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Nonmelanoma skin cancer treated with electronic brachytherapy: Results at 1 year

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ABSTRACT

PURPOSE: We report clinical outcomes at 1 year or more after high-dose-rate (HDR) electronic brachytherapy (EBT) using surface applicators for the treatment of nonmelanoma skin cancer (NMSC).

METHODS AND MATERIALS: From July 2009 to April 2012, 122 patients with 171 NMSC lesions were treated with EBT to a dose of 40 Gy in eight fractions, delivered twice weekly. At followup, patients were assessed for acute and late toxicities, cosmesis, and local control.

RESULTS: Treatment of 171 lesions was completed in 122 patients with a mean age 73 years. There have been no recurrences to date with a mean followup of 10 months (range, 1–28 months). Followup data at 1 year or more were available for 46 lesions in 42 patients. Hypopigmentation (all Grade 1) was present in 5 (10.9%) of 46 lesions at 1 year. Other late effects at 1 year included dry desquamation, alopecia, and rash dermatitis, which occurred in 1 (2.2%), 1 (2.2%), and 3 (6.5%) of 46 lesions, respectively. No Grade 3 or higher adverse events were observed at any time point. Cosmesis was evaluated at 1 year for 42 of 46 lesions and was excellent for 39 (92.9%) and good for 3 (7.1%) of the 42 evaluable lesions.

CONCLUSIONS: Treatment of NMSC with HDR EBT using surface applicators was effective with no recurrences, good to excellent cosmesis, and acceptable toxicities at 1 year or more after treatment. HDR EBT provides a convenient nonsurgical treatment option for NMSC patients.

Keywords: Nonmelanoma skin cancer; Electronic brachytherapy; Basal cell carcinoma; Squamous cell carcinoma

Introduction

Nonmelanoma skin cancer (NMSC) is the most common malignancy and affects 2–3 million people each year in the United States (1). Although NMSC has a low mortality rate, its incidence continues to rise; it significantly affects quality of life and has a substantial financial impact on the health care system (1–3). Treatment options include surgery, radiation therapy, and topical agents, with surgery providing the most frequently used treatment. Radiation therapy may especially be used when NMSC is located in areas such as the eyelid, ear, or nose that may result in disfigurement if surgical options are used (4).

A variety of radiation therapy techniques have been used to treat NMSC (12). The techniques include superficial x-rays, orthovoltage x-rays, megavoltage photons, electron beam irradiation, and high-dose-rate (HDR) brachytherapy with surface applicators (12–18). ^{192}Ir-HDR brachytherapy using surface molds has been used in the treatment of NMSC with a 5-year local control rate of 98% and no severe early or late complications (19). HDR electronic brachytherapy (EBT) was developed in the last decade to provide patients with a shorter treatment schedule and physicians with a more convenient form of radiotherapy that does not require radioactive isotopes or dedicated treatment vaults. EBT has been used in the treatment of breast cancer, endometrial cancer, and NMSC (5–7) after clearance of the device by the U.S. Food and Drug Administration.

The EBT system used for this study (Axxent eBx; Xoft—a subsidiary of iCAD, Inc., Sunnyvale, CA) uses a miniaturized x-ray source at its tip, capable of delivering HDR and low

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energy radiation without the use of radioactive isotopes. The air kerma strength for the source is measured using an integrated well-ionization chamber before the delivery of each fraction of radiation. The source is connected, controlled, and powered by a controller. The controller supplies high voltage, filament current, and circulates cooling water to the x-ray source. It moves the x-ray source in a stepped linear manner through the applicator based on pullback dwell times and dwell positions provided by the operator. The patient's treatment plan is uploaded to the controller, and radiation is delivered based on this treatment plan.

