Superficial x-ray in the treatment of basal and squamous cell carcinomas: A viable option in select patients

Armand B. Cognetta, MD,[a] Brett M. Howard, BA,[b] Henry P. Heaton, BA,[c] Earl R. Stoddard, MD,[d] Hyokyoung Grace Hong, PhD,[e] and W. Harris Green, MD[a]
Tallahassee, Florida; Brooklyn and New York, New York; and Pocatello, Idaho

Background: Effective nonsurgical modalities are limited in the treatment of basal cell carcinoma (BCC) and squamous cell carcinoma (SCC).

Objective: We sought to evaluate the efficacy and viability of superficial x-ray therapy in the treatment of BCC and SCC in an outpatient setting.

Methods: A retrospective analysis was performed on 1715 histologically confirmed primary cutaneous BCC and SCC treated with superficial x-ray therapy at Dermatology Associates of Tallahassee in Florida between 2000 and 2010.

Results: Of the 1715 tumors reviewed during this period, 712 were histologically proven BCC (631 nodular and 81 superficial), 994 were SCC (861 SCC in situ and 133 invasive SCC), and 9 displayed distinct features of both BCC and SCC in the same biopsy specimen. Kaplan-Meier estimates (with 95% confidence intervals) of cumulative recurrence rates of all tumors at 2 and 5 years were 1.9% (1%-2.7%) and 5.0% (3.2%-6.7%), respectively; of BCC at 2 and 5 years were 2% (0.8%-3.3%) and 4.2% (1.9%-6.4%), respectively; and of all SCC at 2 and 5 years were 1.8% (0.8%-2.8%) and 5.8% (2.9%-8.7%), respectively. Tumors on male patients and those with a diameter greater than 2 cm were associated with a statistically significant increase in recurrence likelihood.

Limitations: This study represents only patients treated in 1 dermatology office in North Florida and may not be representative of the general patient population.

Conclusions: Superficial x-ray therapy remains a viable nonsurgical option for the treatment of primary BCC and SCC in patients where surgical intervention is declined, unadvisable, or potentially associated with significant cosmetic or functional limitations. (J Am Acad Dermatol 2012;67:1235-41.)

Key words: basal cell carcinoma; photon therapy; radiation; radiation therapy; skin cancer; squamous cell carcinoma; superficial radiation therapy; superficial x-ray therapy; x-ray; x-ray therapy.

Superficial x-ray therapy (SXRT) has been used by dermatologists for over a century for skin cancers. It differs from modern electron beam radiotherapy (EBRT) in that light is the energy source rather than a charged particle, the machines are smaller and less expensive as a linear accelerator is

From Dermatology Associates of Tallahassee[a]; Florida State University College of Medicine[b]; State University of New York Downstate Medical Center, Brooklyn[c]; Idaho Skin Institute[d]; and Department of Statistics and Computer Information Systems, Baruch College, City University of New York.[e]

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Reprint requests: W. Harris Green, MD, Dermatology Associates of Tallahassee, 1707 Riggins Rd, Tallahassee, FL 32308. E-mail: DATresearch@gmail.com.

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not required, and the applied physics and dosimetry are inherently simpler. With SXRT, a bolus is not needed to deliver 100% of the dose to the skin surface as is required with EBRT. In addition, the beam and delivered dose with SXRT are more tightly cuffed with less lateral edge beam drop-off in the umbra of the treatment site.[1,2] Although SXRT is more cost-effective in terms of equipment and patient costs, EBRT can be used to treat broader areas of the skin than can typically be used with SXRT and has an established role in adjunctive therapy in tumors with perineural invasion and in the treatment of cutaneous T-cell lymphoma.[3-5]

Despite the low recurrence rates, favorable cosmesis, ease of use, lack of patient discomfort, and relatively low costs of outpatient SXRT, the percentage of dermatology clinics in the United States administering SXRT has decreased significantly over the years for a variety of reasons, including the development and availability of Mohs micrographic surgery (MMS).[6,7] Amidst a relative paucity of large-scale studies on the subject in the literature, the aim of this study is to evaluate the efficacy and viability of SXRT in the treatment of basal cell carcinoma (BCC) and squamous cell carcinoma (SCC) in an outpatient setting.

