Consensus Guidelines on the Use of Superficial Radiation Therapy for Treating Nonmelanoma Skin Cancers and Keloids

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ABSTRACT

Background: The use of superficial radiation therapy (SRT) has experienced a renaissance for treating nonmelanoma skin cancers (NMSCs) and recurrent keloids; however, published treatment guidelines are lacking. **Objective:** The objective of this work was to provide consensus guidelines on the use of SRT for treating NMSC and recurrent keloids based on a review of the literature and expert opinion. **Methods and Materials:** A search of the medical literature was performed to obtain published information on the use of SRT for review. A group of qualified dermatologists convened to discuss their views on the use of SRT for the treatment of NMSCs and recurrent keloids. The various guidelines were considered to have consensus based on a supermajority two-thirds vote. The final consensus guidelines are thus based on the medical literature, when available, and expert opinions. **Results:** Agreement on consensus guidelines was reached for numerous aspects of SRT use, including appropriate tumor types for SRT; anatomical areas suitable for SRT; energy, fractions, and scheduling recommendations for SRT; use of SRT in the presence of comorbidities; safety factors; and treatment recommendations for recurrent keloids, based the literature and on both the opinions of the expert group and a survey of experienced users. **Conclusion:** Consensus was reached that SRT is a safe and effective treatment for basal cell and squamous cell carcinomas and should be considered as the first-line form of radiation treatment. Postsurgical treatment of keloid excision suture lines with SRT significantly reduces keloid recurrence rates.

KEYWORDS: Superficial radiation therapy, nonmelanoma skin cancer, literature review, consensus guidelines

Nonmelanoma skin cancer (NMSC), which includes basal cell carcinoma (BCC) and squamous cell carcinoma (SCC),[1] is the most frequently diagnosed type of cancer in humans,[2] with an incidence that continues to increase. The mean annual number of adults treated for NMSC grew from approximately 3.0 million from the years 2002 to 2006 to 4.3 million from the years 2007 to 2011 ($p<0.001$).[2] Well-known risk factors for developing NMSC include chronic exposure to ultraviolet radiation, fair complexion, advancing age, and immunosuppression.[1,2] While most cases of NMSC are relatively benign and respond to treatment, a small number of SCCs result in metastasis and death (mortality ratio estimates are 1.25 to 1.30).[3,4]

The economic burden of skin cancer treatment is substantial and continues to rise with increasing incidence. The mean annual total cost for treating NMSC skin cancer in the United States increased from $2.7 billion from the years 2002 to 2006 to $4.7 billion from the years 2007 to 2011 ($p<0.001$). During this time, the mean cost per patient rose from $882 to $1,105 ($p=0.04$).[5]

The range of available treatment options for NMSC includes surgery, cryotherapy, curettage and electrodessication, and radiation therapy (RT). RT includes superficial radiation therapy (SRT), photodynamic therapy, various forms of brachytherapy, and chemotherapeutic agents.[6–12] Treatment decisions are based on tumor type, anatomical location, patient age, tumor stage and classification, physician preference, and/ or treatment setting.[1] The choice of treatment becomes more complex among the elderly due to frailty, limited life-expectancy, and comorbidities.[1] Anatomical location also becomes an important factor, as NMSC lesions commonly occur on the ears, eyes, and nose[13] where treatment can have significant cosmetic consequences.

Among the available treatments, superficial radiation therapy (SRT) is one of the oldest, having been developed more than 100 years

ago.[14] For many years, SRT played a major role in the practice of dermatology; by 1975, 55.5 percent of dermatology offices in North America were equipped with SRT or Grenz ray devices and 44.3 percent of dermatologists reported using them regularly.[15] At that time, dermatologists were routinely trained on the use of SRT and were familiar with its indications and treatment protocols.[16] Despite the abundance of clinical trial data demonstrating the effectiveness of SRT for treating NMSC,[17–24] including long-term studies,[25–27] the use of SRT declined as new surgical techniques gained popularity and replacement SRT devices became unavailable. Dermatology residency programs no longer provide training on the use of SRT.

Recently, SRT has experienced a renaissance as advocates strive to fill knowledge gaps regarding its use and demonstrate again its efficacy with large studies.[14] One retrospective study assessed the results of 1,715 histologically confirmed, nonaggressive BCCs (n=712), SCCs (n=994), and tumors with combined features (n=9) that were treated with SRT over a 10-year period.[25] The mean patient age was 79 years, and the mean duration of follow-up was 31.5 months (range: 1–120 months). The overall five-year recurrence rate was 5.0 percent. Specific five-year recurrence rates were also determined for BCC (4.2%), SCC (5.8%), invasive SCC (6.7%), and SCC in situ (5.5%). Treated areas included the cheeks, nose, forehead, lips, chin, and scalp, with excellent cosmetic results.

