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Skin surface brachytherapy: A survey of contemporary practice patterns

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ABSTRACT

PURPOSE: The aim of this study was to define current patterns of care among radiation oncologists who use skin surface brachytherapy for the treatment of cutaneous squamous cell carcinoma (cSCC) and basal cell carcinoma (BCC) in academic and community settings.

METHODS AND MATERIALS: A 30-question electronic survey was administered to clinician members of the American Brachytherapy Society. The respondents were asked to provide details regarding their clinical practice and their approach to skin surface brachytherapy.

RESULTS: A total of 16 surveys were returned. Among the respondents, aggregate experience varied from 8 to 1800 cases. Most preferred brachytherapy over external beam radiation because of shorter treatment course, conformality of treatment for irregular or curved targets, and shallow dose deposition. Of the total, 60% of respondents routinely estimated lesion depth via ultrasound before initiating treatment. Treatment margin on gross disease varied widely (range, 3−15 mm; median, 5 mm). Hypofractionation was the preferred dose schedule. Prescribed doses ranged from 30 Gy in five fractions to 64 Gy in 32 fractions (EQD2, 40 Gy−65 Gy). There was a tendency to increase the number of fractions for larger targets, although some used the same fractionation regardless of anatomic location or lesion size. There was no consensus on dosimetric constraints, and some respondents reported cases of severe toxicity, particularly when treating the pretibial skin.

CONCLUSIONS: This pattern of care study suggests that skin brachytherapy can be a convenient and safe tool for treatment of BCC and cSCC. Prospective trials and the development of expert consensus guidelines would be beneficial for optimizing skin surface brachytherapy and reducing practice variation.

Keywords: Nonmelanoma skin cancer; Basal cell carcinoma; Squamous cell, carcinoma; brachytherapy; High dose rate; Electronic brachytherapy; Valencia applicator; Leipzig applicator; Ir-192

Introduction

Skin cancer is the most prevalent malignancy with an estimated incidence of more than two million cases in the United States alone (1). The vast majority of these

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are basal cell (BCC) and cutaneous squamous cell carcinomas (cSCC). Treatment approach is varied and includes surgical excision, cryosurgery, electrocautery, radiotherapy, topical chemotherapy, immune response modifiers, and photodynamic therapy. Although surgical excision is considered to be the gold standard for treatment in the United States, some patients may not be surgical candidates due to medical comorbidities, functional outcome, or personal preference. For these patients, radiation therapy has been an effective alternative with control rates of 75%−100% for early stage BCC/cSCC reported in the literature (2−6).

Radiation techniques for treatment of cutaneous malignancies are diverse. They include external photon beam, external electron beam, electronic brachytherapy, and radionuclide brachytherapy. Radiation delivery requires attention to target delineation, dose, fractionation, and delivery schedule. All these have an impact on probabilities of local control and complications.

External beam radiation therapy using standard fractionation remains the most common treatment modality for skin cancer. Nonetheless, the introduction of commercially available electronic brachytherapy units and tungsten-shielded applicators for remote after-loading technology has led to a rapid rise in utilization of skin surface brachytherapy for cutaneous malignancies. The ease of delivery in conjunction with favorable reimbursement has led to high rates of adoption in radiation oncology and dermatology offices and to a lesser extent in academic settings (7).

This positive trend is welcomed, as brachytherapy is an underutilized modality capable of elegant treatment delivery. The hypofractionation afforded by the superficial deposition of dose using this methodology has allowed delivery of radiation using fewer fractions with good cosmetic results (8−12). The primary challenge facing the field of skin surface brachytherapy is absence of prospective trials and clinical guidelines. This pattern of care study was conducted to understand and define the current practice for skin surface brachytherapy in both academic and community settings.

Methods and materials

The first and senior authors developed a 30-question electronic survey which was sent to clinician members of the American Brachytherapy Society (Supplement 1). The survey was hosted via a free online Adobe Forms Central application and was available for 1 month. The respondents were asked to provide details regarding their clinical practice and their approach to skin surface brachytherapy using eight common clinical scenarios. Survey results are summarized in this report. For calculations of EQD2, the linear quadratic equation was used with an α/β of 10 for both cutaneous SCC and BCC. Descriptive statistics and two-sided Student t test were used.