Our initial study of EBT using surface applicators evaluated early treatment effects in 37 patients with 44 cutaneous malignancies, all of whom were treated successfully with no recurrences (7). Treatment was well tolerated with radiation-associated rash dermatitis, the most common early adverse event. Cosmetic results were good or excellent in all patients. This study group was subsequently expanded to include 122 patients with 171 lesions with additional follow-up. With this expanded group, we report the late treatment effects of HDR EBT using surface applicators for the treatment of NMSC at 1 year or more of followup.

Methods and materials

Study design

From July 2009 to April 2012, 122 patients with 171 NMSC lesions were treated with an EBT system and surface applicators (Axxent eBx; Xoft—a subsidiary of iCAD, Inc.). Patients had a diagnosis of NMSC confirmed by biopsy and were treated at Cancer Treatment Services Arizona. The protocol was approved by Integreview Ethical Review Board. The methodology for this study is described in detail in the initial report of this study (7).

Treatment

Patients with facial lesions were immobilized for treatment using a thermoplastic mask (Uni-frame; Civco, Orange City, IA) as shown in Fig. 1a, and extremities with lesions were immobilized using custom-molded cushions (Vac-Lok; Civco). The surface applicator was secured with a customized articulated arm setup to maintain contact with the skin lesion during each treatment as shown in Fig. 1c. The gross tumor volume was assessed visually, and a CT scan was used to assess skin depth before treatment. An appropriately sized skin applicator (10, 20, 35, or 50 mm) was used to allow for an acceptable margin of treatment around the lesion, with a goal of a 5-mm margin if feasible, as shown in Fig. 1b. Treatment planning was focused on calculating a dwell time to deliver the prescribed dose to the specified depth as previously described (7). Treatment depth was based on CT assessment; if CT was not performed, 3 mm was used. The prescription dose was 40 Gy in eight fractions, 5 Gy per fraction, delivered twice weekly with a minimum interval of 48 h between fractions.

At this clinic, patients were treated in the CT simulator room. The radiation oncologist or other personnel can remain in the room with the patient during treatment, and a flexible shield is used to cover the applicator to minimize radiation exposure as shown in Fig. 1c. This system shown in Fig. 1 is described in detail elsewhere (8). Patients were

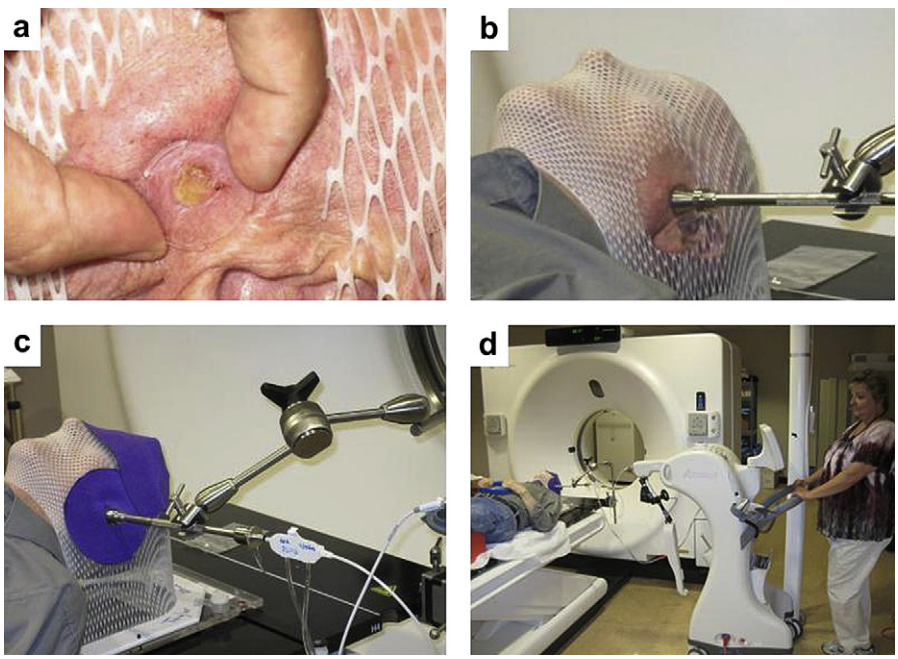

Fig. 1. Treatment setup for a patient with facial lesion showing (a) thermoplastic mask cut out around the lesion, (b) surface applicator in contact with skin, (c) shielding and applicator setup, and (d) electronic brachytherapy controller to the right of the patient.