Similarly to NMSC, an enormous body of literature has demonstrated the effectiveness of SRT as an adjunctive therapy for the treatment of recurrent keloids; nevertheless, SRT also remains an underutilized therapy for this distressing condition.[28–30]

In addition to decades of clinical data on the use of SRT, the recent increase in its use has also been greatly aided by the commercial availability of a new and advanced SRT device that has been cleared for treating NMSC and recurrent keloids (SRT-100™; Sensus Healthcare, Boca Raton, Florida).

A group of qualified and experienced dermatologists convened in South Beach, Florida, on March 1, 2018, to discuss their views on the use of SRT for the treatment of BCC, SCC, and recurrent keloids. In the absence of guidelines on the use of SRT for these conditions, the goal was to provide consensus guidelines regarding the use of SRT for the

TABLE 1. Summary of consensus guidelines for SRT	
1.	Multiple treatment modalities are available for treating NMSC, but radiation therapy, specifically SRT, should be a first option for treating appropriate types of NMSC in appropriate patients.
2.	There are significant differences between SRT and other energy-based therapies, but SRT is superior to EBRT and EBX for treating most cases of NMSC.
3.	Several tumor types are more appropriate for treatment with SRT, such as primary BCC and SCC; significant SCC in situ; and, in certain cases, cutaneous lymphomas and Kaposi sarcoma; however, other tumors should be treated by other forms of radiation therapy.
4.	Measuring NMSC tumors and identifying tumor margins for SRT are similar to surgery based on the fact that the penumbra for SRT is only 1mm.
5.	Some anatomical areas are more suitable for treating NMSC with SRT, including on the lower extremities below the knee and the nasal alar rim, ear, and perioral and periorbital areas.
6.	Some patients are more appropriate as candidates for treatment with SRT based on local skin factors and comorbidities, especially patients who cannot be treated surgically due to advancing age, preexisting medical conditions, or patient preference.
7.	The consideration of patient safety factors is mandatory, including custom site shielding.
8.	Optimal energy, fractions, and scheduling for treating NMSC leads to superior outcomes.
9.	Pausing treatment due to significant radiation dermatitis is an important part of the SRT treatment algorithm.
10.	There are no data indicating whether topical treatments for radiation dermatitis for use during and/or after SRT affects treatment outcomes, but such treatments might possibly reduce cure rates.
11.	SRT is safe and effective in treating recurrent keloid scars that are resistant to other therapies with three post-surgical fractions

SRT: Superficial radiation therapy; NMSC: nonmelanoma skin cancer; BCC: basal cell carcinoma; SCC: squamous cell carcinoma; EBRT: electron-beam radiotherapy; EBX: electronic brachytherapy

treatment of NMSC and recurrent keloids. The eight participants had a combined 250 years of dermatology practice and 78 years of experience with SRT and had treated approximately 8,750 patients with SRT. The various guidelines were considered to have consensus based on a supermajority two-thirds vote.

METHODS

Literature search. Several weeks prior to the meeting, searches of the Cochrane Library (http://www.cochranelibrary.com) and PubMed (https://www.ncbi.nlm.nih.gov/pubmed) databases were performed to identify the available information regarding treatment of BCC, SCC, and recurrent keloids. PubMed searches included articles published from January 1, 1998, to June 30, 2018, with inclusion restricted to articles dealing with human patients and in the English language. As the subject matter was broad, numerous searches were performed using combinations of medical subject heading terms: *nonmelanoma skin cancer, basal cell skin cancer, squamous cell skin cancer, squamous cell skin cancer* in situ, *Bowen's disease, treatment, therapy, radiation therapy, superficial radiation therapy, superficial X-ray therapy, soft X-ray therapy, surgery, Mohs surgery, Mohs micrographic surgery, brachytherapy, electronic brachytherapy, electron beam radiotherapy, photodynamic therapy, radiation dermatitis*, and *clinical trials*.

