ORIGINAL RESEARCH

The Treatment of Non-Melanoma Skin Cancer with Image-Guided Superficial Radiation Therapy: An Analysis of 2917 Invasive and In Situ Keratinocytic Carcinoma Lesions

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ABSTRACT

Introduction: An image-guided form of superficial ionizing radiation therapy (IGSRT) is becoming a commonly used alternative to surgery for non-melanoma skin cancer (NMSC). However, there is little literature evidence evaluating the efficacy and safety of this approach. This study evaluates the efficacy and safety of IGSRT in treating a large number of patients with NMSC.

Methods: The medical records of 1632 stage 0–II patients with 2917 invasive and in situ NMSC lesions treated from years 2017 to 2020 were reviewed. No patients had clinical evidence of regional lymph node or distant disease at presentation.

Results: Treatment, guided by pre-treatment ultrasound imaging to adjust radiation energy and dose, combined with a fractionation treatment schedule of 20 or more treatment fractions, was safe and well tolerated. Of 2917 NMSC lesions treated, local tumor control was achieved in 2897 lesions, representing a 99.3% rate of control.

Conclusion: IGSRT should be considered as a first-line option for treating NMSC tumors in suitable early stage patients. Cure rates observed in this initial period of follow-up are similar, and potentially superior with further follow-up, to traditional superficial radiation therapy (SRT) and surgical options.

Keywords: Basal cell carcinoma; Image-guided superficial radiation therapy; Non-melanoma skin cancer; Squamous cell carcinoma; Squamous cell carcinoma in situ

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Key Summary Points

Image Guided Superficial Radiation Therapy (IGSRT) was safe and well tolerated in this study, involving 1632 patients with non-melanoma skin cancer (NMSC). Of 2917 NMSC lesions treated, local tumor control was achieved in 2897 lesions, representing a 99.3% rate of control.

IGSRT should be considered as a first-line option for treating stage 0–II NMSC lesions in suitable patients, especially those who are not candidates for surgery or who decline surgery.

NMSC is a highly prevalent condition, with an estimated annual incidence in the U.S. of 5.5 million tumors in 2012.

This study presents a retrospective evaluation of efficacy and safety of image-guided superficial radiotherapy, a nonsurgical treatment option, in 2917 NMSC lesions (1632 patients).

Treatment with IGSRT resulted in local tumor control in 2897 lesions, representing a 99.3% rate of control.

IGSRT was safe and well-tolerated in this study.

These results suggest IGSRT should be considered as a first-line option for treating NMSC in suitable patients.

DIGITAL FEATURES

This article is published with digital features, including a summary slide, to facilitate understanding of the article. To view digital features for this article go to https://doi.org/10.6084/m9.figshare.13521686.

INTRODUCTION

Keratinocytic carcinoma (KC) of the skin, as a subgroup of non-melanoma skin cancer (NMSC), comprises basal cell carcinoma (BCC) and invasive squamous cell carcinoma (SCC). NMSC is a highly prevalent and rapidly increasing condition, with an estimated annual 2012 incidence in the USA of 5.5 million tumors in 3.3 million affected patients, an increase of 35% from 2006 [1]. The condition can cause significant morbidity.

Various therapies are considered standard of care for treatment of NMSC, depending on tumor characteristics and clinician preference. Tumors that are small, superficial, and otherwise considered low risk are often amenable to cryotherapy, electrodesiccation and curettage, topical chemotherapy or immunomodulation, photodynamic therapy, or standard surgical excision. Other, less commonly used treatments for NMSC include electron-beam radiotherapy (EBRT) and electronic brachytherapy (EBX). Mohs micrographic surgery (MMS) is appropriate for cases of NMSC that exhibit high-risk histopathologic features, those arising on critical anatomic sites, recurrent tumors, and tumors in immunocompromised patients [2]. Many authors currently consider MMS to be the most effective modality to treat NMSC because of its high cure rate and tissue-sparing properties [3–8].