Table 1
Cosmetic rating scale (10)

Excellent	No changes to slight atrophy or pigment change or slight hair loss or no changes to slight induration or loss of subcutaneous fat
Good	Patch atrophy, moderate telangiectasia, and total hair loss; moderate fibrosis but asymptomatic; slight field contracture with less than 10% linear reduction
Fair	Marked atrophy and gross telangiectasia; severe induration or loss of subcutaneous tissue; field contracture greater than 10% linear measurement
Poor	Ulceration or necrosis

instructed to apply a petrolatum ointment (Eucerin Aquaphor ointment; Beiersdorf, Inc., Wilton, CT) to the treated area three to four times per day during the treatment period. For 1 month after the treatment period, patients applied an Aloe Vera gel to the treated area.

End points

End points included safety outcomes, cosmetic results, and short- and long-term efficacy. Safety was evaluated in terms of adverse events reported during treatment or followup visits. The common terminology criteria for adverse events version 3 manual were used to categorize and grade adverse events (9). Cosmetic results were assessed at each followup visit using a standardized cosmesis scale (Table 1) (10).

Table 2
Demographics at baseline

Demographics	*N*	%
Histology (by lesion)		
Basal cell	91	53.2
Squamous cell	70	40.9
T-cell lymphoma	3	1.8
Merkel cell	2	1.2
Basosquamous	1	0.58
Not available	4	2.3
Tumor stage (by lesion)		
Tis	10	5.8
T1	138	80.7
T2	4	2.3
Recurrence	15	8.8
Not available	4	2.3
Ethnicity (by patient)		
Caucasian/non-Hispanic	118	96.7
Hispanic	3	2.5
Native American/Alaskan	1	0.8
Gender (by patient)		
Male	77	63.1
Female	45	36.9
Lesion locations (by lesion)		
Nose	49	28.7
Face	53	31.0
Ear	22	12.9
Extremity	22	12.9
Scalp	14	8.2
Torso	11	6.4

Table 3
Applicator sizes and corresponding lesion size range

Applicator size (mm)	Lesion size range (cm)	Number of lesions	Total lesions (%)
10	≤1	73	42.7
	>1 and ≤2	3	1.8
20	≤1	19	11.1
	>1 and ≤2	42	24.6
	>2 and ≤3	1	0.58
35[a]	≤1	7	4.1
	>1 and ≤2	17	9.9
	>2 and ≤3	5	2.9
50	>1 and ≤2	1	0.58
	>3	2	1.2
	5	1	0.58

[a] Cut out shielding was used with the 35-mm applicator to treat six lesions ≤1 cm and seven lesions >1 and ≤2 cm.

Results

Patient demographics

The study included 122 patients with 171 lesions and a mean age of 73 years (range, 49–97 years). Baseline characteristics of patients and lesions are summarized in Table 2. Most (65%) patients had previously been treated for skin cancer. The mean duration of followup was 10 months (range, 1–28 months). Followup data at 1 year or more were available for 46 lesions in 42 patients. The lesion sizes (<1–5 cm) and corresponding applicator sizes are summarized in Table 3. The dose depth (1–7 mm) and treatment time (3.9–13.8 min) are summarized in Table 4 by lesion type.

Efficacy results

The prescription dose of 40 Gy was completed in eight fractions, 5 Gy per fraction, given twice weekly, by all patients for all lesions. All lesions resolved with treatment, and there have been no recurrences reported to date. Photos of representative patients are shown in Figs. 2–4.