Consensus guideline development. One author (MSN) identified clinical topics for group discussion, which included the following:
- Available forms of radiation therapy for NMSC and recurrent keloids
- SRT versus other radiation therapies
- Electronic surface brachytherapy
- Tumor types for SRT
- Appropriate patients for SRT
- Suitable anatomical areas for SRT
- Measuring tumors and tumor margins for SRT
- Energy, fractions, and scheduling for different tumor types and anatomical areas
- Topical treatments for radiation dermatitis
- Patient safety factors
- Pausing treatment for radiation dermatitis
- Treating recurrent keloids using SRT.

Each topic included several discussion points. These topics and discussion points were sent

to each meeting participant for review and generation of comments prior to the planned discussion and were included in the final document prior to the group meeting. Following the expert opinion meeting, the discussion points were revised and resent to all participants until a consensus was reached. The guidelines were considered to have consensus based on a supermajority two-thirds vote. The following guidelines statements are based on the medical literature and expert consensus opinions. A summary of these statements is provided in Table 1.

CONSENSUS GUIDELINES FOR SUPERFICIAL RADIATION THERAPY

1.0—Multiple treatment modalities are available for treating NMSC, but radiation therapy, specifically SRT, should be a first option for treating appropriate types of NMSC in appropriate patients.

1.1   Currently available treatments for NMSC include destruction, surgery, photodynamic therapy, topical therapies, and several energy-based therapies and various forms of RT, although no specific treatment choice algorithm exists.[31–33]

1.2   In many cases, cure rates using RT, and specifically SRT for the treatment of MSC, are similar to surgical options.[34] Cosmesis with appropriate energies and fractions might be superior to surgery for NMSC in certain anatomic locations.[6,10,34,35]

1.3   Radiation therapy, specifically SRT, should be a first option for treating appropriate types of NMSC tumors (see 3.1).[7,20,25,35] Patient consent for NMSC should include a discussion of all treatment options including SRT.[36]

1.4   Contraindications to the use of SRT include aggressive tumor histology or deep tumor invasion, previously irradiated lesions, and some types of NMSC occurring on organ transplant recipients.[14]

2.0—There are significant differences between SRT and other energy-based therapies, but SRT is superior to electron-beam radiotherapy (EBRT) and electronic brachytherapy (EBX) for treating most cases of NMSC.

2.1   EBRT utilizes electrons to treat NMSC[37] and EBX involves the application of short-contact X-rays to treat NMSC lesions.[9,38]

2.1.1. There are significant differences in the physical and clinical properties of these treatment modalities, such as beam profile and depth of penetration. The beam and delivered dose of SRT have dramatically less lateral edge beam drop-off (1mm) in the penumbra at the treatment site compared with EBRT (8–10mm).[39] EBRT requires higher energy to successfully encompass a superficial lesion and is associated with lower overall cure rates for NMSC.

2.1.2. SRT is therefore superior to EBRT for treating most NMSC and results in better cosmesis.[40,41]

2.1.3. To some extent, different energy-based therapies can be optimal for different tumor types and anatomical areas.[38,42] For example, EBRT has an established role as adjunctive therapy in tumors with perineurial invasion, treatment of cutaneous T-cell lymphomas, Merkel cell carcinoma, dermatofibrosarcoma protuberans, and select melanomas of the head and neck that demonstrate extracapsular spread in lymph nodes or are spindle cell subtypes.[43]

2.2   EBX should be considered short-contact SRT, since the energy source is the same and the technology is virtually identical to short-contact SRT devices.[44,45]

2.2.1. SRT is superior to electronic surface EBX based on its abilities to vary energies from 50 to 100cGy and employ larger spot sizes. In contrast to EBX, clinical data on thousands of patients support long-term cure rates and cosmesis with SRT.[10,25]

2.2.2. Although the energy source is the same, SRT is currently more cost-effective in terms of equipment and patient cost.[14]

3.0—Several tumor types are more appropriate for treatment with SRT, such as primary BCC, SCC, significant SCC *in situ*, and certain cases of cutaneous lymphomas and Kaposi sarcoma. However, other tumor types should be treated using other forms of radiation therapy.

3.1   SRT is a viable nonsurgical option and chief indication for primary BCC and SCC and for significant SCC *in situ*.[25,46] However, similar to surgical options, using SRT to treat large, deep tumors can have lower cure rates than smaller tumors, except for superficial ones.[47,48]

3.2   SRT can also be used in certain cases to treat cutaneous lymphomas and Kaposi sarcoma.[49–51] However, other tumor types (e.g., tumors with perineurial invasion, cutaneous T-cell lymphomas, Merkel cell carcinoma, dermatofibrosarcoma protuberans, and select melanomas of the head and neck that demonstrate extracapsular spread in lymph nodes or spindle cell subtypes) should be treated by other forms of radiation therapy such as EBX.[43]

4.0—Measuring NMSC tumors and identifying tumor margins for SRT are similar to surgery—the penumbra for SRT is only 1mm.

