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SHORT REPORT

Predictors of recurrence after radiotherapy for non-melanoma skin cancer

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ABSTRACT

Predictive factors of recurrence were examined in 448 non-melanoma skin cancers (72% basal cell carcinoma, 28% squamous cell carcinoma) treated with radiotherapy. The overall recurrence rate was 15.8% at a median follow-up of 18.4 months. In multivariate analysis, significant factors for recurrence were age ($p = 0.0197$), tumour size 2 cm or greater ($p = 0.0095$), immunosuppression ($p = 0.0082$), and treatment modality ($p = 0.0009$).

KEY WORDS

Skin cancer, recurrence, radiotherapy

1. INTRODUCTION

Non-melanoma skin cancers (NMSCS) are the most common malignancy in North America[1]. Basal cell carcinoma (BCC) and squamous cell carcinoma (SCC) are the two most common types of NMSC[2]. A number of treatment modalities are available for management, with surgery and radiotherapy being the mainstays[3]. Radiotherapy is also used as postoperative adjuvant therapy when high-risk features for recurrence are present. Depending on patient and tumour characteristics, the treatment volume, modality (orthovoltage, electrons, or photons), and dose fractionation regime can vary.

Local control rates after radiotherapy for primary BCC and SCC have been reported to be 87%–98% and 56%–97% respectively[2,4–9]. Factors predictive of local recurrence have been reported to include tumour size, depth, pathology, and differentiation; perineural invasion; site, recurrent tumours, and scar carcinoma; host immunosuppression; and treatment modality, total dose, and dose per fraction[2,4–9]. Several of the relevant studies have been smaller retrospective series. Our centre has a large multidisciplinary NMSC clinic and maintains a prospective database for patients treated with radiotherapy. The purpose of the present study was to determine predictive factors for recurrence in patients treated with radiotherapy for NMSC.

2. METHODS

At the Odette Cancer Centre multidisciplinary clinic, patients are jointly assessed by a dermatologist, a plastic surgeon, and a radiation oncologist. Patients receiving radiotherapy for BCC or SCC between January 2007 and December 2011 were included in the study. Approval was obtained from the Sunnybrook Health Sciences Centre Research Ethics Board.

The clinic's prospective database records patient and tumour factors at initial consultation and treatment outcomes at follow-up. Patient factors recorded include age; tumour size; site; pathology; and whether the disease is primary, recurrent, or treated postoperatively. Any immunosuppressant-related predisposing conditions—including but not limited to chronic lymphocytic leukemia, solid organ transplantation, HIV infection, and lymphoma—are recorded. Treatment factors recorded include dose and fractionation, biologic equivalent dose in 2-Gy fractions (EQD_2), and treatment modality.

Radiotherapy was delivered using orthovoltage X-rays, electrons, or megavoltage photons. Orthovoltage energies used were 100 kV, 180 kV, 250 kV, and 300 kV (dose prescribed at skin surface, with a focus-to-skin distance of 30 cm or 50 cm). Electron energies used included 6 MeV, 9 MeV, 12 MeV, 14 MeV, 15 MeV, and 18 MeV, with dose prescribed to 95%. Bolus was used to ensure a full skin dose. Photons were delivered in a 1- or 2-field technique, with intensity-modulated radiotherapy used in selected cases. The choice of treatment modality and energy depended on the tumour size, depth, and location. For tumours thicker than 1 cm or larger than 3 cm, electrons or photons were used. Clinical mark-up was used to define the gross tumour volume in most cases, with computed tomography planning reserved for deep-seated tumours. The treatment volume included

the gross visible and palpable disease or surgical bed with a 1- to 2-cm margin to field edge depending on histology, size, and location of disease and treatment modality and energy used.

Patients were followed at 6–8 weeks after treatment, and every 3–4 months thereafter until discharge at 2 years (BCC) or 3 years (sclerosing BCC and SCC) to their family physician or dermatologist. At each visit, treated lesions were assessed clinically and categorized as clear or recurrent. Local recurrence was calculated from the last day of radiotherapy, and the last follow-up date was used to determine the status of the lesion. Demographic data are summarized for continuous variables; numbers and percentages are presented for categorical variables. Descriptive statistics summarize the radiotherapy parameters.