Results

Practice characteristics

Of the approximately 400 electronic invitations sent to ABS members, a total of 16 surveys were returned fully completed. One survey was returned incomplete and was ultimately excluded from the analysis after the responder failed to answer follow-up communication. Nearly all the respondents were based in the United States, whereas one was from Spain. Table 1 summarizes respondents' practice characteristics. The type of practice was evenly distributed between academic, hospital-based, and private settings. Aggregate experience varied from 8 to 1800 cases. Because of the large variation in practice experience, we separately

Table 1
Practice characteristics of the respondents

Characteristic	Number of respondents (%)
Type of practice	
Private practice	7 (44)
Hospital	6 (38)
Academic	3 (18)
Years in practice	
1−5	2 (13)
6−10	5 (31)
11−20	5 (31)
>20	4 (25)
Cases per year	
1−50	6 (38)
51−100	6 (38)
>100	4 (24)
Cases treated with brachytherapy during career	
1−50	6 (38)
51−100	1 (6)
101−1000	5 (31)
>1001	4 (25)
Years using skin surface brachytherapy	
1−3	6 (38)
4−5	2 (13)
6−10	5 (31)
>10	3 (19)
Top 2 reasons to choose brachytherapy over EBRT	
Shorter treatment course	13 (41)
Conformality of treatment when target is irregular or curved	11 (34)
Better cosmesis	4 (13)
Shallow dose deposition	2 (6)
Small target	1 (3)
Other	1 (3)
Methods of delivery	
Leipzig applicator	12 (75)
Multi-catheter flaps	11 (69)
Custom mold	12 (75)
Valencia applicator	8 (50)
Electronic brachytherapy	5 (31)
Interstitial	1 (6)
Percentage of patients treated with shielded applicators	
Shielded applicators	50% (median)
Surface molds	30% (median)

Note that some answer choices are not mutually exclusive.

examined the responses among practitioners with more experience (>100 cases during their career).

Treatment planning

Overall, survey answers did not significantly differ between seasoned practitioners and those with less experience ($p = 0.1539$). Most respondents preferred brachytherapy to external beam radiation because of shorter treatment course, conformality of treatment for irregular or curved targets, and shallow dose deposition. Common reasons for avoiding brachytherapy included tumor depth over 3 mm, perineural invasion, and previous radiation therapy. Shielded applicators were the most common device used, whereas a few respondents preferred custom molds. When practitioners chose to use surface molds, they cited ability to treat a large area and ability to cover a curved surface as the two most relevant reasons.

Respondents were asked to describe their treatment techniques and dosimetric considerations (Tables 2 and 3). Of the total, 60% routinely estimated lesion depth via ultrasound before initiating treatment. The median maximum depth of prescription was 5 mm (range, 1−8 mm). A majority reported placing catheters anywhere from 5−10 mm from the skin surface, and none placed catheters directly on the skin. Treatment margin on gross disease varied widely (range, 3−15 mm; median, 5 mm). When deciding on clinical target volume (CTV) margins, 70% of respondents reported treating wider margins based on histology.

Table 2
Details of treatment technique

Aspects of treatment planning	Number (%)	Number (%) among those who reported >100 cases in their career
Maximum depth of prescription		
1 mm	1 (6)	1 (11)
3 mm	2 (13)	1 (11)
4 mm	3 (19)	1 (11)
5 mm	8 (50)	4 (44)
7 mm	1 (6)	1 (11)
8 mm	1 (6)	1 (11)
Routine estimation of skin thickness using US or CT		
Yes	10 (63)	5 (56)
No	6 (37)	4 (44)
Typical margin		
Median	5 mm	5 mm
3 mm	1 (6)	1 (11)
4 mm	2 (13)	0
5 mm	9 (56)	6 (67)
7 mm	2 (13)	1 (11)
10 mm	1 (6)	0
15 mm	1 (6)	1 (11)
Variable margin based on histology		
Yes	11 (69)	7 (78)
No	5 (31)	2 (22)
Variable margin based on size		
Yes	11 (69)	5 (56)
No	5 (31)	4 (44)

Table 3
Dosimetric parameters used for plan evaluation

Dosimetric Parameter	Number of respondents endorsing parameter (%)	Number of respondents endorsing parameter (%) among those who reported >100 cases in their career
Max dose at the skin surface	13 (81)	7 (78)
Min dose to CTV	8 (50)	3 (33)
Depth of 90% isodose line	6 (38)	3 (33)
Min dose to skin surface	5 (31)	4 (44)
V150	4 (25)	2 (22)
D95	2 (13)	1 (11)
D100	2 (13)	2 (22)
V200	2 (13)	2 (22)
V120	1 (6)	1 (11)
D 2 cc	0	0
D 1 cc	0	0
D 0.1 cc	0	0

Indications for wider margins included squamous histology (41%) and diffuse morpheaform or other aggressive subtypes of BCC (18%) and recurrent disease (6%). Similarly, 65% respondents adjusted the CTV margin based on the size of the lesion. Several respondents suggested using National Comprehensive Cancer Network (NCCN) guideline definitions of low risk and high risk BCC and SCC for margin definitions.

