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CLINICAL INVESTIGATION **Skin**

RESULTS OF RADIOTHERAPY FOR EPITHELIAL SKIN CANCER OF THE PINNA: THE PRINCESS MARGARET HOSPITAL EXPERIENCE, 1982–1993

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Purpose: To assess the treatment outcome, late toxicity, and prognostic factors for radiotherapy (RT) of carcinoma of the pinna.

Methods and Materials: The charts of 313 patients treated between 01/82 and 12/93 were retrospectively reviewed. There were 334 lesions treated: 201 basal cell carcinoma (BCC), 122 squamous cell carcinoma (SCC), and 11 basosquamous carcinoma. RT was most commonly given by orthovoltage X-rays (278 lesions) or electrons (39 lesions). The most frequently used dose prescriptions were 35 Gy in 5 fractions (123 treatments with median field size = 4.9 cm^2), 42.5–45 Gy in 10 fractions (67 treatments with median field size = 10.5 cm^2), and 50–65 Gy in 20–30 fractions (42 treatments with median field size = 81 cm^2).

Results: The actuarial 2- and 5-year local control rates were 86.6% and 79.2%. Multivariate analysis revealed two factors to be statistically significant for increased local failure: tumor size > 2 cm (hazard ratio [HR] = 2.66, 95% confidence interval [CI] = 1.16–6.08), and a low biological effective dose (BED) (for each decrease of 5 BED units, HR = 1.76, 95% CI = 1.07–2.88). The 5-year actuarial rate of significant Grade 4 late toxicity was 7.3%. Factors statistically significant for this endpoint on univariate analysis were tumor size ($p = 0.035$), T-stage ($p = 0.02$), field size ($p = 0.05$), fraction size ($p = 0.003$), and BED ($p = 0.05$).

Conclusions: RT is an effective treatment option for epithelial skin cancer of the pinna. Large tumor size and low BED were independently statistically significantly associated with increased local failure. Dose-fractionation schedules using fraction sizes < 4 Gy may reduce the risk of necrosis and ulceration, particularly for field sizes > 5 cm^2. **© 2000 Elsevier Science Inc.**

Pinna, Radiotherapy, Basal cell carcinoma, Squamous cell carcinoma.

INTRODUCTION

Epithelial skin cancer of the pinna accounts for 9–19% of all epithelial skin cancers (1–4). As in other facial locations, surgical excision is often curative. Radiotherapy (RT) has an important primary role in order to preserve anatomy and also in elderly patients unfit for surgery. A randomized trial has been performed comparing surgery vs. radiotherapy for treatment of basal cell carcinoma (BCC) of the face. This showed an advantage for surgery with a 4-year actuarial failure rate of 0.7% compared to 7.5% for patients treated with RT. However, the RT given was heterogeneous with the majority of patients being treated with interstitial brachytherapy or superficial contact therapy. Of the 173 patients randomized to RT, only 20 received conventional external beam RT (5).

RT to the pinna has potential problems, including: 1) irregular surface contour of the pinna contributing to dose inhomogeneity; 2) potential for lower rates of local control because of possible deep infiltration of tumor due to the location of the ear within embryonic fusion planes (6); and 3) potential for higher rates of cartilage necrosis due to paucity of subcutaneous tissue overlying cartilage. At the Princess Margaret Hospital, our policy is to treat with primary RT and reserve surgery for salvage.

The objectives of this study are as follows: to assess the local control of epithelial skin cancer of the pinna following RT; to assess the late toxicity of RT to the pinna; and to identify prognostic factors associated with local control and late toxicity following RT for epithelial skin cancer of the pinna.

METHODS AND MATERIALS

The records of 549 patients with a diagnosis of epithelial skin cancer of the pinna referred for management to the

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Table 1. Most common dose prescriptions

Total dose (Gy)	# Fractions	Fraction size (Gy)	# Lesions	Median field size (in cm^2)	BED ($\alpha/\beta = 3$)	BED ($\alpha/\beta = 14$)
17.5–20	1	N/A	47	3.1	N/A	N/A
35	5	7	123	4.9	116.7	52.5
42.5–45	10	4.25–4.5	68	10.5	102.7–112.5	55.4–59.5
50–65	20–30	<3	41	81	83.3–121.3	57.1–77.1

BED = biological effective dose.