CAPSULE SUMMARY

- Superficial x-ray therapy has been successfully used by dermatologists for the treatment of skin cancers for almost a century.
- Our 10-year experience and reported data suggest that superficial x-ray therapy yields reasonable 2- and 5-year clearance rates for primary nonaggressive basal and squamous cell carcinoma.
- Superficial x-ray therapy remains a viable treatment option for select tumors in some patients who are poor surgical candidates or who decline surgery.

METHODS

Using records obtained from Dermatology Associates of Tallahassee in Florida, a retrospective analysis was performed on 1715 histologically confirmed primary, nonaggressive cutaneous BCC and SCC treated with SXRT between 2000 and 2010 in this practice. Pertinent clinical information regarding the tumor characteristics was recorded including anatomic location, lesion diameter, histologic morphology, and evidence of recurrence at follow-up. Initial and recurrent carcinomas were staged according to the American Joint Committee on Cancer staging system for nonmelanoma skin cancer.

Patients

The patients in the study were patients referred to our practice for MMS. All tumors treated were reviewed histologically by one of us (A. B. C.) to address whether the tumor was aggressive or nonaggressive and to ascertain the tumor depth. During informed consent process, if appropriate, patients older than 65 years with nonaggressive nonmelanoma skin cancers of the face or scalp were given various treatment options including radiation therapy. If the tumors were aggressive and the patient opted for radiation therapy, they were referred to a local radiation oncologist or to a nearby teaching hospital where EBRT was typically used. The tumors in this study include only the ones treated at our practice.

Equipment

Between 2000 and September 2008, a Universal Treatmaster Superficial X-Ray Unit (Universal X-Ray Products Inc) was used, which was backed up by a Picker Superficial X-Ray Unit (Picker X-Ray Corporation) The Universal unit was predominantly used at 80 kV, 5 mA, with a time dose factor (TSD) of 12.5 cm, half value depth (D1/2) of 6.7 mm with a 3-cm cone and 6.4 mm with a 5-cm cone. From 2008 until the present, the majority of lesions were treated with the TOPEX SRT-100 (TOPEX, Inc) (now Sensus SRT-100 [Sensus Healthcare]) machine while the Universal machine was kept as a backup. TSD, kV, milliamperes, cone size, and D ½ values varied with the newer machines yet the overall dosages, fractionation scheme, and time dose factors were unchanged.

Treatment

The patients' lesions were treated with 5 sessions (fractions) of 700 cGy for a total of 3500 cGy. Occasionally, 7 sessions of 500 cGy were used when we were treating areas such as the lip, as mucositis was a concern. Lead eye shielding and thyroid shielding were regularly performed while lead intranasal, buccal, and eye shields were used when appropriate. The radiation field of every tumor was determined by delineation of the clinical border of the tumor by careful examination. A radiation field was then drawn out 5 to 10 mm (the umbra) beyond the tumor into clinically uninvolved skin and a lead shield was custom made to treat both the tumor and the umbra. All patients were treated with various size cones, which overlapped the lead cutout shields. Treatments were performed 3 times a week for a total of 5 to 7 treatments. The exposure and fractionation

Abbreviations used:

BCC: basal cell carcinoma
EBRT: electron beam radiotherapy
MMS: Mohs micrographic surgery
SCC: squamous cell carcinoma
SXRT: superficial x-ray therapy

schemes were set up in such a manner to maintain a time dose factor within the optimal range between 90 and 110.[8]

Statistical methods

Because length of follow-up varied, recurrence rates were calculated using Kaplan-Meier method, and the statistical differences were assessed using the log rank test. The χ^2 test was used to determine possible significant differences between variables. The Cox proportional hazards model was used for multivariate analysis. In our data set, 1715 tumors were discovered in 1149 patients, indicating that approximately one third of patients had 2 or more tumors treated with SXRT. Therefore, to account for possible within-subject correlations, the frailty model was used. *P* values less than .05 were considered statistically significant. Because of the small number of patients, "combined" type was not included in the statistical analyses. Statistical analyses were performed using an R software package (R Development Core Team, Vienna, Austria).

Recurrence determination

Any tumor that arose in or contiguous to a radiation treatment field (which extended 5-10 mm beyond the clinical tumor) was counted as a recurrence unless it was a different tumor histologically (eg, a superficial BCC arising in or contiguous to a previous SCC in situ treatment site). If there was any doubt whether the lesion was contiguous or outside the radiation treatment field, it was counted as a recurrence.