Therapy with superficial radiation therapy (SRT) is another long-established and effective treatment for NMSC. Patient outcomes with radiation therapy, whether using superficial orthovoltage X-rays or EBX, are comparable to MMS, with patients experiencing low rates of complication and favorable cosmetic results [9]. Advantages of SRT include the lack of pain and scarring associated with surgery. However, older published series indicate an overall lower rate of cure compared with MMS; for example, the 2000 study by Silva et al. reported actuarial 2-year and 5-year local control rates of 86.6% and 79.2%, respectively [10]. Accordingly, the American Academy of Dermatology currently recommends SRT for NMSC mainly when surgery is infeasible or contraindicated (e.g.,

patients with poor general health, bleeding tendency, etc.) [11]. However, more recent studies of patients treated in the outpatient setting have shown a higher rate of control of NMSC [12, 13]. The 2020 National Comprehensive Cancer Network (NCCN) Guideline states that for basal cell and squamous cell skin cancers, "[s]urgical approaches often offer the most effective and efficient means for accomplishing cure, but considerations of function, cosmesis, patient preference, and performance status may lead to choosing RT [radiation therapy] as primary treatment in order to achieve optimal overall results" [14, 15].

There are several potential explanations for the discrepancies in the published literature regarding the efficacy of SRT to treat NMSC. First, the setting in which SRT is administered to treat NMSC has changed over the years. Many decades ago, dermatologists often provided SRT in their offices, but this practice pattern changed to the point where SRT came to be rarely offered in the outpatient dermatology setting. While there has subsequently been a substantial resurgence in the use of SRT in dermatologist's offices in the USA, it remains less common today than in past times [16]. Thus, much of the SRT literature concerns the particular patient population referred out to radiation oncologists; that is, when the patient presents with NMSC considered not amenable to treatment by dermatologists [10]. This circumstance introduces potential selection bias, in that NMSC cases referred for SRT may have an increased proportion of larger or more aggressive tumors with a higher risk of recurrence [16–18].

Change in the technique of SRT may lead to further developments in its demonstrated efficacy to treat NMSC. Recent years have seen technical advances in the delivery of SRT, including image-guided approaches made more readily available through inclusion of high-frequency ultrasound capabilities with SRT delivery technology [19]. An ultrasound unit specifically designed to detect dermatologic structures using frequencies of 22 MHz (which is ideal for visualizing superficial skin depths of 0–6 mm) has been integrated with the commercial IGSRT unit (Sensus Healthcare). This allowed generally easy determination and verification of the tumor depth as well as lateral extent of the lesion. Knowing the depth of the tumor and correlating with the percentage depth dose (PDD) tables of the IGSRT machine from the manufacturer allow the optimal choice of energy (50, 70, or 100 kV) to be selected before and during the course of treatment, allowing adjustments to be performed accordingly. This paper reports experience with an image-guided form of SRT (IGSRT) in a large group of patients with NMSC for whom IGSRT was used. The study cohort represents a subset of data (Texas location only) presented by Yu et al. at the May 2020 Annual Meeting of the Society for Investigative Dermatology (SID) [20]. This data was combined with data collected and analyzed from similarly treated NMSC lesions in South Carolina and two sites in Indiana (Yu et al. manuscripts in preparation). Our findings indicate that application of IGSRT results in an excellent rate of cure, and that IGSRT is a highly effective first-line treatment method for NMSC.

METHODS

Patients

A direct chart analysis of 1632 patients with a histopathologic diagnosis of NMSC treated with IGSRT was performed. Diagnosis and staging of lesions had been completed prior to treatment on the basis of a tissue biopsy performed by a dermatologist at each site. The dermatologist referred patients for IGSRT on the basis of patient and lesion characteristics, which included pathologic confirmation of SCC, BCC, or SCC in situ (SCCIS), the latter most often with suspicion of invasion or full-thickness atypia. The ultimate decision of referral for IGSRT was determined by individual providers. Treatment data and lesion characteristics at the time of treatment were collected retrospectively. The medical records of 702 female and 930 male patients (mean age 73.2 [SD ± 10.93] years) with 2917 lesions treated from years 2017 to 2020 were retrospectively reviewed. Every lesion was considered as an independent cancer