Princess Margaret Hospital between January 1, 1982 and December 31, 1993 were identified and their charts reviewed. Patients with either a histologically confirmed or clinical diagnosis of BCC, squamous cell carcinoma (SCC), or basosquamous carcinoma (BSC) were eligible for review. Patients treated with primary surgery who never received RT as well as patients with lesions where the epicenter was within the external auditory canal were excluded. A total of 313 patients form the basis of this report. There were 21 patients who had two geographically metachronous lesions for a total of 334 lesions treated.

Treatment

Patients were assessed in a multidisciplinary clinic with both a plastic surgeon and a radiation oncologist, and radiotherapy was deemed the treatment of choice. Approximately 95% of patients were treated with a single field with direct skin apposition. Orthovoltage RT (100–250 kV, half-value layer [HVL] 2.2 mmAl–1.1 mmCu) was used in 83% of all patients and electron RT in approximately 12%. The rest were treated with megavoltage X-rays (primarily ^{60}cobalt with average photon energy = 1.25 MeV) usually with a homolateral wedge pair of fields (5%). Table 1 outlines the most commonly used dose prescriptions along with their median field size and the biological effective dose (BED) for tumor control and for late effects. The majority of dose-fractionation schedules were of duration 4 weeks or less (323 of 334 treatments). Selection of radiation modality and dose-fractionation was based on considerations for tumor and treatment factors such as tumor size, volume of underlying brain, tumor depth (estimated clinically and/or via a diagnostic CT), and whether disease was primary or recurrent, and patient factors such as performance status, comorbidity, and age. For patients treated with electron RT, no corrections were made to the prescribed dose for the relative biological effectiveness (RBE) of electrons. Electron RT doses were prescribed as follows: skin surface (1 patient), 90% isodose (9), 95% isodose (13), ≥100% isodose (16). Treatment field size was assessed from the dimensions of the lead cutout used to delineate the field, from the diameter of the cone size (orthovoltage RT), or from the dimensions of the electron trimmers and calculated in square centimeters. Typically, BCC were treated with a 0.5-cm margin unless they were of the sclerosing subtype or recurrent, in which the margin was 1 cm. SCC were typically treated with a 1-cm margin. The BED was calculated using the linear-quadratic formula. For tumor control, an α/β ratio of 14 was chosen based on the work by Trott *et al.* (7). For late effects, an α/β ratio of 3 was chosen based on the work by Bentzen *et al*. derived from patients with breast cancer treated with postmastectomy RT (8).

Follow-up

The median follow-up among 218 patients alive at last follow-up was 3.3 years (range 0.12 to 13.37 years). Patients were usually followed every 3 to 6 months in the first 2 years and then yearly thereafter until death or until they were lost to follow-up. The follow-up durations for these patients are as follows (total 218 patients): < 1 year (19%), 1–3 years (26%), 3–5 years (25%), 5–7 years (17%), 7–10 years (7%), 10–14 years (5%).

Statistical analysis

The sample size used in this study was not based on prestudy considerations of statistical power but on the available number of cases from the relevant time period. The primary endpoint was time to local failure measured from the start of radiation therapy, where local control was defined as the absence of locally persistent or recurrent disease. A secondary endpoint, time to significant Grade 4 late toxicity, was also studied. This outcome was defined as the time from the completion of radiation therapy to the appearance of necrosis and/or ulceration that occurred for a duration of at least 3 months or that required surgical intervention.

The prognostic factor analysis for time to local failure was carried out in two steps. Firstly, the candidate prognostic factors (see Table 3 for exact definitions) age, previous history of skin cancer, tumor size, histology, T stage, cartilage necrosis, mode of referral, location within the pinna, field size, RT modality, total dose, RT fraction size, treatment time, and BED were individually tested for their association with outcome. For categorical variables, the log-rank test was used; if the variable was defined by three or more categories and there was a natural ordering for these categories, then the log-rank test for trend was used also (9). Treatment time was defined on a continuous scale (i.e., duration from start of treatment to the end of treatment was measured in number of days) and was tested using the Cox proportional hazards (PH) model (10). Secondly, based on clinical considerations and the results of the univariate analysis (i.e., $p < 0.05$ with missing data not exceeding