RESULTS

A total of 1715 tumors in 1149 patients were treated with SXRT from 2000 and 2010 at our practice. Of the 1715 tumors reviewed during this period, 712 were histologically proven BCC (631 nodular and 81 superficial), 994 were SCC (861 SCC in situ and 133 invasive SCC), and 9 displayed distinct features of both BCC and SCC in same biopsy specimen. The locations of the tumors are listed in Table I and the tumor types and recurrences are listed in Table II. The male-to-female ratio was 2:1. The mean age at the time of diagnosis was 79 years. The length of follow-up was calculated from the date that the radiation therapy was initiated and the average duration of follow-up was 31.5 months ranging from 1 to 120 months.

The raw recurrence rate of all tumors treated was 2.6%. Because of the variation in follow-up lengths among patients, Kaplan-Meier estimates were used to estimate the control rates. Kaplan-Meier estimates (with 95% confidence intervals) of cumulative recurrence rates of all tumors at 2 and 5 years were 1.9% (1%-2.7%) and 5.0% (3.2%-6.7%), respectively; of BCC at 2 and 5 years were 2% (0.8%-3.3%) and 4.2% (1.9%-6.4%), respectively; of all SCC (including SCC in situ) at 2 and 5 years were 1.8% (0.8%-2.8%) and 5.8% (2.9%-8.7%), respectively; of invasive SCC at 2 and 5 years were 1.2% (0%-3.7%) and 6.7% (0%-14.5%), respectively; and of SCC in situ were 1.9% (0.7%-3.0%) and 5.5% (2.5%-8.3%) (Fig 1). The recurrence-free rate of tumors 2 cm or smaller was significantly lower than tumors larger than 2 cm ($P < .001$). Male patients received significantly worse prognosis than female patients ($P = .02$). There was no difference in recurrence-free rate among patients with different age, tumor types, sites, and T stage. The clinicopathological variables tested in the univariate analysis are shown in Table III. In multivariate analyses, male compared with female sex and tumor size greater than 2 cm compared with less than or equal to 2 cm were associated with higher recurrence (likelihood ratio $P = .06$; Wald $P = .02$; score (log rank) $P = .02$; Cox proportional hazards model) (Table III). The frailty model gave similar results with the multivariate survival analysis using the Cox proportional hazard model. The adjustment on the within-subject correlation might not be significant because of the high censoring rates in this data set. Male compared with female sex and tumor size greater than 2 cm compared with less than or equal to 2 cm were associated with higher recurrence (likelihood ratio $P = .06$; Wald $P = .03$; score (log rank) $P = .02$; frailty model).

DISCUSSION

Of the 1715 primary lesions treated with SXRT in our study, 45 were considered to be recurrent at follow-up. The raw recurrence rate for all tumors treated was 2.6%. Because of the variation in follow-up lengths among patients, Kaplan-Meier estimates were used to estimate the control rates for all tumors at 2- and 5-year intervals and were found to be 98.1% and 95.0%, respectively. These numbers are conservative for a number of reasons. Any tumor in the study that arose within or contiguous to the treatment site was counted as a recurrence. The treatment sites included both the carefully delineated clinical lesion and an additional 5- to 10-mm umbra or rim of

Table I. Number of patients in categories by site, and final diagnosis

Site	Nodular BCC	Superficial BCC	Invasive SCC	SCC in situ	Combined
Cheek	48	13	40	259	1
Nose	522	51	32	210	6
Forehead	30	9	18	135	1
Lips	6	2	3	5	0
Neck	2	0	0	2	0
Chin	10	0	0	0	0
Mastoid	0	0	0	1	0
Scalp	13	6	40	249	1
All sites	631	81	133	861	9

BCC, Basal cell carcinoma; *SCC*, squamous cell carcinoma.