lesion. All patients included in this analysis were at stage grouping 0, I, or II (i.e., Tis, T1, or T2 without clinical evidence of regional lymph node or distant disease (N0 and M0)) at presentation, based on the American Joint Committee on Cancer (AJCC) 8th Ed. Cancer Staging Manual [21]. While AJCC 8th Ed. staging pertained to cutaneous SCC of the head and neck, these same criteria for staging were applied in this study to all BCC, SCC, and SCCIS lesions throughout the entire body to be consistent. Follow-up interval and data were initially gathered manually from written and electronic medical records. Subsequent updates to patient follow-up intervals were accessed electronically with the assistance of algorithmic analysis provided by a healthcare data company (Sympto Health, Inc.).

The authors adhered to the principles established in the Federal Policy for the Protection of Human Subjects, referred to as the "Common Rule," as well as the pertinent sections of the Helsinki Declaration and its amendments. The data have been de-identified for use in this study. All patients gave informed consent before treatment.

Treatment Guidelines

All lesions received IGSRT, consisting of energies of 50, 70, or 100 kV based on a standardized, proprietary protocol developed by a board-certified radiation oncologist in conjunction with a board-certified dermatological surgeon. There are a wide range of dose regimens to choose from that have been established over decades of radiation therapy treatment depending on situations, ranging from total fractions of less than 5 to more than 35 and daily doses ranging from 120 cGy (twice a day) to 2250 cGy [22, 23]. For curative treatments of all tumors (not just skin) the most common present-day regimen employed by radiation oncologists is 180–200 cGy given daily five times per week for 30–36 treatments to a dose of 5400–7200 cGy.

Skin treatments involving small fields are amenable to a hypofractionated regimen of 2–4 times per week at higher "daily" fractions of (generally) 220–400 cGy. A common regimen amongst radiation oncologists experienced with head, neck, and skin cancer treatments uses 20 fractions of 250–260 cGy.[1] This "middle of the road" regimen was felt by some radiation oncologists/dermatologists to deliver the optimum in cure, cosmesis, and convenience while minimizing complications (Yu et al. Annual SID Meeting, May 2020). The specific treatment prescription for each patient was determined by the treating clinician not involved with this study, which is a retrospective, observational review of this "real-world" evidence. A mean total treatment dose of 5219.9 (SD ± 224.47) cGy was given in the entire group. The energy administered to each tumor was selected on the basis of that particular tumor's characteristics, including anatomic location, histogenetic type, lesion depth, and skin curvature. In 2017 and 2018, the treatment guideline in use recommended their "most common protocol" of 255 cGy × 20 total fractions with either 50 or 70 kV (based on lesion depth less than or greater than 1.5 mm, respectively) given three times a week. Tumors less than 2 cm or greater than 4 cm were treated four times per week at 245 cGy or 240 cGy for 20 or 25 fractions, respectively. Lesions below the knee were optionally treated five times a week at 180 cGy for 30 fractions.

Starting in 2019, a more detailed proprietary protocol with a new guidance table developed by Dermatology and Radiation Oncology (Ladd–Yu table) was employed incorporating specific TDF[2]/dose/fractionation/energy recommendations based on ultrasound depth and tumor type. This modified the "most common

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[1] The IGSRT machine is not designed to deliver doses based on centiGray but instead based on time (minutes) the beam is turned on to 2 decimal points. For example, a field of 2 cm diameter giving 70 kV for 0.42 min will deliver a dose of 271.74 cGy, whereas a time of 0.43 min would deliver a dose of 278.21 cGy. Therefore, it is nearly impossible for a guideline protocol to mandate an exact dose per fraction of, say, 255.0 cGy but rather, depending on the "beam on time," the treatment dose that comes closest to that dose is generally selected.

