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“Prognostic factors in patients with high-risk locally advanced salivary gland cancers treated with surgery and postoperative radiotherapy”

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Abstract

Background: We sought to study the outcome of patients with locally advanced salivary gland cancers treated with surgery and postoperative radiotherapy.

Patients and methods: We conducted a retrospective review of patients with salivary gland cancers registered in University of Pittsburgh databases from 1990-2006.

Results: 74 patients were analyzed. Histologic types included salivary duct carcinoma, 24%; adenoid cystic carcinoma, 23%; adenocarcinoma, 19%; mucoepidermoid carcinoma, 14%; N2, 39%; N0-1, 58%; major salivary gland origin, 80%. With a median follow-up of 4.1 years, the 5-year recurrence-free survival (RFS) was 49%, and the 5-year overall survival (OS) 55%. The 5-year local RFS was 76% and the 5-year distant RFS 60%. Using Cox-regression analysis, advanced nodal stage (N2) was the only significant predictor of both RFS and OS.

Conclusions: The long-term outcome of patients with high-risk, locally advanced salivary gland cancers is unsatisfactory. Nodal stage is a strong predictor of recurrence and overall survival.

Introduction

Salivary gland cancers are an uncommon group of tumors comprising only 3-5% of all head and neck cancers and 0.5% of all malignant neoplasms.^{1, 2} Salivary gland cancers can arise

from either the major (parotid, submandibular or sublingual) or minor salivary glands located within the upper aerodigestive tract. Surgery is the mainstay of treatment of salivary gland cancers; however, the prognosis of patients with salivary gland cancers varies considerably. The clinical behavior of these cancers is dependent upon histology, grade, and stage.³ There are nearly 40 histologic types of salivary glands tumors, with some being exceedingly rare. Salivary gland cancers are generally classified into low-grade, intermediate and high-grade categories. The degree of differentiation tends to correlate with the incidence of lymph node metastases, extent of local invasion, and overall survival.⁴⁻⁹ Overall, tumor stage may be the most critical factor for determining the outcome of patients with salivary gland malignancies.¹⁰ Other pathologic features that may affect prognosis include positive surgical margins, extracapsular extension, bone invasion, or perineural invasion.

Most patients with low-grade T1 and T2 salivary gland cancers can be adequately treated with surgery alone. However, patients with either advanced tumors (stage III or IV) or certain histologies, such as adenoid cystic carcinoma that has a propensity for perineural invasion, are at an increased risk of locoregional recurrence. Retrospective studies have shown the addition of adjuvant radiotherapy to surgical resection provides superior disease control.¹¹⁻¹⁴ In advanced parotid cancers, Spiro et al showed the local recurrence rate after surgical resection is 50-60%.^{15,16} Although there are no randomized trials comparing surgery alone to surgery with adjuvant radiotherapy, retrospective studies suggest that combined modality therapy is superior to surgery alone for patients with advanced tumor (T) or nodal (N) stage.¹⁷⁻²²

The rarity of salivary gland cancers poses challenges in their study and design of novel therapeutic interventions for this disease. We sought to review our experience with patients with locally advanced salivary gland cancers treated with definitive surgery and postoperative radiation therapy in our center and identify predictors of recurrence-free and overall survival in a group of homogeneously treated patients. Our analysis may be useful in the design of prospective clinical trials in this clinical setting.

Patients and methods

This was a retrospective review of patients with malignant salivary gland tumors registered with University of Pittsburgh databases from 1990-2006. Our review was approved by the Institutional Review Board and was in compliance with Health Insurance Portability and Accountability Act regulations. Salivary gland cancers were staged according to the tumor-node-metastasis (TNM) staging system of the American Joint Committee on Cancer (AJCC). Histopathology types were classified using the World Health Organization classification. Our selection criteria included newly diagnosed stage III or IV salivary gland cancer treated by surgical excision with a curative intent without macroscopic residual disease followed by postoperative radiotherapy. Patients with early stage or distant metastatic disease, history of other malignancies (including skin cancers), non-salivary gland pathology, history of immunosuppression, or previous treatment were excluded.

Overall survival (OS) was measured from the time of surgery to last follow-up or death, and was estimated using the Kaplan Meier method. Recurrence-free survival (RFS) was measured from the time of surgery to the date of recurrence, death from any cause, or last follow up, and was estimated using the Kaplan Meier method as well. In addition to RFS, which includes any site of disease recurrence, local RFS, and distant RFS were estimated.

To identify prognostic factors that might influence survival, log rank tests were performed to examine the univariate associations between survival and parameters of interest, which included: age, gender, stage, primary site, histological type and pathologic features (grade, perineural invasion, extracapsular spread and positive margins), year of treatment, pathological nodal (N) stage, pathological tumor (T) stage and treatment type. Histologic grade risk group categorization is detailed in Table 1.

A step-down Bonferroni adjustment of p values was used to control for multiple comparisons.²³ Cox proportional hazard regression analysis was used to model OS as a function of age, primary site (parotid and submandibular vs. minor, and pathological nodal stage (stages 0, 1 vs. stage 2) and RFS as a function of primary site and pathological nodal status.²⁴ All analyses were performed using SAS v 9.1.3 (Cary, NC).