Not all the respondents looked at dosimetric parameters when evaluating plans. This is understandable, as some of the respondents reported using only applicators where a simple calculation to depth suffices for treatment planning. Nonetheless, the ones who did routinely assess dosimetry predominantly evaluated maximum dose to skin and CTV coverage (Table 3). Maximum allowable dose to skin ranged between 125% and 150% (median 135%) of prescribed dose. CTV coverage parameters ranged between 90% and 100% (median, 95%).

Toxicities

Respondents were asked to describe cases of unexpected acute and late toxicity. Eight specifically mentioned cases of severe acute and late toxicity when targets were on the lower extremity, especially at the pretibial skin. One case was that of a patient who developed a nonhealing ulcer after developing lower extremity edema post-treatment due to other systemic causes. Three other respondents referred patients with nonhealing ulcers in the radiation field for hyperbaric oxygen.

Clinical scenarios

Eight clinical scenarios were devised to underline differences in dose and fractionation for commonly encountered situations (Table 4). Respondents were asked to provide their recommendation for a "nonmelanoma skin cancer lesion," without histology specification (BCC vs cSCC).

Table 4
Recommendations for dose and fractionation for various clinical scenarios

Respondent	0.5-cm nose	2-cm nose	2-cm neck	5 cm neck	2 cm pretibia	5 cm pretibia	1 cm periorbital	2 cm helix
1*	30/5	36/6	51/17	51/17	51/17	60/30	51/17	36/6
	twice a week	twice a week	daily	daily	daily	daily	daily	twice a week
2*	40/8	55/15	55/15	55/15	60/20	60/20	45/10	45/10
	twice a week	daily	daily	daily	daily	daily	daily	daily
3	42/7	40/8	42/7	40/10	40/10	40/10	42/7	42/7
	twice a week	twice a week	twice a week	twice a week	twice a week	twice a week	twice a week	twice a week
4*	40/8	40/8	40/8	40/8	36/8	36/8	40/8	40/8
	twice a week	twice a week	twice a week	twice a week	twice a week	twice a week	twice a week	twice a week
5	42/7	42/7	42/7	Conventional EBRT	Conventional EBRT	Conventional EBRT	42/7	Conventional EBRT
	every other day	every other day	every other day				every other day	
6	42/6	42/7	42/7	40/10	40/10	40/10	42/7	42/7
	every other day	every other day	every other day	every other day	twice a week	twice a week	every other day	every other day
7	40/8	45/10	40/8	60/30	45/10	60/30	45/10	40/8
	twice a week	twice a week	twice a week	daily	twice a week	daily	twice a week	twice a week
8*	40/8	40/8	40/8	40/8	40/8	40/8	40/8	40/8
	twice a week	twice a week	twice a week	twice a week	twice a week	twice a week	twice a week	twice a week
9*	42/6	35/10	35/10	45/10	35/10	45/10	42/6	35/10
	twice a week	twice a week	twice a week	twice a week	twice a week	twice a week	twice a week	twice a week
10*	42/6	42/6	42/6	40/8	39/6	40/10	39/6	39/6
	every other day	every other day	every other day	every other day	every other day	every other day	every other day	every other day
11*	50/20	51/17	51/17	51/17	50/20	50/20	50/20	50/20
	daily	4 times a week	4 times a week	4 times a week	daily	daily	daily	daily
12	42/6	48/12	48/12	64/32	48/12	64/32	48/12	48/12
	every other day	every other day	every other day	daily	every other day	daily	every other day	every other day
13	40/8	40/8	40/8	48/16	48/16	48/16	40/8	40/8
	twice a week	twice a week	twice a week	4 times a week	4 times a week	4 times a week	twice a week	twice a week
14	40/8	40/8	40/8	44/10	45/15	45/15	45/15	45/15
	twice a week	twice a week	twice a week	every other day	daily	daily	daily	daily
15*	39/6	44/8	39/6	44/8	45/10	40/10	39/6	45/10
	every other day	twice a week	every other day	every other day	twice a week	twice a week	every other day	twice a week
16	40/8	40/8	40/8	40/8	44/10	36/12	44/10	44/10
	twice a week	twice a week	twice a week	twice a week	twice a week	daily	twice a week	twice a week

Header designation refers to horizontal size of skin cancer and its location. Answers are shortened to Gy/number of fractions and schedule. Asterisk marks those practitioners who reported having treated at least 100 cases in their career.