4.1   Tumor margins are similar to those used in surgery.[52] The most appropriate method for establishing the margin is to measure the tumor using the same margins necessary to achieve adequate cure rates if it were treated surgically.

4.2   The initial measurement for the NMSC should include all clinical areas that could have tumor present, similar to the way drawn surgical excision margins are estimated. The maximum diameter of this measured area should be reported as tumor size. Additional SRT treatment margins can then be 5mm or less of clinically normal skin due to the fact that the penumbra for SRT is only 1mm. Older literature based on EBRT, which had a penumbra of over 6mm, estimated that the radiation field should extend 5 to 10mm (the umbra) beyond the tumor into clinically normal skin.[25]

TABLE 2. Recommendations for using superficial radiation therapy on various anatomical treatment areas

ANATOMICAL TREATMENT AREA	TUMOR TYPE	DEPTH	THERAPEUTIC DOSING RANGE[a]	TOTAL DOSE FRACTIONS	NUMBER OF DOSES (FRACTIONS)[b]	DOSING FREQUENCY
Scalp, cheeks, forehead, nose, trunk, arms, and neck	Superficial BCC, SCC *in situ*	50 kV	4,500–5,500cGy	98–100cGy	6–18	1–5 fractions/week (2–3/week optimal)
	Infiltrative BCC, nodular BCC, SCC superficial	70 kV				
	Infiltrative SCC, thick SCC, keratoacanthoma	100 kV				
Lower extremities, bony prominences, mucosal membrane borders (lips and eyelids)	Superficial BCC, SCC *in situ*	50 kV	4,500–5,500cGy	94–96cGy	6–18	1–3 fractions/week (2/week optimal)
	Infiltrative BCC, nodular BCC, SCC superficial	70 kV				
	Infiltrative SCC, thick SCC, keratoacanthoma	100 kV				

SRT: Superficial radiation therapy; NMSC: nonmelanoma skin cancer; BCC: basal cell carcinoma; SCC: squamous cell carcinoma
[a]Use lower total dose fractionation if treatment area has a high fat content.
[b]A smaller number of fractions results in the same cure rate but is more likely to result in ulceration and other long-term sequelae as well.

5.0—Some anatomical areas are more suitable for treating NMSC with SRT. These include extremities below the knee, nasal alar rim, ear, perioral, and periorbital areas.

5.1 In areas where tissue-sparing is important, SRT might be better suited than surgery, which can have undesirable cosmetic and functional consequences requiring reconstructive surgery.[20,53,54]

5.2 SRT has particularly favorable cosmesis on the nasal alar rim, ear, and perioral and periorbital areas.[19,20,22,26,34,47,48,55,56] SRT has been shown to be particularly beneficial for certain cases of NMSC on the lower extremities below the knee with site-specific radiation planning, dosimetry, and fractionation.[57]

5.3 Surgical site infection rates for Mohs micrographic surgery and wide local excisions performed below the knee range from 2.3 to 8.3 percent, respectively.[58] Among 151 lower-extremity NMSC lesions treated with SRT, there were no treatment-related infections.[57]

6.0—Some patients are more appropriate for treatment with SRT based on local skin factors and comorbidities, especially patients who cannot be treated surgically due to advancing age, preexisting medical conditions, or patient preference.

6.1 Patients with NMSC present with varying ages,[59,60] medication use patterns, and comorbidities.[60] SRT is beneficial and cost-effective for NMSC on the lower extremities, which might otherwise be associated with cellulitis and infection—especially among frail, elderly patients.[14,25]

6.2 SRT is especially indicated for treating patients who cannot be treated surgically due to advancing age; preexisting medical conditions such as diabetes, stasis dermatitis, chronic edema, and circulatory compromise;[54,61,62] concomitant drug therapy (e.g., anticoagulation); or patient preference.[63,64]

6.3 As there is no anesthesia or cutting associated with the use of SRT, making it is ideal for patients who fear surgery.[42]

7.0—The consideration of patient safety factors is mandatory, including custom site shielding.