[2] Time dose fractionation (TDF) is a useful system of tables representing biologic equivalent doses often used by radiation oncologists/therapeutic radiologists specifically for treatment of skin cancers with different fractionation schedules.

protocol" to a fractionation dose range of 245–279 cGy for 20 fractions three or four times per week to achieve a therapeutic biological dose range of 90–99 or greater TDF using 50, 70, or 100 kV energy (see Table S1 in the electronic supplementary material). Larger, deeper, and high-risk legions were recommended higher doses per fraction and/or more fractions (greater than or equal to 22) to achieve higher biologically effective doses. Providers/therapists were encouraged to consult with the national radiation oncologist and/or chief medical officer during weekly grand rounds or through email discussions in these situations. These treatment protocols were initially developed by a board-certified radiation oncologist and further refined by a dermatologic surgeon (Dr. Ladd) in collaboration with another board certified radiation oncologist (Dr. Yu) on the basis of sound radiation and dermatologic treatment principles and generally conform to the biological dose ranges suggested by the NCCN for cutaneous BCC and SCC [14, 15]. In retrospect, the independently derived hypofractionated regimens are consistent with current ASTRO Clinical Practice Guideline for cutaneous SCC and BCC [24]. Pre-treatment ultrasound imaging was performed prior to delivery of each treatment fraction to evaluate lesion depth and configuration. Adjustments to prescribed energy and daily dose were made on the basis of ultrasound findings to minimize radiation exposure, optimize clinical outcomes, and reduce potential toxicity. The percentage changes in energy (mixed energies) during the course of treatment were collected to reflect the impact of image guidance on the treatment.

The treatment fractions were administered by a radiation therapist at a frequency of 3, 4, or 5 times per week, based on the discretion of the treating practitioner and in accordance with standardized treatment protocols as discussed above which are consistent with typical radiation oncology recommendations for treatment of small early stage neoplasms in curative, non-palliative cases where cosmesis is of importance. Patients treated with a range of 20–30 fractions were included. Patients falling out of this guideline range were excluded from this analysis. Medical physics consultations were also provided during the course of treatment. A median of 20 fractions were delivered, and the mean follow-up was 69.8 weeks (range 0–220.9 weeks).

Study Endpoints

The endpoints include the absence of local evidence of disease at follow-up visits and Radiation Treatment Oncology Group (RTOG) toxicity, including the most common toxicities and their severity [25]. RTOG toxicity was prospectively documented in the charts routinely after every 5-fraction increment and these findings were extracted and documented as the highest RTOG grade throughout the entire course of treatment.

Statistical Analysis

Demographic and baseline characteristics, original lesion depth, tumor staging, treatment information, lesion response, survival status, and RTOG toxicity levels were summarized descriptively. All lesions meeting inclusion criteria were included and summaries provided by patient and lesion. The duration of follow-up was summarized and defined as the date of last follow-up minus date of completion plus 1 day and then converted to both weeks and months.

Summary statistics for continuous outcomes included the number of observations (n), mean, standard deviation, minimum, median, and maximum while categorical outcomes were summarized with frequency and percentages. Missing data were not imputed and Fisher's exact tests were performed to evaluate significant differences between histologies. SAS v9.4 was used for all analyses.

RESULTS

A total of 2917 NMSC lesions treated with IGSRT from 2017 to 2020, consisting of 1406 BCC, 920 SCC, and 603 SCCIS lesions (certain lesions had combinations of two or more of these histologies), were retrospectively reviewed. Clinical efficacy was evaluated in a

Table 1 Anatomic distribution of NMSC lesions

Head and neck (H&N)	1692/2917 (58.0%)
H&N sublocation[a]	
Ear	270/2917 (9.3%)
Cheek	403/2917 (13.8%)
Nose	479/2917 (16.4%)
Cutaneous lip	71/2917 (2.4%)
Mucosal lip	10/2917 (0.3%)
Forehead	265/2917 (9.1%)
Temple	69/2917 (2.4%)
Neck	110/2917 (3.8%)
Extremities	615/2917 (21.1%)
Trunk	182/2917 (6.2%)
Hand	140/2917 (4.8%)
Back	128/2917 (4.4%)
Shoulder	86/2917 (2.9%)
Chest	81/2917 (2.8%)