Adverse events

All patients tolerated the treatment without significant toxicities; there were no Grade 3 or higher adverse events at any time point. The most common early adverse events were rash dermatitis and pruritus, which occurred in 142 (83.0%) and 31 (18.1%) of 171 lesions at 3 months or less

Table 4
Treatment time and dose depth by lesion type

Histopathology of lesion	Number of lesions	Mean dose depth (range), mm	Mean treatment time (range), min
Basal cell	91	3.6 (1.0–7.0)	5.6 (4.0–8.2)
Squamous cell	70	3.7 (1.0–5.0)	5.8 (3.9–12.5)
T-cell lymphoma	3	4.3 (3.0–7.0)	8.4 (5.7–13.8)
Merkel cell	2	4.0 (3.0–5.0)	5.8 (4.6–6.9)
Basosquamous cell	1	3.0 (3.0–3.0)	5.2 (5.2–5.2)
Not available	4	4.7 (4.0–5.6)	7.3 (4.5–11.2)

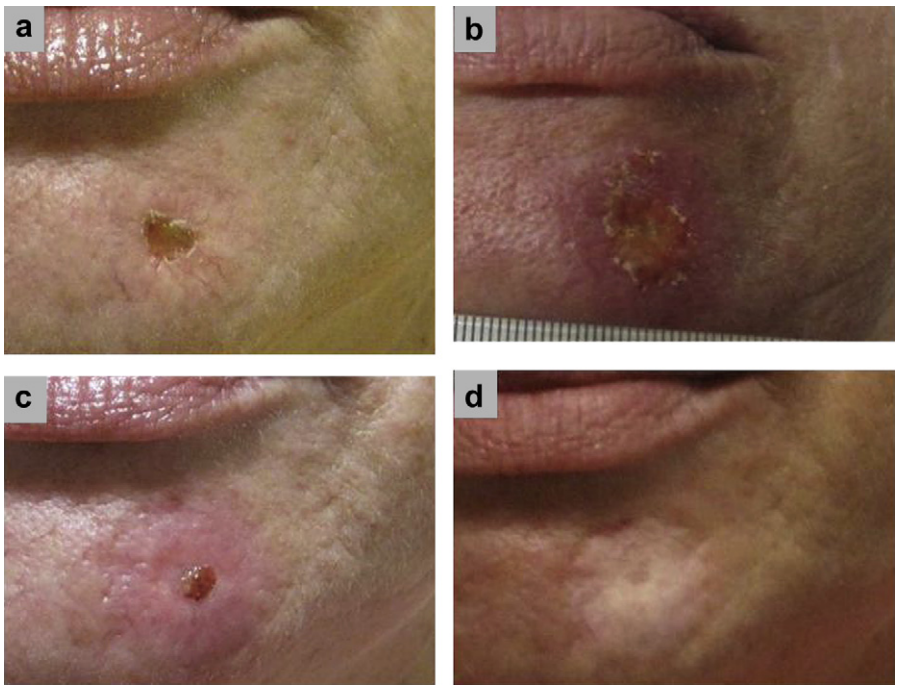

Fig. 2. A 56-year-old woman with basal cell carcinoma on chin treated with 20 mm surface applicator using 40 Gy to a 3-mm depth at (a) pretreatment, (b) last treatment in eight fractions, (c) 1 month, and (d) 12 months with hypopigmentation.

followup, respectively. The most common late adverse event was hypopigmentation, which occurred in 5 (10.9%) of 46 lesions at 1 year or more followup. All hypopigmentation was Grade 1. Other adverse effects at 1 year or more included rash dermatitis, alopecia, and dry desquamation, which occurred in 3 (6.5%), 1 (2.2%), and 1 (2.2%) of 46 lesions, respectively. There was no atrophy, hyperpigmentation, or telangiectasia in any of the 46 lesions at 1 year or more. Late adverse events are summarized in Table 5.