In these scenarios, prescribed doses ranged from 30 Gy in five fractions to 64 Gy in 32 fractions (EQD2 40–65 Gy). All respondents except one were comfortable with large fraction sizes for perhaps the most common clinical scenario of a small lesion on the nose. There was a tendency to increase the number of fractions for larger targets, although one practitioner, who reported having treated at least 100 cases in their career, used the same fractionation regardless of anatomic location or lesion size. Approximately half of the respondents adjusted their dose and fractionation for lesions in the periorbital areas and on the ear when compared to lesions on the nose. There was nearly unanimous adjustment of dose and fractionation for targets on the pretibial skin, with 10 respondents (63%) using 2–3 Gy per fraction. It is important to note that the respondents avoided daily treatment schedules when using hypofractionation.

There was no consensus on dosimetric constraints, and nearly all respondents reported rare cases of severe toxicity, especially when treating the pretibial skin. When asked about indications for gentler fractionation schemes, large number of respondents reported targets on the lower extremities or larger CTV diameter. The cut point for changing fractionation varied widely with a median of 3 cm and range of 2–5 cm.

Discussion

The effects of ionizing radiation on the skin were among the first to be studied after the discovery of the therapeutic potential of X-rays. Because those initial experiments, the last century has seen several modalities of radiation used in the treatment of cutaneous malignances including Grenz rays, superficial, orthovoltage photons, megavoltage electrons, and brachytherapy. In more recent years, brachytherapy has seen increased interest because of the introduction of newer delivery systems such as electronic brachytherapy and high-dose-rate after-loading systems.

Brachytherapy is particularly elegant for the treatment of superficial malignancies. Unlike linear accelerator–based photon or electron beam radiation, it does not entail dose build up at the surface. Furthermore, rapid dose fall-off from the source spares connective tissue in the subcutaneous layer, allowing for safe hypofractionation. As the result, the course of treatment can be as short as five fractions, compared to a typical 12-to-35-fraction course with external beam approaches. One important caveat is that the shallow dose deposition can be a proverbial ‘‘double-edged sword’’ leading to a marginal miss at the deep aspect of the target in cases where true depth of invasion is underestimated on physical examination or by ultrasonography.

From a practical standpoint, daily set up with electronic brachytherapy or cup-shaped applicators obviates the need for bulky electron cones or skin collimation. Furthermore, skin brachytherapy has the advantage of greater patient convenience, comparable cosmesis, and perhaps decreased cost compared to external beam therapy (8, 10, 13, 14). A simple comparison of Medicare reimbursement rates for a 6-fraction single-channel high-dose-rate treatment and a 20-fraction electron beam course showed that brachytherapy was half as costly. We acknowledge that this advantage may vary with the number of fractions and channels used for brachytherapy.

Literature on definitive radiation treatment of cutaneous BCC and cSCC is limited. Randomized, prospective comparisons of surgery and radiation consist of a single study of BCC published in 1997 (15). Although this study showed a local control and cosmetic advantage to surgery, its relevance to contemporary surface brachytherapy is restricted by its allowance of multiple radiation modalities (conventional external beam therapy, interstitial brachytherapy, surface brachytherapy) and dated techniques for treatment planning. The current evidence for modern brachytherapy techniques mainly consists of case reports and retrospective series of electronic brachytherapy and radioisotope-based brachytherapy systems. These recent studies tended to have more strict patient selection criteria compared to older data on external beam radiotherapy. Coupled with a rather short follow-up, it is not surprising that they report control rates at or beyond 95% in tandem with good to excellent cosmesis (11–14, 16, 17). Only prospective phase III trials comparing different radiation modalities or comparing variations (i.e., dose, fraction, or margin) within a particular technique will be able to establish difference in clinical effectiveness.

Given this conspicuous absence of prospective trials and guidelines at the time of our survey, practitioners have based their practice of skin surface brachytherapy on their own individual experience and training, vendor courses, and limited retrospective literature. This survey identifies the resultant convergences and divergences of opinion in regard to this technique.