Lesion locations not exclusive

[a] Other H&N sublocations = 15

Table 2 Cancer types and initial lesion size

Cancer types[a]	n = 2917
BCC	1406/2917 (48.2%)
SCC	920/2917 (31.5%)
SCCIS	603/2917 (20.7%)
Lesion diameter (cm) at start	n = 2892
Mean ± SD	1.2 ± 0.65
Range	0.0–5.5
Median	1.0
BCC lesion depth (mm) at start	n = 1303
Mean ± SD	1.2 ± 0.52
Range	0.0–4.8
Median	1.2
SCC lesion depth (mm) at start	n = 855
Mean ± SD	1.2 ± 0.60
Range	0.0–4.4
Median	1.1
SCCIS lesion depth (mm) at start	n = 530
Mean ± SD	1.0 ± 0.41
Range	0.0–3.4
Median	0.9

[a] Certain lesions had combinations of multiple histologies

total of 1632 patients. Patients were predominantly men (57%). The mean age of patients was 73.2 (SD ± 10.93) with the range from 31.8 to 101.4 when they received the first IGSRT.

Table 1 demonstrates the anatomic distribution of NMSC lesions. The most common sites of the lesions were head and neck as a group (58.0%), extremities (21.1%), followed by the head and neck subgroups nose (16.4%) and cheek (13.8%).

Table 2 demonstrates cancer cell types and initial lesion size at initiation of therapy. BCC (48.2%) and SCC (31.5%) were more common than SCCIS (20.7%). The mean diameter of measured lesions was 1.2 cm (SD ± 0.65), ranging from 0.0 to 5.5 cm. The mean depth was 1.2 mm (SD ± 0.52) for BCC, 1.2 mm (SD ± 0.60) for SCC, and 1.0 mm (SD ± 0.41) for SCCIS.

Table 3 shows lesions by diameter and histology. Of note, eight lesions greater than or equal to 4 cm were all SCCIS.

Table 4 summarizes the total number of treatments, total treatment dose, duration of treatment, and follow-up interval. The mean total number of fractions was 20.1 (SD ± 0.71) with the range from 20 to 30. The mean total treatment dose was 5219.9 cGy (SD ± 224.47), with the range from 3716.0 to 7363.7 cGy. All lesions were treated with energies ranging from 50 to 100 kV. The majority of these lesions were treated for 6–7 weeks and followed for a mean of approximately 69.8 weeks.

Among 1632 patients, 1612 patients (98.8%) did not have evidence of disease at their last follow-up visit, and 20 patients (1.2%) had evidence of disease at their last follow-up visit. Specific to individual lesions, of the 2917 lesions that underwent IGSRT treatment, 2897 lesions (99.3%) did not have evidence of disease

Table 3 Diameter distribution of NMSC lesions

Diameter[a]	BCC and SCC	BCC only	SCC only	SCCIS only	Total
0 to < 2 cm	8	1167	752	516	2427
2 to < 4 cm	3	236	164	60	457
≥ 4 cm	0	0	0	8	8

[a] Missing values = 25

Table 4 Treatment fractions, dose, duration, and follow-up interval

Characteristic	Statistic	(n = 2917)
Total number of treatments	N	2917
	Mean ± SD	20.1 ± 0.71
	Range	20.0 to 30.0
	Median	20.0
Total treatment dose (cGy)	N	2917
	Mean ± SD	5219.9 ± 224.47
	Range	3716.0 to 7363.7
	Median	5188.4
Duration of treatment (weeks)	N	2917
	Mean ± SD	7.1 ± 1.55
	Range	4.0–22.6
	Median	6.7
Duration of follow-up (weeks)	N	2917
	Mean ± SD	69.8 ± 54.62
	Range	0.0–220.9
	Median	63.1

at their last follow-up visit. There were 20 lesions (0.7%) that did not respond completely to IGSRT or recurred.

Among 1632 patients, 1591 patients (97.5%) were alive as of October 2020 and 41 patients (2.5%) had died. All deaths were deemed unrelated to the treatment of NMSC by IGSRT. This death rate is not substantially different from the general population in the same age group [26].

Table 5 demonstrates the treatment by energy. Of note, 847 lesions were treated with a mix of two or more energies, representing 29% of the lesions.

Table 6 summarizes the safety results by lesion. Among 2177 lesions with RTOG toxicity grade data available, only 20 lesions (0.9%) were RTOG grade 3 or 4 in severity.