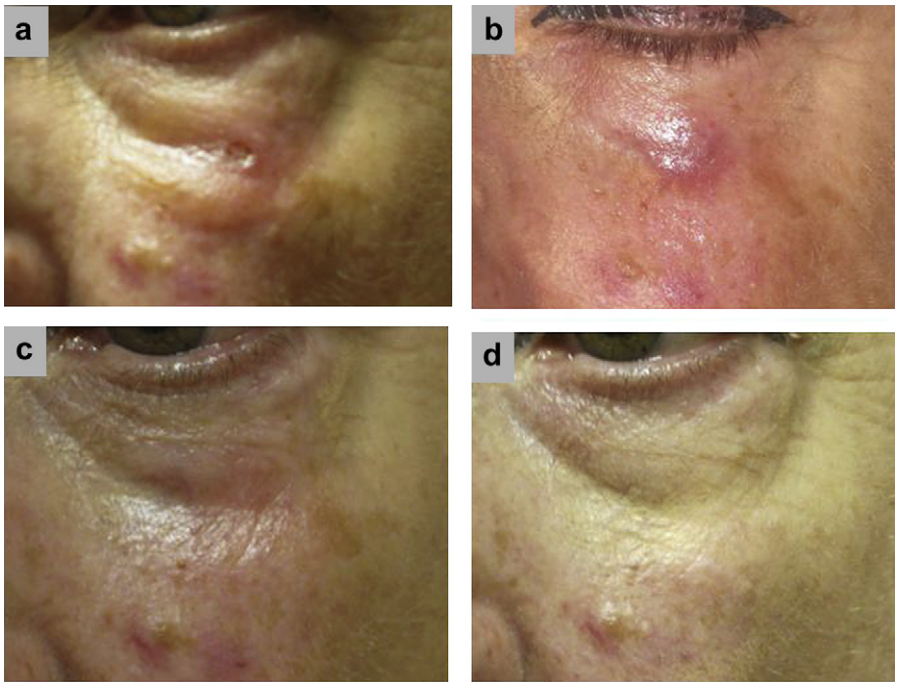

Fig. 3. A 68-year-old woman with squamous cell carcinoma below left eye treated with 10 mm surface applicator using 40 Gy to a 3-mm depth at (a) pretreatment, (b) 1 month, (c) 2.5 months, and (d) 20 months.

