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Outcomes and prognostic factors for major salivary gland carcinoma following postoperative radiotherapy

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SUMMARY

Purpose: To report outcomes of postoperative radiotherapy (PORT) for major salivary gland carcinoma (SGC) and identify patients at high risk of distant metastases (DM).
Methods and materials: Patients with major SGC treated between 2000–2012 were identified. All patients underwent initial primary resection, with neck dissection (ND) therapeutically (if N+) or electively in high risk N0 patients. PORT was delivered using 3D-CRT or IMRT. Multivariable analysis (MVA) assessed predictors for DM, cause-specific (CSS) and overall survival.
Results: Overall 304 patients were identified: 48% stage III–IVB, 22% lymphovascular invasion (LVI), 50% involved margins and 64% high risk pathology. ND was performed in 154 patients (51%). Adjuvant chemotherapy was used in 10 patients (3%). IMRT was delivered in 171 patients (56%) and 3D-CRT in 133 (44%). With a median follow-up of 82 months, the 5-(10-) year local, regional, distant control, CSS and OS were 96% (96%), 95% (94%), 80% (77%), 83% (82%) and 78% (75%), respectively. DM was the most frequent treatment failure ($n = 62$). On MVA, stage III–IVB and LVI significantly correlated with DM, CSS and OS, while positive margins predicted DM and CSS, and high risk pathology predicted DM. No grade $\geqslant 4$ RTOG late toxicity was reported; 9 patients had grade 3, including osteoradionecrosis ($n = 4$), neck fibrosis ($n = 3$), trismus ($n = 1$) and dysphagia ($n = 1$).
Conclusions: Surgery and PORT with 3D-CRT/IMRT produced excellent long-term outcomes. Further research is required for patients with stage III–IVB, LVI, positive margins and high risk pathology to determine the incremental benefit of systemic therapy in management of SGC.

Introduction

Major salivary gland carcinomas (SGC) represent <5% of all head and neck cancers. These tumors are not only rare but also very heterogeneous, with over 20 histological subtypes with varying prognoses. The mainstay treatment of SGC is surgical resection. In well-selected patients with early-stage, low-risk disease and R0 resections, surgery alone is appropriate. In all other cases, combined modality treatment is recommended [1].

A number of studies have indicated that postoperative radiotherapy (PORT) significantly improved locoregional control (LRC) [2–4] and survival [5–7] in SGC patients with adverse pathologic features. However, despite bimodality therapy for aggressive disease, locoregional failure (LRF), distant metastases (DM) and poor survival have been frequently reported for certain prognostic features such as stage III/IV, lymphovascular invasion (LVI), positive surgical margins and high risk pathology [3,4,8–12]. The recognition of these adverse prognostic factors suggests a role for intensifying therapy in this group of patients.

In our institution, intensity modulated radiotherapy (IMRT) has become the standard of care for SGC in the postoperative setting since 2005. The rationale for conducting this study was to retro-

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spectively review patients with major SGC following PORT to describe the clinical outcomes and to identify patients at high risk of DM who might benefit from the addition of chemotherapy or targeted therapy in multimodality management of SGC.

Methods

Study population

After institutional research ethics board approval, we identified all patients with previously untreated, pathologically confirmed primary non-metastatic major SGC, treated with curative intent in our institution between 2000 and 2012 with surgery and PORT. Patients younger than 18 years, those with squamous cell carcinoma (SCC) histology and features suggesting nodal spread from an undetected skin primary, and those with minor SGC or patients treated with surgery alone were excluded from this analysis. Clinical information including outcomes was retrieved from the Head and Neck Anthology of Outcome system, in which clinical and outcome data were prospectively collected at point-of-care since 2003, using the "Formatted Anthology Synoptic Tick Sheet" (FAST) process [13]. Missing data were retrospectively retrieved from patients' medical records.

Pathologic classification

Central pathology review is part of our routine practice. High risk pathology was defined with histologic grade and WHO histologic subtype criteria, and included: adenoid cystic carcinoma (ACC), salivary duct carcinoma, SCC, G2/3 adenocarcinoma, G2/3 mucoepidermoid carcinoma (MEC), G2/3 carcinoma ex-pleomorphic adenoma, carcinosarcoma, undifferentiated (small-, large-cell or lymphoepithelial) carcinoma and G3 of other histologic subtypes [14].

Diagnostic approach

All patients were evaluated and managed by a multidisciplinary head and neck team. Staging evaluation consisted of history and physical examination, head and neck CT and/or MRI, and chest X-ray and/or CT chest.