Table 2. Patient characteristics

	BCC	SCC	BSC	Total
# Lesions (%)	201 (60)	122 (37)	11 (3)	334
Male:Female	7.7:1	60:1	4.5:1	11:1
Median age (range)	73 (41–104)	75 (42–98)	74 (56–91)	74 (41–104)
Median tumor size, cm (range)	1.2 (0.2–7)	1.5 (0.3–12)	1.3 (0.7–5)	1.5 (0.2–12)
Previous skin cancer history (%)				
No	106 (53)	71 (58)	10 (91)	187 (56)
Yes	95 (47)	51 (42)	1 (9)	147 (44)
Mode of referral (%)				
Primary	171 (85)	93 (76)	8 (73)	272 (81)
Recurrent	26 (13)	21 (17)	3 (27)	50 (15)
Adjuvant	4 (2)	8 (7)	0	12 (4)
T Stage (%)				
Tx	0	1 (1)	0	1 (0.3)
T1	159 (79)	71 (58)	7 (64)	237 (71)
T2	25 (12)	24 (20)	2 (18)	51 (15)
T3	0	1 (1)	0	1 (0.3)
T4	17 (9)	25 (21)	2 (18)	44 (13)
N Stage (%)				
N0	201 (100)	115 (94)	11 (100)	327 (98)
N1	0	7 (6)	0	7 (2)
M Stage (%)				
M0	201 (100)	121 (99)	11 (100)	333 (99.7)
M1	0	1 (1)	0	1 (0.3)
Location (%)				
Anterior surface	109 (54)	72 (59)	9 (82)	190 (57)
Posterior surface	62 (31)	32 (26)	0	94 (28)
EAM/Concha	27 (13)	16 (13)	2 (18)	45 (14)
Unknown	3 (2)	2 (2)	0	5 (2)
Radiotherapy modality (%)				
Orthovoltage X-rays	176 (88)	92 (75)	10 (91)	278 (83)
Electrons	15 (8)	23 (19)	1 (9)	39 (12)
Other	10 (5)	7 (6)	0	17 (5)

Abbreviations: BCC = basal cell carcinoma; SCC = squamous cell carcinoma; BSC = basosquamous carcinoma; EAM = external auditory meatus.

20%), the variables tumor size, histology, mode of referral, RT modality, and BED were included in a multivariable analysis for local failure using the Cox PH model with all subset selection based on the global score chi-squared statistic. Results from these analyses are summarized by hazard ratios (HR) for local failure and their 95% confidence intervals (CI).

The prognostic factor analysis for time to significant Grade 4 late toxicity included age, tumor size, histology, T stage, cartilage necrosis, mode of referral, location within the pinna, field size, RT modality, total RT dose, fraction size, treatment time, and BED (see Table 5 for exact definitions). Categorical variables were tested for their association with outcome using the log-rank test and the log-rank test for trend (see above). Similarly, treatment time was defined on a continuous scale and tested for association with outcome using the Cox PH model (see above). Given the paucity of outcome data no multivariable analysis was attempted.

The Kaplan-Meier (K-M) estimate was used in describing local relapse-free rate curves and the cumulative proportion with significant Grade 4 late toxicity. A cumulative incidence curve was produced, which acknowledges rather than censors the competing risk of death. However, given that the results were very similar to the K-M plot, this result is not described further.

RESULTS

Patient characteristics

Characteristics of patients entered are detailed in Table 2. There were almost twice as many patients with BCC compared to those with SCC. The majority of patients were male. Patients referred were elderly with a median age of 74 years for all the patients. In general, there was selective referral by plastic surgeons and dermatologists of cases deemed unsuitable for surgery. Most patients were referred with no previous therapy (81%). A small percentage of patients were referred for management of recurrence after previous surgical treatment (15%) or for adjuvant treatment where there was complete excision of gross disease but with microscopically positive margins (4%). The BCC and SCC groups were similar with respect to age, median tumor size, and tumor location within the pinna. The majority of T4

patients had SCC. As expected, very few patients presented with nodal disease. A higher percentage of patients with SCC were treated with electron RT compared to those with BCC.

Recurrence

There were 58 recurrences overall, 50 with local recurrence only, 4 with regional nodal recurrence only, and 4 with both local and regional nodal recurrence. Of the 54 local recurrences, 46 were in-field recurrences and 8 were marginal. All 8 of the patients with regional nodal recurrence had a diagnosis of SCC. The cause-specific survival rate at 2 and 5 years was 96% (SE = 2.2% and 3.2% respectively). Overall survival at 2 and 5 years was 83.8% (SE = 1.2%) and 63.8% (SE = 1.4%) respectively.