Subgroup Analysis

All Lesions with More Than 12 Months of Follow-up

The cohort with greater than 12 months of follow-up (mean 107.7 ± 41.31 weekly) was analyzed (1639 lesions). There were no substantial

Table 5 NMSC lesion distribution by energy

Energy (kV)	BCC only	SCC only	SCCIS only	Combined BCC and SCC	Number of lesions[a]
50	818	683	554	10	2165
70	828	524	124	4	1480
100	50	64	0	0	114
Mixed	400	364	80	3	847

[a] Energy classification not exclusive

Table 6 Safety—by lesion

Characteristic	Grade	Description	(*n* = 2177)
Highest RTOG toxicity grade	1	Follicular, faint, or dull erythema; epilation; dry desquamation; decreased sweating	1717/2177 (78.9%)
	2	Tender or bright erythema, patchy moist desquamation; moderate edema	440/2177 (20.2%)
	3	Confluent, moist desquamation other than skin folds; pitting edema	16/2177 (0.7%)
	4	Ulceration, hemorrhage, necrosis	4/2177 (0.2%)

RTOG Radiation Treatment Oncology Group

differences (greater than 5%) in this cohort compared to the entire group in terms of age, gender, age at first treatment, tumor location, size of lesion, and tumor stage. This subgroup had 5.8% fewer BCCs (42.4%) than the entire group, where BCC comprised 48.2% of cases. In this cohort, the median of treatments remained at 20 with a mean treatment dose of 5175 cGy (SD ± 215.80) with a range of 3716.0–6797.7 cGy. While the percentage of mixed energy use remained the same at 29%, this subgroup cohort had approximately 10% higher utilization at 50 kV energy (84.1%) compared to the entire group (74.2%). Use of 70 kV and 100 kV in this subgroup was 43.2% and 1.3% compared to the entire group at 50.7% and 3.9%, respectively. The percentage of disease control by lesion was essentially identical in this subgroup compared to the entire group (1647 of 1659 (99.3%) vs 2897 of 2917 (99.3%) lesion control). Survival percentages (again unrelated to tumor control) were similar at 97.6% (872 of 893) vs 97.5% (1591 of 1632). RTOG lesion toxicity was similar with less than 2% difference at every grade level.

Subgroup of All BCC and SCC Lesions Excluding SCCIS with More Than 12 Months Follow-up

We ascertained the results where SCCIS (stage 0) lesions were eliminated and found that the entire (invasive cancer only) group had essentially the same tumor response by lesions (99.2%). In this invasive BCC/SCC-only subgroup with follow-up greater than 12 months, the results were virtually unchanged with 751 of 761 (98.7%) patients and 1232 of 1242 (99.2%) lesions controlled. Lesion size as well as treatment doses and number of treatments were chiefly unchanged across the board for all subgroups (Table 7).

DISCUSSION

Efficacy

The present study documents the results of one of the largest multi-institutional studies of SRT for the treatment with curative intent of primary NMSC of the skin. Of 1632 patients with

Table 7 Control rates by tumor type and length of follow-up	All	All > 12 months	SCCIS	SCCIS > 12 months	Combined BCC + SCC	Combined BCC + SCC > 12 months
No. of lesions	2917	1659	602	417	2315	1242
Mean lesion diameter (cm)	1.2 ± 0.65	1.2 ± 0.60	1.2 ± 0.66	1.2 ± 0.61	1.2 ± 0.64	1.2 ± 0.59
Mean no. of treatments	20.1	20.1	20.1	20.1	20.2	20.1
Mean total treatment dose	5220.0	5175.0	5162.1	5142.9	5235.0	5185.7
Mean follow-up interval (weeks)	69.8	107.7	87.9	117.7	65.1	104.3
Absolute lesion control (%)	99.3	99.3	99.7	99.5	99.2	99.2

NMSC treated, complete eradication of the tumor was achieved in all but 20 patients, representing a 98.8% rate of control of the malignancy at the patient level. It should be noted that the control rate by patient indeed underestimates the actual control rate as many patients have more than one lesion that was treated, making the denominator lower in calculations. In fact, the 20 patients with failures had a total of 66 lesions that were treated synchronously or metachronously. A more accurate measure of efficacy of this modality is control rate by lesion. Of 2917 NMSC lesions treated, local tumor control was achieved in 2897 lesions, representing a 99.3% rate of control. Because 58.0% of the NMSC lesions treated with IGSRT were located on the anatomically and cosmetically sensitive region of the head and neck, the tissue-sparing property of IGSRT is notable.