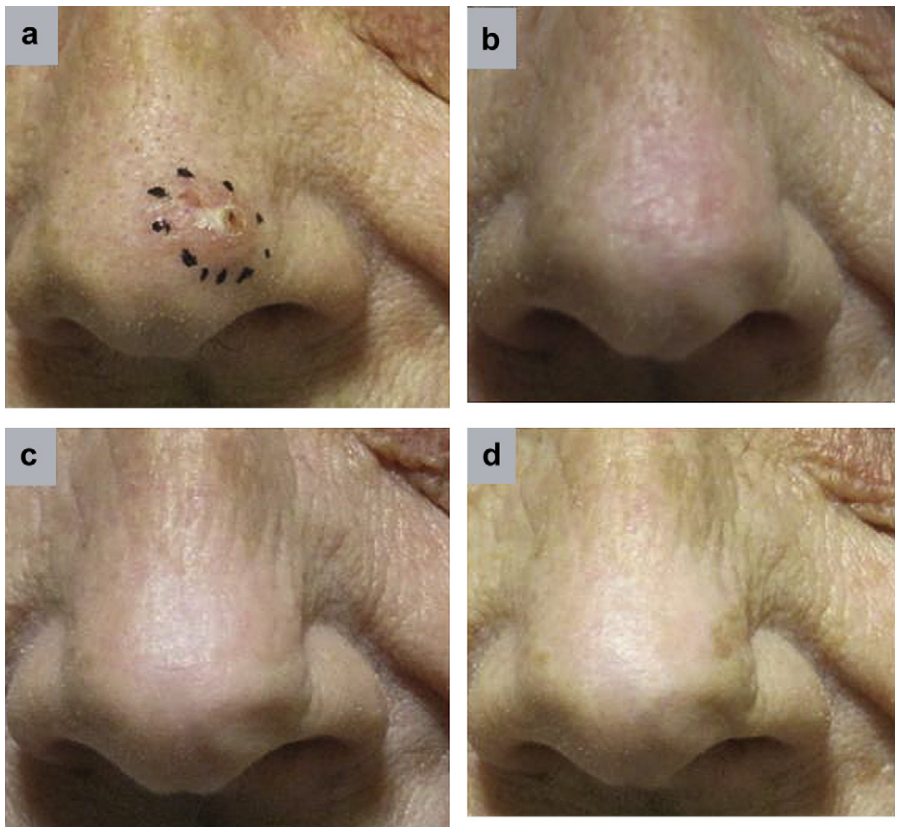

Fig. 4. A 73-year-old woman with basal cell carcinoma on left tip of nose treated with 20 mm surface applicator using 40 Gy to a 3-mm depth at (a) pretreatment, (b) 4 months, (c) 16 months, and (d) 23 months.

Cosmetic results

Cosmesis was assessed at each followup visit based on the radiation therapy oncology group scale (Table 1) (10). All patients had a cosmesis rating of good or excellent at each followup visit. At 1 year or more of followup, 42 of the 46 lesions had cosmesis evaluations. Cosmesis was excellent for 39 (92.9%) and good for 3 (7.1%) of the 42 evaluable lesions.

Discussion

Most NMSC cases in the United States are treated surgically, and rates of recurrence are typically below 5% (11). Radiation therapy has been used to treat NMSC for more than 40 years, and different techniques include superficial x-rays, orthovoltage x-rays, megavoltage photons, electron beam irradiation, and HDR brachytherapy (12–19). The overall rates of recurrence after radiation therapy range from 2% to 22% by type of radiation therapy, lesion size and type, length of followup, and patient risk factors (12–19). To date, no recurrences have occurred after HDR EBT treatment for NMSC. Table 6 provides a summary of EBT and other treatment modalities for NMSC.

Table 5
Adverse events at 1 year or more after treatment

Adverse event	AEs 1-year post-Tx ($N = 46$ lesions) (%)
Hypopigmentation	5 (10.90)
Rash dermatitis	3 (6.5)
Alopecia	1 (2.2)
Dry desquamation	1 (2.2)

AE = adverse events; Tx = treatment.

Patients with NMSC have a variety of treatment options which all have excellent results given the prognosis of this malignancy. Therefore, the patient's decision on the specific treatment modality can be based on a variety of other factors, rather than local control, such as convenience, toxicity, cosmetic result, and financial factors such as cost and insurance coverage.

There are several advantages of HDR brachytherapy compared with external beam therapy. First, the hypofractionated course of eight fractions, delivered twice weekly, can make this treatment much more desirable for patients compared with conventional dose fractionation schedules with external beam therapy. This can be a very important decision factor for patients with NMSC, in which they have a variety of options, which have comparable outcomes. Another advantage is the direct application of the radiation source *via* a surface applicator to the skin surface compared with external beam therapy modalities, such as electron beam. The direct application allows for

Table 6
Summary of NMSC treatment modalities

Treatment modality	Number of patients and lesions	Local control, %	Cosmesis, toxicity, or complication rate
Surgery (11, 24)	487 Patients with 608 lesions at a median of 6.6-year followup (11); 1038 patients with 1343 lesions (24)	94 (11)	1.6% Complication rate (24)
Superficial x-rays, orthovoltage x-rays, megavoltage photons, and/or electron beam irradiation (12–14)	339 Patients (12)	86 (12)	92% Excellent or good cosmesis with 5.5% complication rate (12)
	313 Patients with 334 lesions at 5-year actuarial followup (13)	79 (13)	7.3% Significant Grade 4 late toxicity (13);
	468 Patients with 531 lesions at a median of 5.8-year followup (14)	89 (14)	92% Excellent or good cosmesis with 5.8% complication rate (14)
HDR brachytherapy (18, 19)	520 Patients at 10-year followup (18);	92 (18)	No severe late radiation reactions (18);
	136 Patients at 5-year actuarial followup (19)	98 (19)	Excellent treatment tolerance in all cases and no severe, early, or late complications (19)
HDR electronic brachytherapy (herein reported study)	122 Patients with 171 lesions at 1-year followup	No recurrences to date	98% Excellent or good cosmesis