Table II. Type-specific recurrences after therapy

Type	No. of tumors	No. of recurrences
Nodular BCC	631	20
Superficial BCC	81	2
Invasive SCC	133	4
SCC in situ	861	19
Combined	9	0
Total	1715	45

BCC, Basal cell carcinoma; *SCC*, squamous cell carcinoma.

clinically uninvolved skin. Many of these patients had extreme sun damage and, at baseline, were exhibiting multiple skin cancers arising synchronously or metasynchronously in individual areas of the head and neck. This display of multiple discontiguous tumor growths in such patients has often been attributed to the field effect first described by Slaughter et al[9] and is often encountered with superficial, multicentric BCC and SCC in situ tumors in heavily sun-damaged areas of the skin. In our study, any occurrence in or contiguous to the radiation treatment field could represent a de novo cancer but was always counted as a recurrence. In cases where it was not possible to adequately judge from the clinical presentation and the medical documentation photographs whether a new cancer was outside, contiguous to, or within the previous treatment site, it was counted as a recurrence.

Furthermore, the Kaplan-Meier estimates tend to overestimate recurrence rates in the context of high follow-up dropout by patients who continued subsequent care under their referring physician, who experienced no reportable problems with the treatment site, or who died from other health problems in their advanced age. It is common for patients and the referring physicians to report back in follow-up when there is problem within the treatment site and, in this way, the proportion of patients in follow-up at 5 years without recurrences to those who have a suspected recurrence is very low often creating an overestimation of the proportion of patients with recurrence in the Kaplan-Meier estimations. Nevertheless, the success rates in this study remain favorable and are comparable with the success rates of SXRT reported in previous smaller studies in the last few decades.[4,10-19]

In 1992, Silverman et al[20] reported 5-year recurrence rates of 862 primary BCC at 7.4%. Similarly, in 1992, according to Goldschmidt et al,[21] Pannizon reported estimated recurrence rates of 5.1% in 297 nonsclerosing BCC and 22% in 36 BCC with a sclerosing component during a follow-up of 7.9 years. In 2003, Zagrodnik et al[13] reported 5-year Kaplan-Meier recurrence rates of 8.2% for 103 nodular BCC, 26.1% for 25 superficial BCC, and 27.7% for 47 sclerosing BCC treated with SXRT in 154 patients.

In our study, there was no significant correlation between age of the patient, tumor type, or anatomic location and control rates. Tumors of male patients, and those of a stage of T2 (having a diameter >2 cm) were more likely to have a recurrence than tumors on female patients and those of smaller diameters. It is unclear as to why male patients had a significantly higher likelihood of recurrence when the treatment regimens were identical. All of the recurrences had a stage of T1 or less, had an average recurrent size of 0.89 cm, and were amenable to surgical salvage. The average time interval until recurrence was 34.7 months. There was no evidence of metastasis in any of the patients and no tumor-related deaths occurred.

Although cosmesis was not included as a quantifiable variable in this study, it is the opinion of the authors that cosmesis was good to very good in all of the patients. None of the results were considered poor. Fig 2 shows an example of a typical result after radiotherapy. The most common cosmetically unfavorable side effects experienced were hypopigmentation and a relative increase in telangiectasias within long-standing treatment areas. Cosmesis could have been improved by using a higher fractionation protocol. A large majority of tumors were on the alar rim, where, in the authors' opinion, the cosmetic result with superficial radiation in this sebaceous area surpasses the cosmetic result of MMS with closure by plastic surgery while offering comparable cure rates. Another advantage of radiation therapy is that, in certain cases, it may produce better functional and cosmetic results than surgical excision for carcinomas that are larger than 1 cm and involve the eyelids; tip or other areas of the nose; or skin of the upper lip.[2,11,22,23]

A practical limitation of this study is that it does not provide information regarding the treatment of