Treatment approach

All patients underwent initial primary resection. Neck dissection (ND) was performed therapeutically in node positive disease (N+) or considered electively for clinically node negative (cN0) cases with T3/4-category or high-grade pathology. PORT was delivered using 3D-CRT or IMRT in cases with one or more risk features: T3/4, N+, positive or close (<5 mm) microscopic margins, high risk pathology, LVI and perineural invasion (PNI).

Clinical target volumes (CTVs) were defined using all available information, including radiological, pathological and operative findings. In cases with a positive surgical margin or nodal ECE, a high risk clinical target volume (CTV1) was recommended around the original site of the gross lesion prior to excision, and/or identified positive margin-ECE locations with a 5–10 mm margin. The site of preoperative gross disease (primary or nodal) with 5–10 mm margins and the entire operative bed were defined as CTV2. At risk nodal regions (if treated electively) and the course of a named nerve back to the base of the skull (if microscopically involved or in ACC histology) were defined as CTV3.

PORT dose was specified as 66, 60 and 54–56 Gy to CTVs 1, 2 and 3, respectively, in an overall treatment time of 6–6.5 weeks. In the early years of this study (2000–2004), accelerated fractionation (45–55 Gy in 20 fractions at 2.25–2.75 Gy per fraction over 4 weeks) was occasionally used.

Concomitant or sequential adjuvant chemotherapy is generally not indicated for salivary gland tumors. It is not given as a standard policy in our institution; however, in highly selected cases it may be considered. High risk situations (e.g. gross residual disease), high grade and/or potentially chemosensitive histology, and a young, fit and well-informed patient may prompt such a discussion.

Evaluation and follow-up

Patients were typically seen in a multidisciplinary clinic with a full head and neck examination 2–6 weeks after the end of radiotherapy (RT), then every 3 months for the first 2 years, every 4 months in the third year, every 6 months in the 4th and 5th year, and annually thereafter until the 10th year. Post-treatment imaging evaluation was performed 10–12 weeks after the end of RT, then as clinically indicated. Severe late RT-related toxicity (LT) was defined as late RTOG $\geqslant$ grade 3 toxicity starting >3 months after the end of RT.

Statistical methods

Local (LC), regional (RC), distant control (DC) and cause-specific survival (CSS) were analyzed by the competing risk method. LT was assessed by the cumulative incidence function. Overall survival was calculated with the Kaplan-Meier method. Multivariable analysis (MVA) using Cox proportional hazards model was applied to identify factors associated with DM, CSS and OS.

Results

Patient characteristics

A total of 304 eligible patients with major SGC were identified. The most common primary site was the parotid gland ($n = 237$; 78%). MEC ($n = 56$, 18%), ACC ($n = 55$, 18%), acinic cell ($n = 49$, 16%) and salivary duct carcinoma ($n = 40$, 13%) were the most prevalent histologies. High risk pathology was found in 190 patients (64%): ACC ($n = 55$), salivary duct carcinoma ($n = 40$), SCC ($n = 11$), G2/3 adenocarcinoma ($n = 15$), G2/3 MEC ($n = 35$), G2/3 carcinoma ex-pleomorphic adenoma ($n = 22$), and G3 rare histologic subtypes ($n = 12$). The details of patient and tumor characteristics are summarized in Table 1.

Treatment characteristics

Surgery

The operation was individualised based on location and extent of disease, tumor stage, performance status and comorbidities. Two hundred and three patients (67%) had total or subtotal parotidectomy, 34 (11%) superficial parotidectomy, 63 (21%) submandibular gland resection, and 4 had sublingual gland tumors resected. Maximal resection with preservation of major nerves was employed unless the nerve was encased by tumor. Margin status was: involved ($n = 152$, 50%), very close $\leqslant$1 mm ($n = 98$, 32%), close <5 mm ($n = 22$, 7%), clear $\geqslant$5 mm ($n = 19$, 6%) and undetermined ($n = 13$, 4%).

Neck dissection was performed in 154 patients (51%): selective neck dissection (SND) in 78 (26%), modified radical neck dissection (MRND) in 72 (24%), and radical neck dissection (RND) in 4 (1%). Limited dissection of first echelon nodal station was performed for diagnostic purposes in 19 patients. Of all patients with lymph nodes identified in their surgical specimens ($n = 173$), 32 (18%) had nodal ECE.