Of the 58 recurrences, salvage treatment was given in 38 patients, 31 with surgery and 7 with further RT. Further recurrence after salvage treatment was reported in only 2 of the 38 patients treated. One additional patient with recurrence was treated with palliative intent by RT.

Local control

The overall actuarial local control rates at 2 and 5 years respectively were 86.6% (standard error [SE] = 2.1%) and 79.2% (SE = 2.8%). Prognostic factors for time to local failure were assessed in a univariate analysis and are presented in Table 3. Tumor size > 2 cm (Fig. 1), higher T-stage, presence of cartilage necrosis, recurrent lesions, field size > 6 cm^2, electron RT (Fig. 2), and longer treatment time were found to be statistically significant for increased local failure rate. Total dose was also statistically significantly associated with local failure rate; however, the relationship was not inversely proportional, as evidenced by the statistically nonsignificant *p*-value using the log-rank test for trend. Univariate analyses for prognostic factors for local failure were also carried out separately on patients with BCC and those with SCC, and the results were similar to that of the overall analysis when the two histologic groups were considered together (results not shown). Figure 3 shows the local control by histology. The actuarial local control rates at 2 and 5 years were 93% and 83% for BCC, and 82% and 79% for SCC ($p = 0.09$).

Tumor size, histology, mode of referral, RT modality, and BED were further assessed for statistical significance with time to local failure in a multivariate analysis. Tumor size > 2 cm ($p = 0.02$), electron RT ($p = 0.006$), and decreasing BED (Fig. 4, where every 5-unit decrease in BED was associated with HR for local failure = 1.69, $p = 0.03$) were statistically significant for increased local failure rate (Table 4). To further study the relationship between radiation modality, BED, and local failure, the multivariate analysis was repeated using the same 5 variables except for BED where a corrected BED for electron and megavoltage X-rays was used by multiplying BED with 0.85, as estimated by Sinclair *et al.* (11). In the final model, only tumor size > 2 cm ($p = 0.02$) and RBE-corrected BED ($p = 0.03$) remained statistically significant (Table 4).

Table 3. Univariate analysis of prognostic factors for local failure*

Variable	Sample size	Worst subgroup	*p*-Value
Age quartiles			0.36
41–64	82		0.41 (trend)
65–74	87		
75–81	87		
82–104	76	√	
Previous skin cancer history			0.32
No	186	√	
Yes	146		
Tumor size			<0.0001
≤2 cm	250		
>2 cm	80	√	
Histology			0.094
Basal cell carcinoma	200		
Squamous cell carcinoma	121	√	
T Stage			<0.0001
T1	236		<0.0001 (trend)
T2	50		
T3	1		
T4	44	√	
Cartilage necrosis			0.004
Not T4	287		
T4	44	√	
Mode of referral			0.008
Primary	270		
Recurrent	50	√	
Adjuvant	12		
Location			0.33
Anterior	190		
Posterior	92		
EAM/Concha	45	√	
Field Size			0.01
≤6 cm^2	168		
>6 cm^2	162	√	
Radiotherapy modality			<0.0001
Orthovoltage X-rays	276		
Electrons	39	√	
Other	17		
Total dose			0.036
<20 Gy	47		0.13 (trend)
30–34.9 Gy	22		
35 Gy	124		
40–44.9 Gy	48		
45 Gy	43		
50–59.9 Gy	42	√	
≥60 Gy	6		
Fraction size			0.16
<4 Gy	65	√	0.084 (trend)
4–4.99 Gy	67		
5–5.99 Gy	7		
6–6.99 Gy	20		
7–8 Gy	126		
>8 Gy	47		
Treatment time†			0.02
Continuous variable	332		
BED Quartiles ($\alpha/\beta = 14$)			0.18
<52.5 Gy	24		0.88 (trend)
52.5 Gy	123		
52.6–58.9 Gy	89	√	
>58.9 Gy	49		

EAM = external auditory meatus.

* Two cases were deleted because date of recurrence was not known.

† Treatment time was also analyzed by adjusting for tumor size, and this analysis showed it to be statistically nonsignificant.

