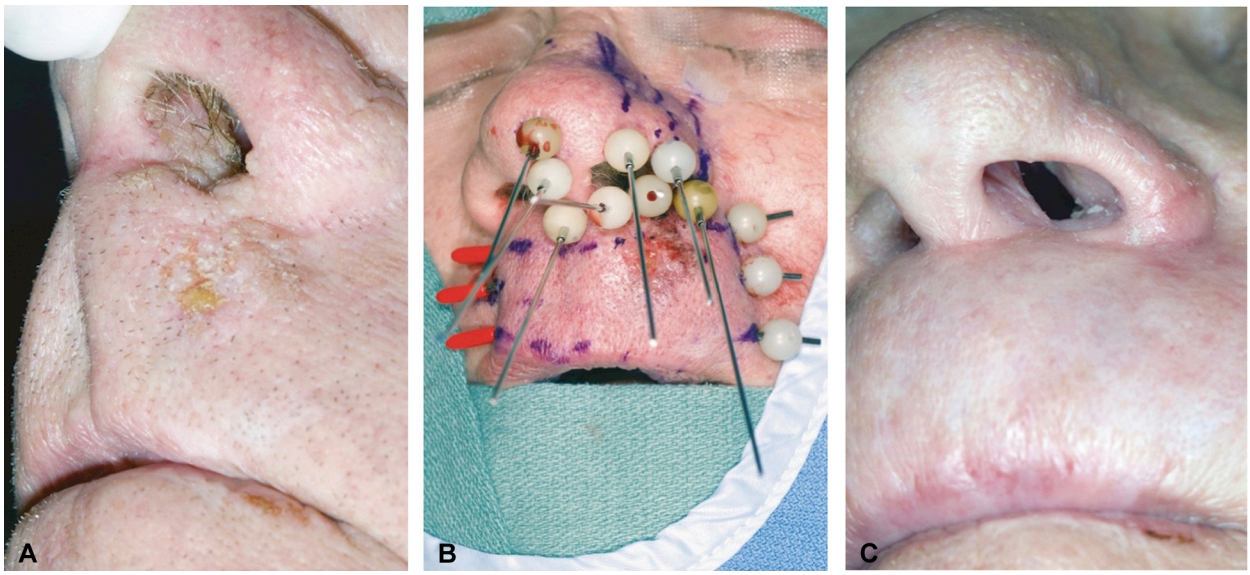

Fig 6. Interstitial brachytherapy. **A,** A 65-year-old man with cSCC of the left nasal vestibule that extended to the upper cutaneous lip and nasal ala. **B,** Inserted iridium-192 radioactive catheter to deliver 25 Gy over 51 hours followed by EBRT at 50 Gy in 25 fractions, delivered over 5 weeks. **C,** Four months following the completion of radiation therapy. *cSCC,* Cutaneous squamous cell carcinoma; *EBRT,* electron beam radiotherapy. Adapted from Garner et al[1] with permission from Springer Nature.

re-epithelialization.[1] A silver-based dressing may be used in wounds that are at high risk for infection.[1]

If wound healing is delayed beyond 6-8 weeks, soft-tissue infection should be suspected and treated accordingly with oral or topical antibiotics (Fig 7).[1,5] If the wound fails to respond to these measures, a consultation with a multidisciplinary wound care team should be considered for radiation-related dermatitis.[1]

Late reactions after RT can occur months to years after completing therapy and may include

Table III. Common modalities of radiation therapy for basal and squamous cell skin cancers

Radiation modality	Radiation emitted	Radionuclide handling	Bolus needed	Ideal tumor diameter*	Ideal tumor depth*
Electron beam radiotherapy	Electrons	No	Yes	<5 cm	<0.5 cm
Radionuclide surface brachytherapy	Gamma photons	Yes	No	<2 cm	<0.5 cm
Radionuclide interstitial brachytherapy	Gamma photons	Yes	No	<2 cm	>0.5 cm
Electronic brachytherapy	X-ray photons	No	No	<2 cm	<0.4 cm
Superficial radiation therapy	X-ray photons	No	No	<5 cm	<0.5 cm

*For definitive radiation therapy in nonsurgical candidates without contraindications to radiation therapy.[12,13]