Analyses were conducted per tumour because each patient might have multiple tumours. No correction was made for multiple tumours. Univariate and multivariate analyses were performed to determine the factors associated with recurrent disease. In the univariate analysis, logistic regression was used to search for relationships between outcome and other covariates. Odds ratios (ORS) and 95% confidence intervals (CIS) were calculated in the cumulative logit model for each covariate. The modelled probabilities were cumulated for the outcome order 1 = recurrent and 0 = clear. A two-sided p value less than 0.05 was considered statistically significant. Parameters from the univariate analysis with a p value less than 0.10 were selected into a backwards logistic regression analysis to determine the most significant factors related to treatment outcome. All analyses were conducted using the Statistical Analysis Software (version 9.2 for Windows: SAS Institute, Cary, NC, U.S.A.).

3. RESULTS

During the study period, 389 patients received radiotherapy for 448 NMSCS. Median age in this cohort was 78 years (range: 41–99 years). Most lesions were less than 2 cm in size (n = 304, 67.9%), and pathology was BCC (n = 207, 46.2%), sclerosing BCC (n = 115, 25.7%), and SCC (n = 126, 28.1%). Radiotherapy was prescribed as primary treatment (n = 239, 53.3%), for recurrence after prior treatment (n = 133, 29.7%), and postoperatively (n = 75, 16.7%). Of the 133 recurrent lesions, 43 had previously undergone excision, and 60 had been treated with curettage and imiquimod; no data were available on treatment modality for the remaining 30. The face was treated most often (n = 283, 63.2%), followed by ear (n = 69, 15.4%) and scalp (n = 40, 8.9%). Of the treated lesions, 9% (n = 39) occurred in patients who were immunosuppressed.

The most common dose–fractionation regimes used were 50 Gy in 20 fractions (n = 118, 26.3%) and 40 Gy in 10 fractions (n = 65, 14.5%). The orthovoltage modality was used for 184 lesions (41.1%); electrons, for 146 lesions (32.6%); and photons, for 118 lesions (26.3%). Median duration of follow-up was 18.4 months (range: 0–132 months). The overall local control rate was 84.2% (n = 377), with a median time to recurrence of 11.4 months (range: 6.5–23.8 months).

Univariate analysis showed that host immunosuppression (p = 0.0075), pathology (SCC vs. BCC, sclerosing BCC vs. BCC, p = 0.0186), a tumour size of 2 cm or greater (p = 0.0004), and treatment modality (electrons vs. photons, orthovoltage vs. photons, p = 0.0002) were significant predictors of recurrent disease (Table I). Multivariate analysis found four factors significantly related to outcome: age (p = 0.020), tumour size of 2 cm or greater (p = 0.010), immunosuppression (p = 0.009), and treatment modality (p = 0.0009, Table II). No significant interactions between those factors were observed. After backwards selection, pathology was no longer a significant predictor of treatment outcome.

4. DISCUSSION

This series is one of the largest in the literature looking at factors predictive of local recurrence after radiotherapy for NMSC, and one of the few using prospectively collected data. In this cohort of 448 tumours, the overall local recurrence rate was 15.8%, with events occurring at a median of 11.4 months after treatment. We found that older age, a tumour size of 2 cm or greater, host immunosuppression, and use of photons were all associated with a greater chance of local recurrence.

Previous studies also found that lesion size[5,10,11] and immunosuppression[7,10] are predictive for recurrence. Whether age predicts for recurrence is controversial; most published work suggests that it plays no role[7,12]. Radiotherapy modality and treatment energy are chosen depending on tumour and patient characteristics. Our finding that patients treated with orthovoltage and electrons experienced better local control than did patients receiving photons probably reflects differences in the lesions themselves. Superficial lesions are commonly treated with orthovoltage or electrons; photons are reserved for deeper, more extensive lesions that are inherently at greater risk for recurrence. Similar results and conclusions are documented in the literature[2]. Some series have reported inferior outcomes for electrons compared with orthovoltage, but that observation might be a result of inadequate field size and technique[13].

We found that, regardless whether a tumour is primary, recurrent, or being treated postoperatively, the risks of recurrence are similar. Several earlier studies have suggested that recurrent lesions are at higher risk of subsequent recurrence[8,14]. The results of our univariate analysis comparing recurrent with primary lesions demonstrated a trend suggesting that recurrent lesions are at higher risk (p = 0.1014).