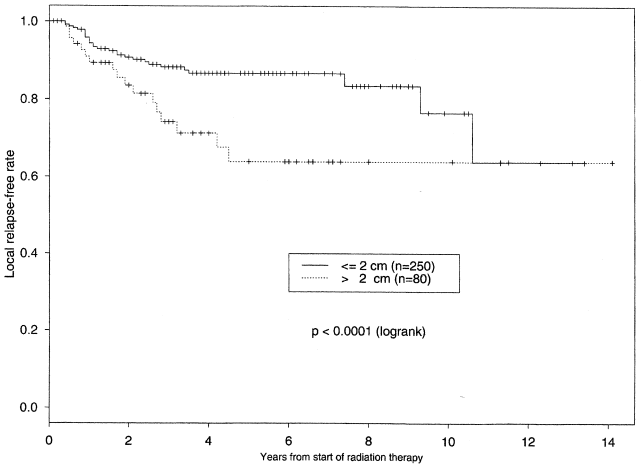

Fig. 1. Local relapse–free rate and tumor size ($\leq$ 2 cm vs. $>$ 2 cm).

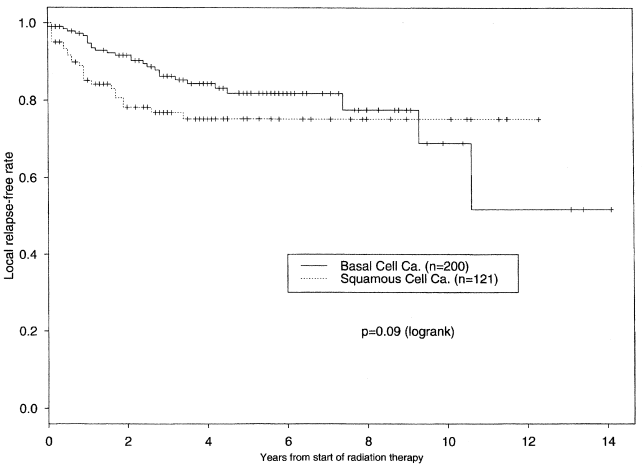

Fig. 2. Local relapse-free rate and histology (BCC vs. SCC).

Treatment time was not included in the multivariate analysis but was also analyzed by adjusting for tumor size (results not shown). After this analysis, increased treatment time was no longer statistically significant for increased local failure rate.

Late toxicity

The 2- and 5-year actuarial rate of significant Grade 4 late toxicity was 4.9% and 7.3% respectively (Fig. 5). Nineteen patients experienced significant Grade 4 late toxicity. Six required surgical intervention and the other 13 were classified as significant Grade 4 late toxicity based on duration of ulceration/necrosis of at least 3 months. Only 1 patient with significant Grade 4 late toxicity had two treatments to the same ear for 2 geographically metachronous primaries.

A univariate analysis for prognostic factors related to time to significant Grade 4 late toxicity revealed tumor size ($p = 0.035$), T-stage ($p = 0.017$), field size ($p = 0.05$), larger RT fraction size ($p = 0.015$), and a higher BED ($p = 0.04$) to be statistically significant (Table 5). Total dose was borderline statistically significant ($p = 0.06$). When the factors of T-stage, total dose, fraction size, and BED were analyzed using the log-rank test for trend, the findings were not statistically significant (Table 5). The relationship between the most commonly used dose-prescriptions, BED, median field size, and incidence of significant Grade 4 late toxicity is shown in Table 6.

DISCUSSION

The results of this study confirm the efficacy of RT as primary treatment of epithelial skin cancer of the pinna. The actuarial 2- and 5-year local control rates were 86.6% and 79.2% respectively. This is comparable to those reported in the literature for RT of ear lesions with local control rates ranging from 81–100% (12–18), as well as local control rates for epithelial skin cancer at other sites (1–4, 19, 20). As expected, the incidence of nodal involvement or recur-