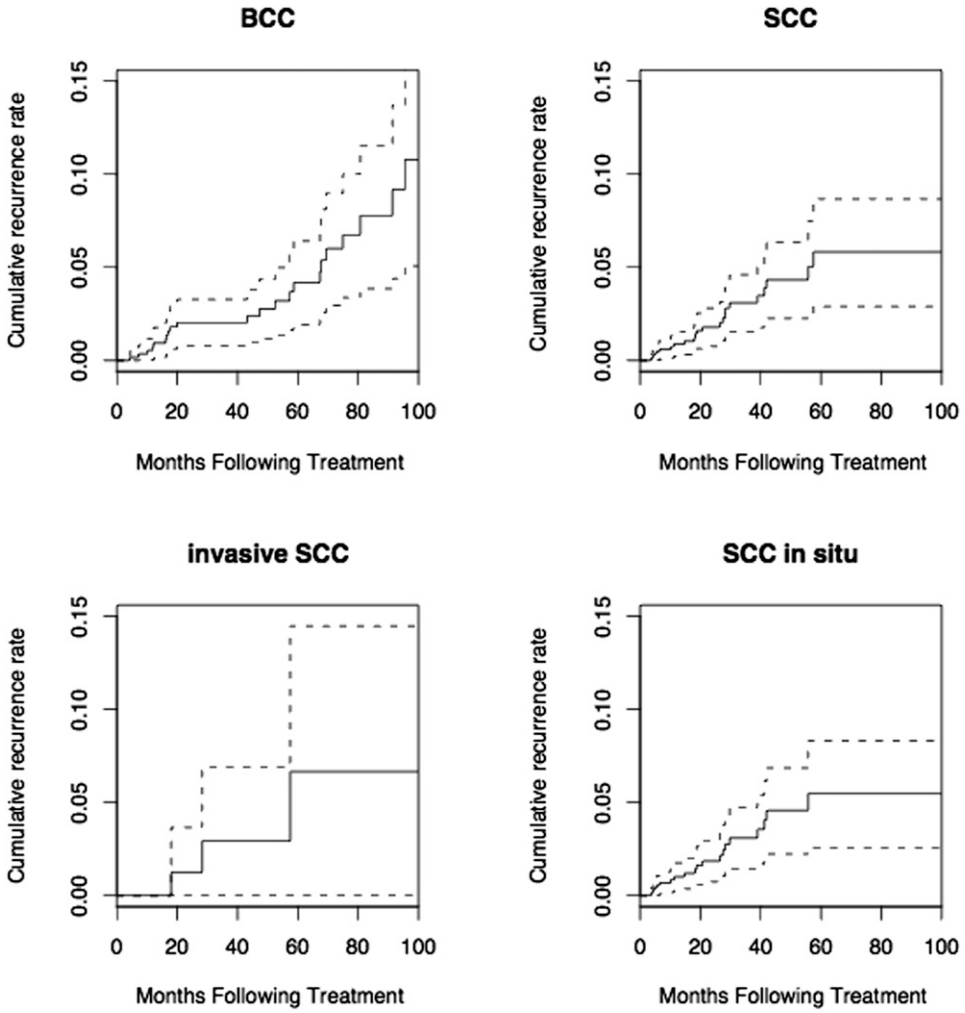

Fig 1. Kaplan-Meier estimates (with 95% confidence intervals) of basal cell carcinoma (*BCC*) at 2 and 5 years were 2% (0.8%-3.3%) and 4.2% (1.9%-6.4%), respectively; of all squamous cell carcinoma (*SCC*) (including SCC in situ) at 2 and 5 years were 1.8% (0.8%-2.8%) and 5.8% (2.9%-8.7%), respectively; of invasive SCC at 2 and 5 years were 1.2% (0%-3.7%) and 6.7% (0%-14.5%), respectively; and of SCC in situ were 1.9% (0.7%-3.0%) and 5.5% (2.5%-8.3%).

aggressive BCC and SCC with SXRT. There are several reports in the literature regarding the successful treatment of aggressive BCC with SXRT albeit with significantly lower cure rates than those reported with the treatment of nonaggressive BCC.[13,21,24] All of the tumors treated in this study were reviewed histologically by the lead author before treatment selection and determined to be nonaggressive and amenable to SXRT. Tumors regarded as aggressive were either treated with MMS or a referral was made to a nearby teaching hospital if the patient declined surgery and opted for radiation therapy. At the outside facilities, EBRT was typically used by a radiation oncologist.

Although the estimated 5-year recurrence rates of primary BCC and SCC treated with SXRT in our study are excellent among nonsurgical treatment modalities, they are not superior to reported recurrence rates where MMS is used. In a review of over 3 decades of studies, Rowe et al[25] reported 5-year recurrence rates of primary BCC treated with MMS to be 1.0%. In a large 10-year study in Australia, Leibovitch et al[26,27] reported 5-year recurrence rates of primary SCC and primary SCC in situ treated with MMS to be 2.6% and 2.5%, respectively. In terms of tumor clearance rates, MMS remains superior and a first line of treatment.

