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Outcomes and prognostic factors in modern era management of major salivary gland cancer

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SUMMARY

Objectives: There is a dearth of prospective evidence regarding cancer of the major salivary glands. Outcomes and management of major salivary gland are based largely on retrospective series spanning many decades and changes in surgical, radiation, imaging and systemic therapy strategies and technique. We sought to report contemporary patterns of relapse and prognostic factors for major salivary gland cancer.

Materials and methods: 112 patients with major salivary gland cancers underwent resection with or without adjuvant therapy between January 1997 and September 2010. Outcomes were documented with follow-up until December 2014. Survival was calculated by the Kaplan–Meier method. Log-rank test and Cox proportional hazards regression were performed with locoregional control (LRC), distant control (DC) and overall survival (OS) as the primary outcome variables.

Results: Median follow-up was 55.1 months. Rates of LRC for stage I/II and III/IV at five years were 95.7% and 61.9% respectively. Rates of DC at five years for stage I/II and III/IV were 93% and 56.9% respectively. Multivariate analysis identified larger tumor size, clinical nerve involvement and in parotid cancers, advanced T stage, no adjuvant radiation, and older age at diagnosis to be associated with increased risk of locoregional recurrence (all $p < 0.05$). Distant metastasis was associated with sublingual site, degree of clinical nerve involvement, high grade, tumor size and in parotid tumors additionally deep lobe involvement on multivariate analysis (all $p < 0.05$).

Conclusion: Several prognostic factors were identified that may help guide decisions regarding adjuvant therapy. DM remains a significant concern in the management of this disease.

Introduction

Malignancies of the major salivary glands – parotid, submandibular and sublingual – represent a diverse subset of head and neck cancers. In all, they represent only 3–6.5% of head and neck cancers [1,2]. The overall annual incidence of this disease is 1.195/100,000 [3]. The relative paucity and diverse biology of salivary gland cancer have made progress in their management challenging. Surgery remains the cornerstone for management of this disease site. Although it has never been evaluated in the setting of a randomized clinical trial, postoperative radiation therapy has been increasingly used for patients with recognized high-risk features, including high grade histologies, size greater than 4 cm, extraparenchymal extension, close or positive margins, lymph node involvement, bone involvement, and perineural invasion among others [4,5]. Local therapies alone are not sufficient in high-risk patients [6–8], and appropriate patient selection for systemic therapy represents another clinical challenge. Unlike many

Abbreviations: LRC, locoregional control; DC, distant control; LRR, locoregional recurrence.

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other head and neck cancers, outcomes in salivary cancer have not improved appreciably over time. Unfortunately patient heterogeneity and paucity have precluded prospective, randomized trials that could guide us in the integration of systemic therapy into the therapeutic armamentarium, and we must rely on retrospective data.

Over the past two decades the management of head and neck cancer has evolved significantly. Preoperative imaging, surgical, and radiation techniques have all become more refined. Intensity modulated radiation therapy, aggressive facial nerve preservation and microsurgical free tissue reconstructions have become *de facto* standards of care [9]. In the present study, we report an updated experience relevant to current standards of practice. With changes in management in head and neck cancer we will particularly focus on prognostic factors for disease recurrence and overall patterns of recurrence within a modern cohort of patients.

Materials and methods

After obtaining Emory Institutional Review Board approval, we reviewed the records of 112 consecutive patients over the age of 18 with malignancies of the major salivary glands. Patients with suspected squamous cell carcinoma skin metastases, metastatic disease at presentation and no documented follow-up visits were excluded. All patients underwent surgical resection at Emory University between January 1997 and September 2010. Outcomes were documented with follow-up until December 1st 2014. Diagnosis was made by an attending head and neck pathologist. Initial staging for all patients included a detailed physical exam and computed tomography; many additionally underwent positron emission tomography (PET) and/or magnetic resonance imaging (MRI). Deaths were verified either by medical records or the Social Security Death Index.

All patients had primary surgery with curative intent as their initial treatment. Adjuvant chemotherapy and radiation usage was dictated at the discretion of the treating physicians, and the decision to give adjuvant therapy was generally driven by high risk factors, e.g. close or positive margins, T3–T4 tumor, perineural invasion, high grade and/or positive lymph nodes. Radiation was performed both at Emory University and outside facilities. All tumors were prospectively or retrospectively pathologically staged according to the 7th edition of the American Joint Committee on Cancer's staging system [10].