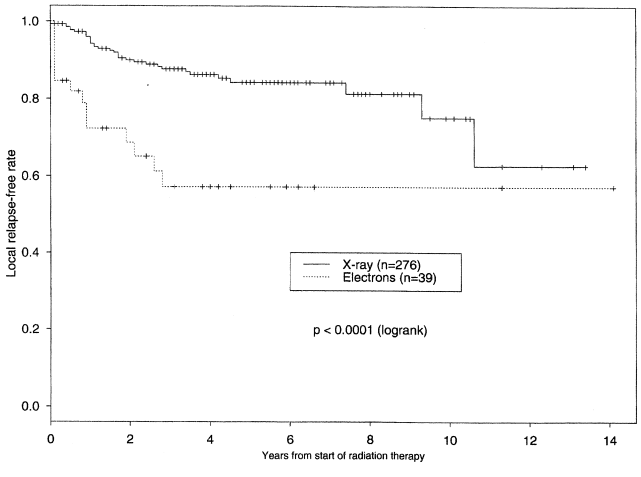

Fig. 3. Local relapse-free rate and RT modality (orthovoltage X-rays vs. electrons).

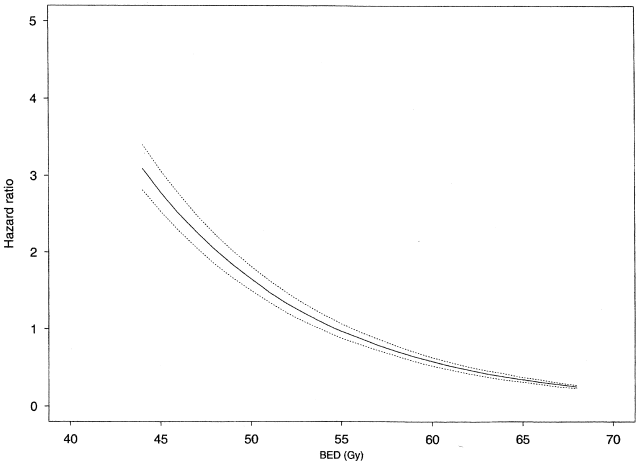

Fig. 4. Hazard ratio for local failure vs. BED for tumor control. The curve for RBE-corrected BED is not significantly different (not shown).

Table 4. Multivariate analysis for factors associated with local failure*

Variable	Description	*p*-Value	Hazard ratio	95% Confidence interval
Tumor size	>2 cm vs. ≤2 cm	0.02	2.63	1.15 to 6.00
BED ($\alpha/\beta = 14$)	5 unit decrease in BED	0.03	1.69	1.05 to 2.78
RT modality	Electrons vs. orthovoltage X-rays	0.006	3.94	1.49 to 10.42
When analyzed with RBE correction factor of 0.85 for electrons and megavoltage X-rays:				
Tumor Size RBE-corrected	>2 cm vs. ≤2 cm	0.02	2.66	1.16 to 6.08
BED ($\alpha/\beta = 14$)	5 unit decrease in BED	0.03	1.76	1.07 to 2.88
RT modality	Electrons vs. orthovoltage X-rays	0.39	1.51	0.59 to 3.87

* Based on a sample size of 255 and 39 events.

rence is low and is only of significance in patients with squamous cell cancer.

In a multivariate analysis involving candidate prognostic factors for the outcome time to local failure, only tumor size > 2 cm and a decreasing BED were found to be statistically significant. Increasing T-stage, presence of cartilage necrosis, and increasing field size were not chosen for multivariate analysis but were found to be statistically significant for increased local failure on univariate analysis. Together with tumor size, these variables act as surrogates of local tumor extent. Studies of epithelial skin cancer at other sites have also found an association between the extent of the primary lesion and local control (2–4, 21).

The finding that electron RT was not statistically significant for increased local failure rate after correcting for RBE is consistent with some reports in the literature of good local control rates with electron RT. Hunter *et al.* achieved local control in 35 of 43 patients with epithelial skin cancer of the pinna, all treated with 10 MeV megavoltage electrons to doses between 45 and 55 Gy (16). Others have also reported good outcome with electron RT with control rates of 86–95% (22–24). However, Lovett *et al.* found electron RT to be associated with worse local control on multivariate analysis in patients with skin cancers at various sites ($p < 0.001$) (2).