In conclusion, our study and reported experience suggest that SXRT continues to serve as a reasonable nonsurgical option for the treatment of primary, nonaggressive BCC and SCC in patients where surgical intervention is declined, unadvisable because

Table III. Results of univariate and multivariate analysis for recurrence, according to patient and tumor characteristics

	Univariate			Multivariate		
Characteristic	**HR**	**95% CI**	***P* value**	**HR**	**95% CI**	***P* value**
Age, y	0.98	0.94-1.01	.32	0.99	0.95-1.02	.43
Sex						
Male*						
Female	0.41	0.19-0.89	.02*	0.42	0.19-0.92	.03*
Type						
BCC*						
SCC	1.14	0.62-2.06	.67	1.06	0.33-3.39	.93
Stage						
S0 (Tis)*						
S1(T1 or T2)†	0.90	0.49-1.66	.74	0.90	0.30-2.72	.86
Site						
Cheek*						
Nose	0.98	0.42-2.29	.98	1.19	0.43-3.25	.74
Forehead, lips, neck, chin, mastoid	0.97	0.28-3.33	.97	0.93	0.27-3.20	.90
Scalp	1.40	0.51-3.88	.51	0.87	0.30-2.49	.79
Size, cm						
≤2*						
>2	3.94	1.74-8.89	<.001*	4.18	1.66-10.53	.002*

BCC, Basal cell carcinoma; *CI*, confidence interval; *HR*, hazard ratio; *SCC*, squamous cell carcinoma.
*Base groups in Cox analysis are: Male, BCC, S0(Tis), Cheek, Size ≤2 cm.
†Because of small number of patients, "combined" type was not included in statistical analyses.

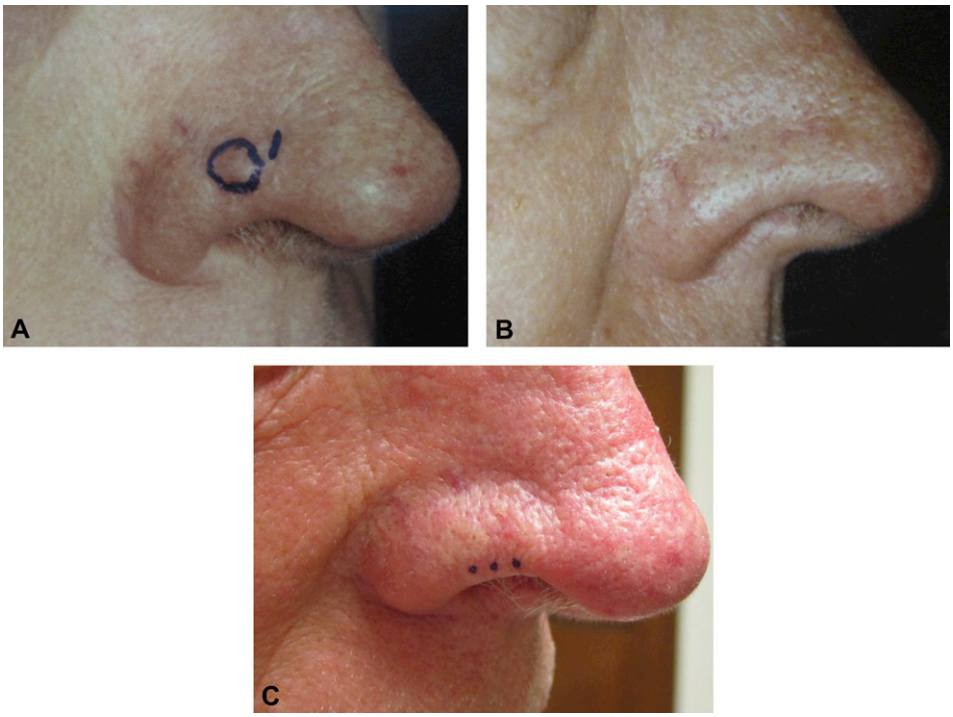

Fig 2. Patient with nodular basal cell carcinoma of right ala before **(A)**, 3 years after **(B)**, and 6 years after **(C)** superficial radiation therapy.

of comorbidities, or potentially associated with significant cosmetic or functional limitations. Although not superior to MMS in terms of tumor recurrence rates, superficial radiation therapy, when used properly and responsibly, continues to serve as an important tool in the dermatologic armamentarium for the management of skin cancer amidst an increasing elderly and frail patient population.

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