These results, while observed with approximately 55% of patients having follow-up for 12 months or more, appear at this time to be at least consistent with the results of standard surgical and nonsurgical modalities used to treat NMSC. Specifically, the finding of a complete lesion response rate of 99.3% on early follow-up for IGSRT compares favorably with that of a study of SRT by Hernández-Machin et al., reporting that SRT treatment of 710 patients led to 5-year cure rates of 94.4% for BCC and 92.7% for SCC, respectively. The authors concluded that SRT was effective for BCC and SCC and could be a suitable first option in many cases [12]. The response rate observed in our study cohort also seems consistent with and, with further follow-up, has the potential to exceed that reported in a study of 1149 patients by Cognetta et al., who found that SRT-treated patients had mean cumulative recurrence rates for BCC of 2.0% and 4.2%, and for SCC of 1.8% and 5.8%, at 2 and 5 years, respectively [13]. The findings of this analysis are in concordance with the previous conclusions presented by Yu et al., with this analysis of the IGSRT data subset using separate statistical software (SAS) by an outside third-party data analysis company (Summit Analytical). A limitation of the results presented here is the shorter period of follow-up (mean follow-up of

69.8 ± 54.62 weeks) compared to these earlier evaluations of SRT. Continued follow-up with these patients to 2 and 5 years is expected to yield additional observations relevant to the use of IGSRT.

In total, 1.2% ($n = 20$) of our patients, representing 0.7% ($n = 20$) of NMSC lesions, failed to achieve local tumor control with IGSRT. An evaluation of demographic and lesion characteristics for these patients was performed to examine any potential commonalities, including histopathology, lesion size and location, and patient demographics. This evaluation did not identify any significant predictor for patient non-responsiveness to IGSRT at this time. We observed that the non-response rate for SCCIS was 0.3% ($n = 2$) versus that for BCC ($n = 13$, 0.9%) versus SCC ($n = 5$, 0.6%). There was no significant difference in control rates between histologies ($p > 0.05$) by Fisher's exact tests. We feel that an explanation of this non-significant difference between differing histologies may, in part, be due to the uniformly excellent control rate achieved in all subgroups with this IGSRT treatment. This suggests that IGSRT is effective in all subsets of NMSC on early follow-up. If this trend continues, a potential advantage of IGSRT in treatment of SCC over other older SRT techniques and MMS may become apparent with longer follow-up. In addition, 41 patients died during the course of the study. These deaths were determined not to be related to their NMSC treatment and had no impact on local control in this study. Indeed, NMSC are generally considered nonfatal, highly curable with rare metastases, and low recurrence with limited impact on mortality and morbidity [27, 28].

Recent studies of the effectiveness of MMS observed 5-year local control rates of 99% and 92–99% for primary BCC and SCC, respectively; the corresponding rates for recurrent BCC and SCC treated with MMS are 90–93% and 90%, respectively [3]. Comparison of the results of this study with those achievable using surgical therapies, such as MMS, may be limited. MMS is indicated for higher-risk NMSC lesions, and situations based on expert opinion, smaller lesions and/or lower risk lesions with cosmetic or functional significance as well [2, 29].