TABLE I Univariate analysis of factors on treatment outcome

Parameter	p *Value*	*OR*	*95% CL*
Age (years)	0.0792	1.023	0.997, 1.050
Biologic equivalent dose in 2-Gy fractions	0.4735	1.007	0.988, 1.026
Immunosuppression (present vs. absent)	0.0075	2.729	1.308, 5.694
Site (4 categories)	0.0633		
Face vs. other	0.0656	0.503	0.242, 1.045
Ear vs. other	0.7497	0.867	0.360, 2.088
Scalp vs. other	0.6817	1.222	0.468, 3.189
Pathology (3 categories)	0.0186		
SCC vs. BCC	0.0301	1.890	1.063, 3.360
Sclerosing BCC vs. BCC	0.4041	0.736	0.359, 1.511
Tumour (3 categories)	0.1647		
Postoperative vs. primary	0.6796	0.847	0.385, 1.862
Recurrent vs. primary	0.1014	1.597	0.912, 2.798
Tumour size (cm)			
≥2 vs. <2	0.0004	2.578	1.529, 4.348
Dose and fraction (3 categories)	0.1076		
5000 cGy in 20 vs. other	0.2978	0.751	0.439, 1.287
4000 cGy in 10 vs. other	0.0399	0.354	0.132, 0.953
Treatment modality (3 categories)	0.0002		
Electron vs. photons	0.0360	0.523	0.285, 0.959
Orthovoltage vs. photons	<0.0001	0.246	0.126, 0.481

OR = odds ratio; CL = confidence limits; SCC = squamous cell carcinoma; BCC = basal cell carcinoma.

TABLE II Multivariate analysis of factors on treatment outcome

Parameter	p *Value*	*OR*	*95% CL*
Age (years)	0.0197	1.034	1.005, 1.063
Tumour size (cm)			
≥2 vs. <2	0.0095	2.090	1.197, 3.649
Immunosuppression (present vs. absent)	0.0082	2.939	1.321, 6.539
Treatment modality (3 categories)	0.0009		
Electron vs. photons	0.0111	0.440	0.234, 0.829
Orthovoltage vs. photons	0.0004	0.285	0.142, 0.572

OR = odds ratio; CL = confidence limits; EQD_2 = biologic equivalent dose in 2-Gy fractions; SCC = squamous cell carcinoma; BCC = basal cell carcinoma.

We did not find that tumour site was an important factor for local control. Also, pathology—although significant in univariate analysis—did not show significance in multivariate analysis. We did find that tumours treated with photons had a higher risk of recurrence, possibly a result of the fact that these lesions were typically larger.

At 84.2%, our overall local control rate was lower than rates seen in some other series in the literature[2,6,9]. The two treatment regimens most commonly used at our institution are 40/10 and 50/20 (EQD_2: 56 and 47 respectively, using an alpha/beta ratio of 10). The van Hezewijk series compared 44/10 with 54/18 (EQD_2: 63 and 70 respectively) and found actuarial 3-year local control rates of 96.1% and 96.9% (p = nonsignificant)[9]. However, comparing outcomes is difficult given the heterogeneous patient populations in these retrospective series.

5. SUMMARY

Extrapolating from the head-and-neck literature, in which local control is associated with dose[15], it seems logical that dose escalation could be considered for

larger SCC tumours. We found higher failure rates with lesions 2 cm or greater in size, and we now consider a higher EQD_2 regime for this population. Van Hezewijk *et al.* recommend their more protracted 54/18 regimen for SCC lesions larger than 5 cm in size[9], and Kwan and colleagues recommend a boost for bulky disease[2]. To improve local control rates for larger tumours, we recommend a higher EQD_2 than was used in the present series.

Our study is limited by the relatively short period of follow-up (median: 18.4 months); additional time might have yielded more factors predictive for recurrence. However, other large series have reported median times to local recurrence within that range: 10.4 months for BCC and 3.3 months for SCC[9]; and 40.5 months for advanced BCC and 5.0 months for SCC[2].

We recommend an EQD_2 higher than 56 Gy for tumours larger than 2 cm in size. We recognize that higher doses might be associated with worse acute and chronic toxicity; future studies can examine optimal dose–fractionation schedules, as well as patient preferences and quality-of-life outcomes in this largely elderly population.

6. CONFLICT OF INTEREST DISCLOSURES

The authors have no financial conflicts of interest to declare.

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