7.1 To reliably and safely deliver the dose to the tumor bed, proper patient positioning, immobilization, and shielding should be repeatedly tested and finely tuned during treatment simulation. Shielding of the eyes and nontreated areas including the torso and thyroid should be used routinely as well as specific shields for intraoral and intranasal locations when those areas are associated with treatment.[25]

7.2 Custom lead shielding should be fabricated for the specific tumor site in all patients undergoing SRT.[65] Any variance

TABLE 3. Protocol for treating keloid scars on the scalp, cheeks, forehead, nose, trunk, arms, and neck using superficial radiation therapy

Depth	100kV
Therapeutic dosing	3,000cGy
TDF	600cGy
Number of doses (fractions)	3
Dosing frequency	One dose/day for the first three postoperative days

TDF: Total dose fraction

in shield can cause position or radiation therapy cone contact, which might result in undertreatment of a tumor.

7.3 Patients should be informed about expected short-term and long-term side effects,[66] which include various degrees of radiation dermatitis and the occurrence of postinflammatory hypo- or hyperpigmentation among patients with dark skin.

8.0—Optimal energy, fractions, and scheduling for treating NMSC leads to superior outcomes.

8.1 Treatment recommendations are specific for anatomical locations. Altering the fraction size and the overall total dose leads to acute (e.g., radiation dermatitis and ulceration) and latent (e.g., atrophy, telangiectasia, and pigmentation changes) reactions.[18,67] Data indicate that changes in SRT fractionation schemes by increased number and time between treatments have led to better

outcomes.[55,56,68] Additionally, the total dose fraction (TDF) should be between 90 and 110, especially when treating low-vascular areas such as the lower limbs.

8.2 The range of available energy with SRT permits the use of higher energy for deeper NMSC lesions. Cure rates are similar for different fraction numbers provided the TDF is similar, but short- and long-term adverse events can be significantly fewer in number with a larger number of fractions.

8.3 The ideal number of fractions involves discussion with patients and family regarding outcome and cosmesis (more fractions) versus convenience (less fractions). The treatment recommendations in Table 2 are deemed appropriate for each area.[68,69]

9.0—Pausing treatment due to significant radiation dermatitis is an important part of the SRT treatment algorithm.

9.1 Constant evaluation of the treatment site is necessary throughout the course of treatment. There can be minimal pain, swelling, or moist desquamation at the treatment area. There should be a pause (decay) in treatment at the first sign of significant ulceration, swelling, or pain.

9.2 Subsequently, a reassessment and dosimetry calculation should be performed to determine whether a change in treatment parameters is necessary.

10.0 —There are no data indicating whether use of topical treatments for radiation dermatitis during and/or after SRT affects treatment outcomes, but such treatments can possibly reduce cure rates.

10.1 Numerous topical products are promoted for preventing or treating radiation dermatitis. Although there is a hypothesis that inflammation associated with radiation therapy is a mechanism of curing NMSC,[70] there is no clinical study evidence regarding whether reducing inflammation associated with radiation dermatitis impacts cure rates.

10.2 Similarly, there is insufficient evidence to support or refute the use of specific therapies for the prevention or management of radiation-induced skin changes. Additional studies are needed.[71–73]

10.3 The post-SRT management of radiation dermatitis is based principally on the severity of damaged skin.

11.0 —SRT is safe and effective in treating recurrent keloid scars that are resistant to other therapies with three postsurgical fractions.

11.1 There is substantial evidence that SRT is effective for treating recurrent keloid scars that are resistant to other therapies.[74–76] Postsurgical treatment of keloid excision suture lines with several fractions of SRT significantly reduces keloid recurrence rates.[77–82] Although effective outcomes can be achieved with single doses of SRT, long-term sequelae are improved with three doses.[83]

11.2 Fractionation of the SRT dose reduces the risk of hyperpigmentation and other adverse events. The optimal treatment protocol is a biologically effective dose of 3,000cGy in three fractions of 600cGy on the first three postoperative days.[84] The treatment recommendations in Table 3 are appropriate for keloids.[76,85–88]

11.3 There is little evidence that exposing keloids or surrounding healthy skin to SRT at a 3,000-cGy dose causes skin cancer.[89–92]

CONCLUSION

Superficial radiation therapy should be the first option for treating appropriate types of NMSC tumors in suitable patients, as cure rates are similar to most surgical options and there exists superior cosmesis in certain anatomic locations. SRT is also a safe and cost-effective option for treating NMSCs on the lower extremities that might otherwise be associated with medical complications in elderly patients and those with existing comorbidities. Postsurgical treatment of keloid excision suture lines with SRT significantly reduces keloid recurrence rates with no evidence that exposing surrounding healthy skin causes skin cancer.

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