In this study, IGSRT was administered to a range of tumor types and sizes, not only high-risk lesions. It is notable, however, that the median tumor diameter in this study was 1.0 cm, with an upper diameter of 5.5 cm. This indicates that most of the NMSC lesions treated in this study were clinically significant tumors that would have required substantial excisions to achieve surgical eradication—not minute, easily curable lesions. While the results of this retrospective review of IGSRT patients demonstrate a consistent local tumor control rate in a limited follow-up period, retrospective comparisons of matched cohorts or prospective trials with IGSRT given in this manner with further follow-up for additional years would be helpful to evaluate any differences observed in IGSRT and MMS outcomes in the treatment of NMSC. A prospective randomized trial comparing IGSRT vs MMS would provide an ideal comparison; however, ethically and practically, it may prove difficult to conduct a study randomizing patients to a surgical vs non-surgical modality. In this study cohort, patients were given the option of surgical versus non-surgical IGSRT options and they chose the non-surgical method for various reasons that were not documented or extracted. Presumably, many patients may have opted for IGSRT to avoid the pain, scarring, and risk of infection or bleeding that may be associated with surgery.

Absolute and relative contraindications of IGSRT include invasion of underlying bone or muscle, thickness (greater than 6 mm) that cannot be debulked, previous irradiation of the same site, ataxia telangiectasia, active connective tissue disease, active or uncontrolled lupus or rheumatologic conditions, concomitant administration of radiation sensitizing chemotherapy (i.e., doxorubicin), T4 or node positive status, amongst others.

The high rate of local tumor control suggests that the use of daily pre-treatment lesion ultrasound imaging and daily evaluation of tumor depth can improve delivery of the optimal radiation dose and energy over a fractionated treatment scheme. In this study, adjustments to the energy were typically performed after the 5th, 10th, or 15th treatments on the basis of review of the ultrasound depth by the

practitioner. In certain circumstances, a significant change in tumor depth can be detected from one fraction to another, depending on tumor progression or external factors (i.e., bleeding, injury, excoriation, scab formation, etc.) which can prompt the radiation therapist to alert the provider to change the energy in order to cover the entirety of the new tumor configuration accordingly. Thus, pre-treatment ultrasound is reasonable and recommended for this purpose, in addition to daily verification/ localization of the tumor. Indeed, 29% of the lesions treated utilized multiple energies, potentially due in part to the change in imaging characteristics (depth) encountered. Limitations of the ultrasound include that it cannot detect tumor deeper than 6 mm (though tumors invading beyond this depth are contraindicated for treatment with IGSRT). Additionally, ultrasound imaging is difficult to attain if the surface is irregular or actively bleeding, which does not allow adequate contact of the probe with the skin. Further study is warranted to evaluate the impact of pre-treatment ultrasound imaging on SRT efficacy, but an improvement in SRT efficacy with image guidance would be consistent with general principles and published results in radiation treatments at other sites of cancer that utilize image guidance and planning [30–32].

Safety

IGSRT was generally well tolerated and safe. Typical side effects of radiation to the skin, such as erythema, hyperpigmentation, dryness, edema, etc., consistent with historical SRT treatments were seen. RTOG toxicity grades were recorded for 2177 (74.6%) of lesions treated.[3] Among 2177 lesions, grade 3 and grade 4 toxicities were documented in only 16 (0.5%) and 4 (0.1%) lesions, respectively. This overall low level of toxicity is in accordance with prior literature indicating that radiation therapy for NMSC is generally well tolerated, with acute

reactions being site-specific and self-limited [33].

CONCLUSIONS

IGSRT treatment for NMSC in a total of 1632 patients (total of 2917 NMSC lesions) in this study is well tolerated, achieves excellent local tumor control, and should continue to be recommended in the management of this disease. Among these patients, 55% were followed for a minimum of 12 months. Use of pre-treatment ultrasound and ongoing imaging to adjust radiation energy and dose, combined with a fractionation treatment schedule of 20 or more treatment fractions, has the potential to be associated with improved local tumor control in NMSC lesions compared to SRT without ultrasound imaging.

IGSRT is a safe and highly effective modality for treating NMSC. It should be considered as a first-line option for stage 0–II NMSC lesions (including for tumors less than 4 cm in diameter and/or SCCIS with substantial, full-thickness atypia of the epidermis or with strong clinical suspicion of invasion), especially in those patients who are not candidates for surgery or who decline surgery.

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[3] Certain study locations did not maintain a procedure to record RTOG toxicity grades for IGSRT patients in the initial study year(s), accounting for the missing values on this measure of safety.

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Data Availability. Data are available on request from the authors.

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