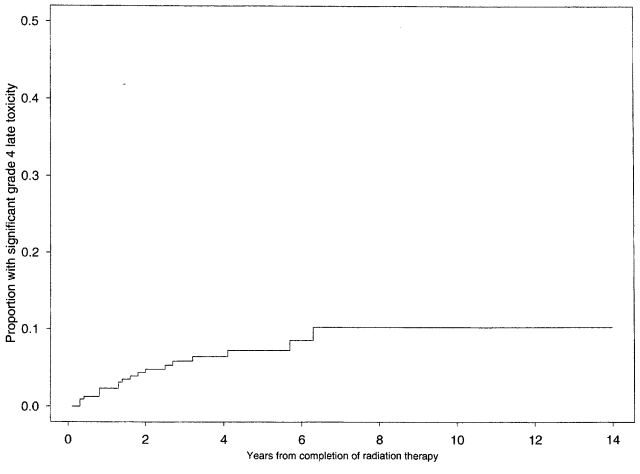

Fig. 5. Actuarial rate of significant Grade 4 late toxicity.

A possible explanation for these conflicting results is the inconsistent application of RBE to correct for electron doses. Furthermore, there are no data on the RBE of electrons for tumors. Since radiobiologically, tumors respond akin to rapidly proliferating tissues like skin, we assumed that electrons for tumors have a similar RBE as electrons for acute skin reactions.

Another important issue is the dosimetric difficulties in the application of electron RT for skin cancer. Electron doses are often prescribed variably as a minimum tumor dose (e.g., 90% or 95% isodose) or to D_{max}. The penumbra as defined by the distance between the 90% and 50% isodose curves is generally wider as compared with orthovoltage X-rays, thereby making the required field size larger for electrons. Additionally, a beam-modifying device is required to achieve full skin dose (e.g., bolus), and dose fall-off is rapid beyond the 80% isodose line. All these dosimetric issues could make electron radiotherapy more prone to mistakes resulting in underdosage of the tumor and hence higher failure rate. With care, electrons by themselves are not inferior to orthovoltage X-rays and this is supported by our multivariate analysis using RBE-corrected BED, resulting in electron RT losing its significance for inferior local control.

Our finding of an association of increasing BED with improved local control supports a radiation dose–response relationship as reported by others (7, 21, 25–27). Lim *et al.* found an association between good local control (> 97%) and time–dose fractionation (TDF) values ≥ 113 (17).

Recurrent lesions were associated with increased local failure rate on univariate analysis but failed to achieve significance on multivariate analysis. Lovett *et al.* found recurrence to be associated with worse local control on multivariate analysis following RT for skin cancer at various sites ($p = 0.01$) (2). Lee *et al.* found that ultimate local control in 67 patients receiving RT for T4 lesions of the skin of the head and neck was worse on multivariate analysis for those with recurrence ($p = 0.0031$), bone involvement ($p =$

Table 5. Univariate analysis of prognostic factors for significant Grade 4 late toxicity

Variable	Sample size	Worst subgroup	*p*-Value
Age quartiles			0.94
41–65	89	√	0.69
66–74	80		(trend)
75–81	88		
82–104	77		
Tumor size			0.035
≤2 cm	251		
>2 cm	81	√	
Histology			0.16
Basal cell carcinoma	201		
Squamous and basosquamous Carcinoma	133	√	
Stage			0.017
T1	237		0.96
T2	51	√	(trend)
T3	1		
T4	44		
Cartilage necrosis			0.34
Not T4	289	√	
T4	44		
Mode of referral			0.75
Primary	272	√	
Recurrent	50		
Location			0.34
Anterior	190	√	
Posterior	94		
EAM/Concha	45		
Field size			0.046
≤6 cm^2	168		
>6 cm^2	164	√	
Radiation modality			0.49
Orthovoltage X-rays	278	√	
Electrons	39		
Total Dose			0.06
≤20 Gy	47		0.35
30–34.9 Gy	22		(trend)
35 Gy	124		
40–44.9 Gy	50	√	
45 Gy	43		
50–59.9 Gy	42		
≥60 Gy	6		
Fraction size			0.003
<4 Gy	65		0.37
4–4.99 Gy	69	√	(trend)
5–5.99 Gy	7		
6–6.99 Gy	20		
7–8 Gy	126		
>8 Gy	47		
Treatment time			
Continuous variable	332		0.82
BED Quartiles ($\alpha/\beta = 3$)			0.05
<102.7	59		0.35
102.7–112.5	101	√	(trend)
112.6–116.7	123		
>116.7	4		

0.0008), and nerve involvement ($p = 0.06$) (28). Rowe had similar findings for patients with recurrence (29).