One notable convergence is that most respondents were comfortable using hypofractionation with fractions as high as 7 Gy. In fact, the ability to hypofractionate was the most common reason for using skin surface brachytherapy in favor of other modalities, and survey respondents were generally not dissuaded from using hypofractionation when treating skin over cartilage, such as at the helix and nasal ala. An important exception is that hypofractionation at the pretibial location did engender concern among some respondents. Several reported severe side-effects in this region which necessitated advanced wound care and hyperbaric oxygen. Most respondents recommended using 2–3 Gy fractions in this sensitive area. We do not exclude the possibility that morbidity of brachytherapy is comparable to that of conventionally fractionated electron beam therapy, but practitioners naturally tend to fall back on the ‘‘tried and true’’ approach when treating areas with inherently high risk of radiation complications.

Another convergence was that most practitioners limited their use of brachytherapy to treatment targets within a

depth of 5 mm from the skin surface. This similarity in practice likely reflects acknowledgment that the rapid dose fall-off in brachytherapy may not adequately reach deep lesions. Interestingly, this limitation of brachytherapy can be circumvented by first de-bulking exophytic tumors before brachytherapy. Doggett *et al.* reported a 0.7% local recurrence at 12.5 months in 524 lesions treated in this fashion (12).

Our analysis demonstrated significant differences among respondents for indications for skin surface brachytherapy, its technical aspects, dosimetric evaluation, and dose/fractionation. These findings are congruent with the recent surveys of Canadian and UK radiation practices: Rose *et al.* reported significant heterogeneity in dose and fractionation for skin surface brachytherapy in Canada despite general agreement on indications for treatment (18). Likewise, a practice survey of external beam radiotherapy in the United Kingdom reported 24 different fractionation schedules and a large variation in biologically effective dose (19). In our study, the degree to which practices diverged is demonstrated by the responses to specific clinical scenarios (Table 4). This diversity of clinical practice, which is unusual in radiation oncology, speaks to a need to better define practice guidelines informed by prospective studies.

Fortunately, there are several single-arm prospective studies that are ongoing and/or in development, such as NCT02131805 (A Pilot Study of Electronic Skin Surface Brachytherapy for Cutaneous Basal Cell and Squamous Cell Carcinoma led by Memorial Sloan Kettering and Lynn Cancer Institute) and NCT01016899 (Electronic Brachytherapy for the Treatment of NMSC sponsored by Xoft, Inc). We also encourage initiation of randomized prospective trials between surgical management and definitive radiation to firmly establish the therapeutic efficacy of skin brachytherapy. Additionally, enhanced clinical practice guidelines, even if initially based on expert opinion, can also help standardize practice and provide a foundation for greater adoption of skin brachytherapy in everyday radiation oncology practice. In that vein, we are pleased that the American Brachytherapy Society issued a working group report on dosimetry and clinical aspects of surface brachytherapy in November 2015 after this survey was conducted (20). We hope that this document acts as a platform for standardizing guidelines as the results of prospective trials become available. Our hope is that prospective trials and evidence-based guidelines will help define treatment pathways that maximize patient outcomes and make it easier to analyze clinical outcomes in the future. An added benefit is that they may also inform value-conscious strategies that lessen the cost burden of treating skin cancer (21).

This survey study has significant limitations. First, although some of the variation in skin brachytherapy practice can be attributed to the lack of standardized guidelines for this technique, it is also possible that the brevity of the clinical description and absence of histology specification left some details to be inferred. Similarly, clinical case photographs may have reduced the response variation. A second limitation is the low response rate among the initially surveyed ABS members, although this may reflect that most ABS members do not use this technology on a regular basis. It is conceivable that the preference for brachytherapy is exaggerated in this sample due to selection bias. Future studies surveying a larger, more diverse group of respondents such as the American Society for Radiation Oncology or the American Academy of Dermatology may result in different conclusions. Finally, some of the divergences between practices may reflect differences in the volume of cases (a third of respondents treated fewer than 50 cases per year), and that these differences in practice may converge as newer centers learned from their initial outcomes.

In summary, the findings of these patterns of care survey confirm that skin brachytherapy holds great potential for patients with nonmelanoma skin cancer insofar as this technique allows for a convenient and safe hypofractionated treatment schedule for patients. Although practitioners agree on certain core principles, significant variation exists with regard to treatment planning and delivery. In order for this modality to become a mainstream treatment, well-designed prospective studies would be beneficial for optimizing safety and efficacy.

Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.brachy.2016.10.006.

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