Statistical analysis

Descriptive statistics were reported for patient and disease characteristics. Kaplan–Meier method was used to produce survival estimates of locoregional recurrence (LRR), distant metastatic (DM) recurrence, and overall survival (OS) along with 5-year event free rate and its 95% confidence interval. Time to events was measured from the date of initial surgical resection. Patients were censored for LRR at time of DM, death or last clinical follow-up. Patients were censored for DM at time of death or last clinical follow-up. Univariate and multivariate survival analysis were carried out with a Cox proportional hazards model. The univariate association with histology and clinical nerve involvement was carried by ANOVA for numerical covariates; and Chi-Square test or Fisher's exact test for categorical covariates, where appropriate. For the multivariate analysis, the initial list of variables contained those with $p < 0.2$ in the univariate analysis as well as clinical relevant variables, such as adjuvant radiation usage in the LRR analysis, with the final model determined by backward elimination using a removal criterion of $p > 0.2$. All analyses were done using SAS 9.3 (SAS Institute, Inc., Cary, North Carolina) and SAS macros developed by Biostatistics and Bioinformatics Shared Resource at Winship Cancer Institute with a significance level of 0.05 [11].

Results

One hundred twelve eligible patients were identified: parotid ($n = 97$ [86.6%]), submandibular ($n = 11$ [9.8%]), and sublingual tumors ($n = 4$ [3.6%]). The median follow-up was 55.1 months, and the median age at diagnosis was 56 years (range: 18–91) Adenocarcinoma was the most common histology encountered ($n = 39$ [34.8%]). Full patient, disease, and treatment characteristics are listed in Table 1.

Adenocarcinoma (56.4%), acinic cell (22.7%) and mucoepidermoid were the most likely histologies to present with pathologic nodal involvement ($p < 0.001$). Adenocarcinoma (61.6%) and adenoid cystic (30%) were most likely to present with advanced T stage ($p = 0.002$). Lymphovascular space invasion (LVSI) was most common in adenocarcinoma (46%) and adenoid cystic carcinomas (40%) ($p < 0.001$). Clinical nerve involvement was most common

Table 1
Patient and treatment characteristic (continued).

Characteristic		$n = 112$ (%)
Primary site	Submandibular	11 (9.8)
	Parotid	97 (86.6)
	Sublingual	4 (3.6)
Parotid lobe	Superficial	59 (64.8)
	Deep	32 (35.2)
	Missing	6
Gender	Male	47 (42.0)
	Female	65 (58.0)
Age	<55	65 (58.0)
	⩾55	46 (42.0)
Tumor size	<2 cm	31 (28.4)
	2–3 cm	33 (30.3)
	⩾3 cm	45 (41.3)
	Missing	3
Lymph node dissection	No	66 (59.5)
	Yes	45 (40.5)
Degree of clinical nerve involvement	None	86 (76.9)
	Partial	15 (13.4)
	Complete	11 (9.8)
T stage	1 or 2	71 (63.4)
	3 or 4	41 (36.6)
Nodal involvement	Yes	34 (30.4)
	No	78 (69.6)
Stage	I/II	63 (56.3)
	III/IV	49 (43.8)
Grade	Low or intermediate	65 (58.0)
	High	47 (42.0)
Positive margin	Yes	41 (36.6)
	No	71 (63.4)
Bone invasion	Yes	4 (3.6)
	No	108 (96.4)
Adjuvant radiation	Yes	61 (54.5)
	No	51 (45.5)
Adjuvant chemotherapy	No	105 (93.8)
	Yes	7 (6.3)
Histology	Adenocarcinoma	39 (34.8)
	Acinic cell carcinoma	22 (19.6)
	Adenoid cystic carcinoma	10 (8.9)
	Mucoepidermoid carcinoma	28 (25.0)
	CEP	9 (8.0)
	Salivary duct carcinoma	2 (1.8)
	Basal cell adenocarcinoma	1 (0.9)
	Basaloid carcinoma	1 (0.9)
Radiation dose (median, Gy)		63 (53–72)
Radiation field including neck	No	7 (31.8)
	Ipsilateral	13 (59.1)
	Bilateral	2 (9.1)
	Missing	29