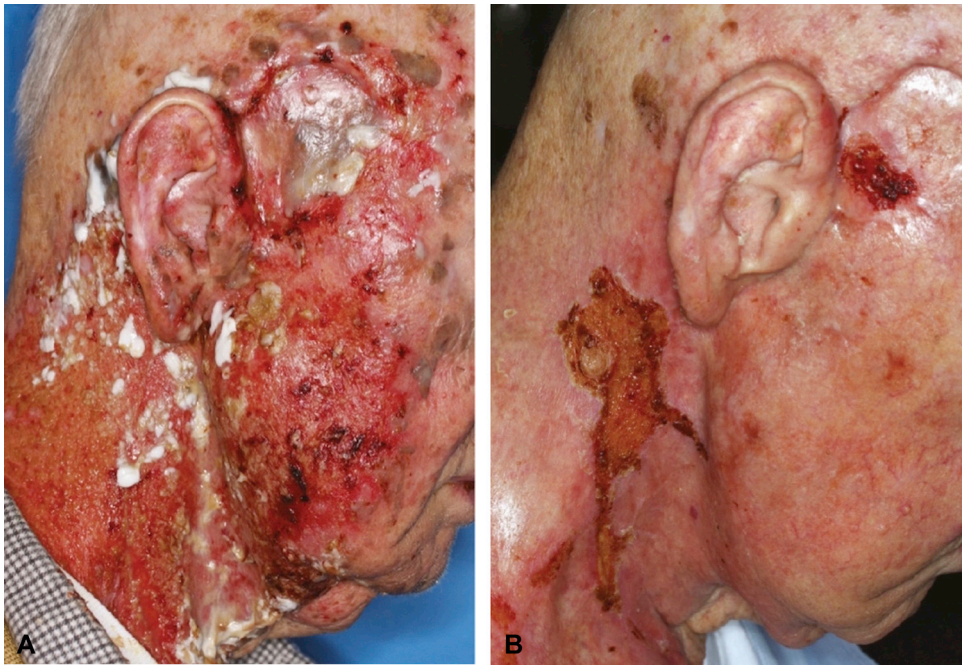

Fig 7. Radiation dermatitis. **A,** Erythema, desquamation, hemorrhagic crusting, and superinfection in the irradiated field in a patient with metastatic SCC. **B,** Marked improvement following topical emollients, topical antibiotics, and oral antibiotics. *SCC,* Squamous cell carcinoma. Adapted from Garner et al[1] with permission from Springer Nature.

telangiectasia, epidermal and sweat gland atrophy, hypo- or hyperpigmentation, alopecia, necrosis of deeper underlying tissues, osteonecrosis, fibrosis, radiation-induced malignancy, and various radiation-induced cutaneous diseases.[17,24-27] Large cohort and population studies of more than 1000 patients have shown statistically significantly higher rates of development of nonmelanoma skin cancers within the treatment field of patients treated with skin-directed ionizing radiation compared to those with no exposure; however, many reports were on patients with dose fractionation schedules that are no longer used, such as those for conditions like acne or tinea capitis.[28-31] The risk of malignancy is higher in patients who receive RT earlier in life, with an approximate latency period of 20 years between the first exposure of ionizing radiation and the appearance of secondary nonmelanoma skin cancers (Fig 8).[28-32] For this reason, the risks versus benefits must be discussed prior to initiating radiation in patients younger than 60 years of age, although this varies with life expectancy.[33-35] Tumor recurrence within the irradiated field complicates future surgical treatment and reconstruction due to tissue atrophy, fibrosis, loss of elasticity, and compromised vascularity.[17,23-26]

A summary of adverse reactions to radiation is shown in Table IV.

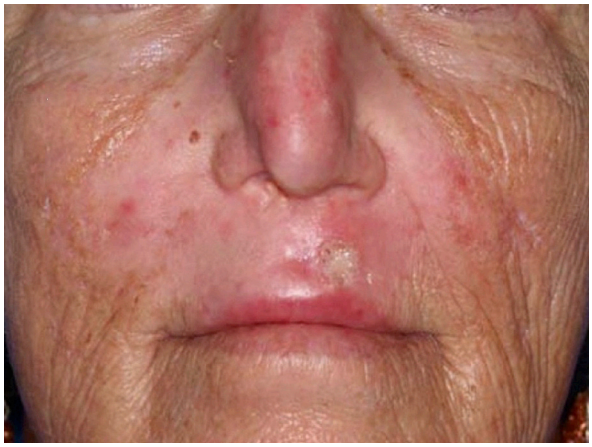

Fig 8. Complications of radiation. A 53-year-old woman developed a cSCC of upper portion of the left cutaneous lip 6 months after undergoing radiation for SCC of the nasal cavity.[32] *cSCC,* Cutaneous squamous cell carcinoma.

Table IV. Side effects of radiotherapy

Acute reactions
Erythema, greater in areas of previous ultraviolet exposure
Dry followed by moist desquamation, particularly in tissue folds
Hypo- or hyperpigmentation
Ulceration, hemorrhage
Pruritus
Temporary alopecia
Temporary loss of fingernails or toenails
Temporary hypohidrosis
Mucositis
Late reactions
Telangiectasia
Fibrosis
Necrosis of soft tissue, cartilage, bone
Hypo- or hyperpigmentation
Permanent alopecia
Hypohidrosis, sweat gland atrophy
Xerostomia
Delayed wound healing in poorly vascularized or edematous tissue

BCC, Basal cell carcinoma; *cSCC,* cutaneous squamous cell carcinoma.
Adapted from Garner et al[1] with permission from Springer Nature.

CONTRAINDICATIONS

RT is contraindicated in patients with genetic conditions that predispose them to radiation-related skin cancer, such as basal cell nevus syndrome or xeroderma pigmentosum.[36-38] One relative contraindication for RT is connective tissue diseases, such as scleroderma or lupus erythematosus, because RT can enhance fibrosis of the skin and soft tissues.[39,40] Other relative contraindications include poorly vascularized, edematous tissues, chronic ulceration, trauma, or thermal burns in addition to RT of recurrent disease within a prior radiation field due to higher complication rates with increasing cumulative radiation dose and poor cosmesis.[17,41] Of note, protracted fractionation may improve cosmesis and can be utilized in cartilaginous areas or locations with poor vascularity.[42] Immunosuppressed hosts, such as solid organ transplant recipients or those with chronic lymphocytic leukemia, tolerate radiotherapy well with no greater toxicity.

CONCLUSION

In appropriately selected patients, radiation of cutaneous malignancies can be a useful therapy that allows for maximal effect on cancer cells and minimal effect on healthy cells. A variety of techniques are available to treat the targeted site adequately while also preserving critical underlying structures. The technique, dosage, targeted outcome, and related side effects vary, depending on each patient's health status, tumor diagnosis, and anatomic treatment site. Communication with a radiation oncologist is helpful when choosing an optimal treatment regimen. Patients should be closely monitored during treatment for signs of acute toxicities, which typically can be managed conservatively. Long-term follow up of patients is advised to monitor for the development of late reactions or secondary malignancies or the recurrence of the disease within the radiation field.

Conflicts of interest

None disclosed.

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