Histologic subtype was not found to be a statistically significant prognostic factor for local control in this study. Few studies in the literature contain large enough numbers of patients to study this factor adequately. Petrovich *et al.* (4) showed local control for SCC to be worse at 5 and 10 years with rates of 94% and 88% respectively compared to 99% and 98% for patients with BCC ($p < 0.02$). Lovett *et al.* could not confirm this (2). A review of the literature by Rowe *et al.* did not find a statistically significant difference between 5-year local failure rate of BCC (8.7%) and SCC (10%) (29, 30).

The actuarial 2- and 5-year rates of significant Grade 4 late toxicity of 4.9% and 7.3% respectively are comparable to those found in other series of RT for epithelial skin cancer of the pinna with necrosis rates reported between 0% and 13% (4, 12–18, 31). The reported rates of severe late complications from RT for skin cancer at other sites are slightly lower at ranges from 0–5% (1–4, 19, 20, 24).

In the present study, univariate analysis showed larger field size and larger tumor size to be associated with worse late toxicity, a finding intuitively expected. The variables fraction size and BED were also associated with worse late toxicity. However, this relationship is not linear through the range of fraction sizes and BED as evidenced by the log-rank test for trend (Table 5). The patients treated with the "intermediate" dose-fractionation schedules consisting of 42.5–45 Gy in 10 fractions had the highest incidence of late toxicity compared to those schedules with larger or smaller fraction sizes (Table 6). One possible explanation for this is that the patients in the worst subgroups for BED and fraction size were treated with larger field sizes than the subgroup of patients treated with larger BED and larger fraction size.

The relationship between increasing T-stage and late toxicity was also not linear with stage T2 being the worst subgroup (Table 5). One may speculate that this relationship too may be a consequence of other confounding factors that are unaccounted for in the univariate analysis for T-stage and late toxicity.

Protracting the treatment and reducing fraction size to less than 4 Gy appeared to significantly reduce the incidence of significant Grade 4 late toxicity, even with relatively large field sizes. When we examined the dose schedules of 50–65 Gy in 20–30 fractions, there were no incidents of significant Grade 4 toxicity among 41 patients despite a median field size of 81 cm^2 (Table 6). Hayter *et al.* reported an actuarial 5-year rate of cartilage necrosis of 13%. A univariate analysis found fraction size > 6 Gy ($p = 0.0093$) and overall treatment time ≤ 5 days ($p = 0.0053$) to be associated with an increased risk of cartilage necrosis (15). Lim *et al.* reported a radionecrosis rate of 9.6% among 62 patients treated with kilovoltage RT. He found that dose schedules with TDF values < 122 or with field sizes ≤ 5 cm^2 had radionecrosis rates < 5% (17).

Lovett *et al.* found electron RT to be associated with decreased cosmesis in RT of skin cancers at various sites (2). It was not possible to systematically assess cosmesis in this study. Others have found good local control and cosmesis with electron RT for skin cancer (22–24).

Table 6. Dose-fractionation, field size, BED, and incidence of significant Grade 4 late toxicity

Total dose (Gy)	# Fractions	Fraction size (Gy)	# Treatments	Median field size (in cm^2)	BED ($\alpha/\beta = 3$)	Late toxicity
17.5–20	1	N/A	47	3.1	N/A	1 (2.1%)
35	5	7	123	4.9	117	7 (5.7%)
42.5–45	10	4.3–4.5	68	10.5	103–113	10 (14.5%)
50–65	20–30	<3	41	81	83–121	0

CONCLUSION

RT is an effective treatment option for epithelial skin cancer of the pinna with local control rates of 90% or more for the majority of patients who present with early-stage lesions less than 2 cm in diameter. Tumor sizes > 2 cm and a low BED were statistically significant for increased local failure rate. Careful attention is required to the RBE and dosimetric issues discussed above in order to obtain good results with electron RT for skin malignancies. Dose-fractionation schedules using fraction sizes < 4 Gy may reduce the incidence of late toxicity, particularly for field sizes > 5 cm^2. We suggest that the overall clinical scenario be considered when deciding on the most appropriate dose-fractionation schedule. Shorter schedules with larger fraction size are associated with higher risk of late toxicity but may be most practical for elderly, debilitated patients with small tumors. Patients with large lesions, recurrence, and/or who have longer life expectancy would benefit from the use of lower dose per fraction (2–2.5 Gy) because of the ability to deliver higher BED for tumor control while keeping a low rate of late toxicity.

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