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Outcome following radiotherapy for head and neck basal cell carcinoma with 'aggressive' features

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ABSTRACT

Objectives: The literature demonstrates that 'aggressive' head-and-neck basal cell carcinomas (HN-BCC) have a higher than expected relapse rate with unfavorable outcomes. We report outcomes following definitive (dRT) or post-operative radiotherapy (PORT) for these tumors.
Methods: We reviewed all HN-BCC patients with 'aggressive' features (primary lesions diameter >10 mm, >2 recurrences, or extra-cutaneous extension), treated with megavoltage dRT or PORT between 1998 and 2013. Loco-regional control (LRC) and relapse-free survival (RFS) were estimated using the competing risk method, and overall survival (OS) by Kaplan-Meier method. Univariable analysis explored factors associated with relapse.
Results: A total of 108 histologically confirmed 'aggressive' HN-BCC patients were identified, including 38 (35%) presenting *de novo* and 70 (65%) treated for recurrence (rBCC). dRT was offered to 72 (66.7%) patients and PORT to 36 (33.3%). Median follow-up was 3.5 years. Actuarial 3-year LRC, RFS, and OS were 87% (95% confidence interval: 77–92), 82% (72–89), and 87% (80–94), respectively. LRC rates for dRT and PORT were similar [hazard ratio (HR) 0.61 (0.17–2.23), p = 0.46]. Factors associated with higher risk of relapse were: rBCC [HR 7.96 (1.03–61.71), p = 0.047], 'H-zone' (mid face, eyes, and ears) location [HR 3.13 (1.07–9.19), p = 0.04], tumor size [HR 1.32 (1.08–1.6), p = 0.006], nodal involvement [HR 3.68 (1.11–12.2), p = 0.03] and stage [HR 3.13 (1.19–8.26), p = 0.02].
Conclusion: RT is an effective treatment for 'aggressive' HN-BCC when used as a definitive modality or as PORT. Non-surgical management with definitive radiotherapy provides an alternative effective option if surgery is not used.

Introduction

Basal cell carcinoma (BCC) is a malignant neoplasm derived from the basal layer of the epidermis [1]. It is the most common cancer type in western countries and the incidence is rising [2]. Most BCCs (80–90%) occur in elderly patients and frequently on sun-exposed body parts such as the head and neck, which is also the most common site [3,4]. Head and neck BCC (HN-BCC) are generally slow growing. However, a subset of HN-BCC may behave more aggressively and lead to greater morbidity and mortality [5]. Reported unfavorable characteristics include unfavorable histologic subtypes, large primary tumor size, 'H-zone' location (mid face, eyes, and ears), and the presence of extra-cutaneous extension; as well, compromised surgical resection margins and recurrent disease, especially in the setting of prior definitive therapy also carry higher risk. These characteristics have been jointly called 'aggressive' HN-BCC [6,7].

The management of HN-BCC is guided by a balance among oncologic, cosmetic, and functional outcomes. A variety of options are available for the treatment of 'aggressive' HN-BCC, the most traditional being surgery or radiotherapy. However little research has been undertaken that adequately compares these treatment modalities. Traditionally, surgery is understandably the initial

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treatment for many cases while definitive RT (dRT) is often used as an alternative for unresectable tumors, patients medically unfit for surgery, or when significant cosmetic or functional outcomes following surgery are anticipated [8–10]. There is a paucity of data regarding the role of RT in the management of 'aggressive' HN-BCC, especially in the definitive setting when RT is the sole treatment modality. A systematic review by Bath-Hextall et al. [11] comparing efficacy of various treatment options for skin BCC found that surgery had lower recurrence compared to radiotherapy in one study for BCC in general, but no difference for recurrence in another study confined to high risk facial BCCs. Other alternatives currently being evaluated include small molecule inhibitors of the hedgehog pathway but so far these new agents are reserved for advanced BCC and specifically "tumors that were no longer amenable to conventional treatment options, including surgery, radiotherapy, or systemic therapy" [12].

In this study, we present a series of patients with 'aggressive' HN-BCCs managed at a tertiary cancer center with definitive radiotherapy (dRT) or postoperative radiotherapy (PORT). The aims of this paper are to report outcomes, discuss when this approach should be considered, and to explore factors associated with risk of relapse in this population.