NMSC = nonmelanoma skin cancer; HDR = high-dose rate.
( ) encloses cited references.

feasible and well-tolerated treatment of amorphous yet cosmetically sensitive areas such as the nose. Given the properties of electron beam with tangential effect and penumbra, treatment of areas such as the nose can require a larger field size and result in increased acute toxicity, thus resulting in a less desirable treatment option for the patient. A limitation of HDR EBT is that lesions larger than 5 cm cannot be treated because the largest skin applicator size is 5 cm in diameter.

An additional benefit of using an electronic source for HDR brachytherapy is the avoidance of radioisotopes, which means the shielding and storage requirements associated with radioisotopes can be avoided. The surface applicators used with iridium-based brachytherapy, Leipzig applicators, are quite similar to those used with EBT, and the two applicators have similar depth dose profiles (7, 20–22). However, the beam profile of EBT reveals approximately 100% of dose prescription across the entire diameter (Fig. 5). With essentially no penumbra, this allows for reduced treatment margins compared with ^{192}Ir-HDR brachytherapy which can be essential for treatment locations near critical structures such as the eye or areas such as the nasal tip, in which it is not possible to have a 5-mm to 2-cm margin, as typically performed with conventional techniques.

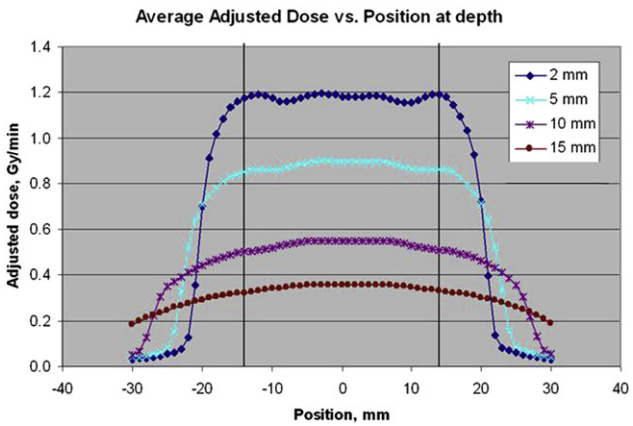

Fig. 5. EBT source beam profile for 30-mm diameter surface applicator. EBT = electronic brachytherapy.

Limitations of this study were the relatively short followup and small number of patients compared with studies of more established treatments for NMSC, although this study does have the largest number of patients with the longest followup to date for treatment of NMSC with EBT. Patients will continue to be followed, and additional patients will be added for further reporting of the outcomes of treatment of NMSC with EBT.

EBT treatment was well tolerated at doses of 40 Gy given in eight fractions over 4 weeks. The most common adverse event 1 year or more after treatment was hypopigmentation, which occurred in 10.9% of patients. Telangiectasia, a common adverse event with electron beam irradiation (23), did not occur with HDR EBT. None of the adverse events were Grade 3 or greater. Cosmetic results were good or excellent in all patients with 1 year or more followup data. Although all patients received the same dose, the dose depth varied from 1 to 7 mm; only 1 patient, who had a cutaneous T-cell lymphoma on the wrist, was treated to 7 mm. The treatment time also varied from 3.9 to 13.8 min with the longest treatment time (13.8 min) and the longest mean treatment time (8.4 min) associated with T-cell lymphoma.

Conclusions

Treatment of NMSC with HDR EBT using surface applicators was effective with no recurrences, good to excellent cosmesis, and acceptable toxicities at 1 year or more after treatment. HDR EBT provides a convenient nonsurgical treatment option for NMSC patients.

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