Methods

Patient selection

Following research ethics board approval, a retrospective review was undertaken of all pathologically confirmed 'aggressive' HN-BCC treated with curative intent at our institution between 1998 and 2013 using megavoltage dRT or PORT. Although there is no universal consensus definition of 'aggressive' HN-BCC, after an extensive literature search, we defined 'aggressive' HN-BCC as tumors with any of the following features according to Vico et al: largest diameter of primary lesion >10 mm, a history of >2 recurrences, or extra-cutaneous extension [8]. The cut-off of 10 mm was also used by various other studies in defining advanced BCC, including the most recent ERIVANCE trial [13,14]. Extracutaneous extension included any extension to underlying muscle, bone, mucosa, dura, adjacent organs or gross cranial nerve involvement. Inclusion criteria were histologically proven HN-BCC with one or more of the aforementioned features, treated with curative intent using dRT or PORT. Patients with synchronous primaries other than BCC were excluded. We excluded patients treated with orthovoltage radiotherapy to avoid heterogeneity of RT as most such patients are treated using megavoltage RT techniques to achieve adequate target coverage and conformality due to their generally larger size and infiltrative nature as well as the need to navigate the complex nature of head and neck anatomy. Clinical and outcome data were prospectively collected at point-of-care and retrieved from a prospective Head and Neck Anthology of Outcomes System [15] and supplemented by reviewing clinic records. Vital status was confirmed by linkage to the Ontario provincial population-based cancer registry.

Treatment

All patients were evaluated and managed in a multidisciplinary setting following institutional guidelines, based on disease location, anticipated functional outcomes, and patient factors. In general, surgery was the mainstay of treatment with PORT considered in selected cases based on adverse pathologic features [positive microscopic resection margin, multiply recurrent disease (>2) or radiological or extensive pathological intratumoral or extratumoral perineural invasion]. Definitive RT was considered when the tumor was technically unsuitable for surgery, for cosmetic or functional considerations, or for patients with high operative risk. Patients were uniformly staged prior to treatment with computerized tomography (CT) and/or magnetic resonance imaging (MRI) scan and according to the 7th edition TNM.

All patients underwent CT simulation for radiotherapy planning. Patients were treated using three-dimensional conformal radiotherapy (3D RT) or intensity modulated radiotherapy (IMRT), while megavoltage electrons were used for superficial targets. Patients were immobilized with customized thermoplastic masks during simulation and treatment, and bolus was used when clinically or dosimetrically indicated. The clinical target volume (CTV) was defined as a 2-cm anatomically constrained margin to the gross disease, while for PORT the entire tumor bed including the surgical scar was included in the CTV. Nodal regions were treated if overt lymph nodes were present (n = 7 cases). Radiotherapy dose and fractionation depended on size, location, and intent (dRT/PORT). PORT generally used conventional fractionation (e.g. 60–66 Gy/30–33 fractions/6–6.5 weeks, 2 Gy per fraction) while dRT was treated with either a hypofractionated schedule (e.g. 50 Gy/20 fractions/4 weeks; 60 Gy/25 fractions/5 weeks) or more conventional fractionation (60–70 Gy/30–35 fractions/6–7 weeks) (Table 1).

Routine follow-up was planned at 2 weeks and 6 weeks post-RT, then three-monthly in year 1–2, four-monthly in the 3rd year, and six monthly in the 4-5th years. In some cases, extra assessments were undertaken due to recurrence or according to patient need.

Statistical analysis

Baseline characteristics were compared between newly diagnosed (*de novo*) and recurrent (rBCC) cohorts. Differences between the groups were assessed by Fisher's exact test and Wilcoxon rank-sum test for categorical variables and continuous variables, respectively. The primary outcome end-point was loco-regional control (LRC), and the secondary endpoints were relapse-free survival (RFS), and overall survival (OS). OS was calculated using Kaplan-Meier methods (considering any death as an event). RFS (any local, regional, or distant failure as an event) and LRC (local or regional failure as an event) were calculated using the competing risk method where death without 'event' was considered as a competing risk. All times-to-event were calculated from the date of commencement of RT. The differences in outcomes between groups were compared by log-rank test. Univariate Cox regression analyses (UVA) were applied to explore the association of tumor factors and LRC and RFS. Hazard ratios (HRs) and 95% confidence intervals (CI) were reported accordingly. Paradoxically, the low event rate prevented the application of multivariable analysis to confirm the prognostication of these tumor factors. All tests were two-sided with a significance level at 0.05.

Results

Patient and disease characteristics

A total of 108 histologically confirmed 'aggressive' HN-BCC patients were identified, including 38 (35%) *de novo* and 70 (65%) treated for recurrence (Table 1). The 'aggressive' features included: initial tumor >10 mm in diameter (n = 105), >2 prior recurrences (n = 24), or extra-cutaneous extension (n = 30). Sixty-one, 40, and 7 patients had 1, 2, 3 risk factor(s), respectively. There were 64 (59%) males and 44 (41%) females, with a median age of 76 (range, 40–94) years. Three patients were immunocompromised (one was post renal-transplant, 1 had chronic lymphocytic lymphoma, 1 had