Results

Between 1990 and 2006, a total of 399 cases with salivary gland cancer of any stage and prior treatment status were identified in our databases. Of these, 74 cases met inclusion criteria. Patient characteristics are displayed in Table 1. The median age was 59 years (range, 21-90 years). Seventy percent of patients had malignancy arising from the parotid gland. The most common histological types were adenoid cystic carcinoma (23%), salivary duct carcinoma (12%), adenocarcinoma (19%), and mucoepidermoid carcinoma (14%); 62% of patients had lymph node metastasis. Of patients with available detailed pathological information, 64% had extracapsular spread in at least one lymph node, 81% perineural invasion, 51% positive margins (13% with a positive margin only at the facial nerve), and 88% high-risk histology. Of 37 patients with positive resection margins, 9 had positive margins only at the facial nerve.

The median postoperative radiotherapy dose was 60 Gy (range, 45 Gy-72 Gy). Fourteen patients (19%) also received adjuvant chemotherapy, 10 of them with concurrent carboplatin. Twelve of the 14 patients who received concurrent chemoradiotherapy had advanced nodal stage (N2).

Recurrence-free and overall survival

The median follow-up of alive patients was 4.1 years with 14 of the alive patients being followed-up for at least 4 years. The median OS was 5.5 years (4.1, 10.3). The 3- and 5-year OS probabilities were 72% (95% CI: 61.9%,83.2%) and 55% (95% CI: 41.1%,66.7%), respectively (Figure 1).

Thirty-three patients (45%) developed a recurrence of their cancer: 11 (15%) had locoregional recurrences, 19 (26%) had distant recurrences, and 3 (4%) had both

locoregional and distant recurrences. The most common sites of distant recurrences were lung (11), bone (6), and liver (3). The median RFS was 4.5 years (95% CI: 3.6,NA) and the probabilities of 3- and 5-year RFS were 64.5% (95% CI: 52.9%,76.0%) and 48.8% (95% CI: 35.3%,62.3%) (Figure 2). Median local and distant RFS have not been reached. The 3- and 5-local RFS were 80.7% (95% CI: 70.2%,90.5%) and 76.0% (95% CI: 61.2%,85.5%), respectively. The 3- and 5-distant RFS were 77.3% (95% CI: 67.1%,87.5%) and 60.2% (95% CI: 45.6%,74.8%), respectively.

Prognostic factors

We examined univariate associations between survival and parameters of interest using the log rank test (Table 1). Of the prognostic factors considered, age at diagnosis had a significant relationship with OS ($p=0.01$). As age increases, the risk of death increased minimally ($HR=1.04$). However, age at diagnosis did not affect risk of recurrence ($p=1.00$).

Patients with an increased nodal stage were at a significant risk of disease recurrence and death. The median RFS for patients with N0-1 nodal stage was 7.6 years and for patients with N2 nodal stage was 2 years ($p=0.004$). The median OS for patients with N0-1 and N2 disease was 6.6 years versus 2.8 years, respectively ($p=0.03$) (Figure 3). Also, primary site (minor vs. major salivary glands) was of potential significance for patient outcome. The median RFS for patients with minor and major salivary gland cancers was not reached and was 3.8 years, respectively, and the median OS was 10.3 and 4.7 years, respectively. The 3- and 5-year RFS for patients with major salivary gland cancers were 59.2% (95% CI: 45.9%, 72.5%) and 40.3% (95% CI: 25.4%,55.8%), whereas the 3- and 5-year RFS for patients with minor salivary gland cancers were 93.3% (95% CI: 80.7%,100%) and 81.7% (95% CI: 57.6%,100%). The 3- and 5-year OS for patients with major salivary gland cancers were 69.3% (95% CI: 57.0%,81.5%) and 45.9% (95% CI: 31.4%,60.5%), whereas the 3- and 5-year OS for patients with minor salivary gland cancers were 85.6% (95% CI: 66.9%,100%) and 85.6% (95% CI: 66.9%,100%), respectively. However, the p -values for the comparison of outcomes between major and minor salivary gland primary sites were not significant after Bonferroni adjustments were made (Table 1).

There was no association between site of recurrence and resection margin status. No differences in local RFS could be detected for margin status (unadjusted log rank $p = .296$) or histology (unadjusted log rank $p = .360$). We used Cox proportional hazards regression to model OS as a function of age, primary site (major versus minor), and pathological nodal stage (N0-1 versus N2). Primary site, age ($HR=1.04$, $p=0.001$) and nodal status ($HR=3.11$, $p=0.001$) were significant predictors of OS (Table 2). Modeling RFS as a function of primary site and pathological nodal stage (N0-1 versus N2) showed that pathological nodal stage was the only significant covariate in the model ($HR=3.05$, $p=0.0021$).

Discussion

In this series, we attempted to define a patient population with high-risk locally advanced salivary gland cancers that was homogeneously treated. Most previous reports have examined prognostic factors in more heterogeneous groups of patients with various stages of disease that were treated with surgery with or without postoperative

radiotherapy^{3, 11, 22, 25-27}. Other reports have focused on certain histologies or primary sites of salivary gland cancers^{11-13, 19-21, 28}. We selected patients with stage III/IV salivary gland cancers who underwent a potentially curative resection followed by postoperative radiotherapy to evaluate the outcome of patients and identify predictors of RFS and OS. Due to our selection criteria (i.e. the requirement for administration of postoperative RT) our patients had several high-risk features, including positive margins (51%), extracapsular spread (64%), and perineural invasion (81%). Also, there was a relatively high representation of patients with salivary duct carcinoma histology (24%), which is a particularly aggressive histologic type. Despite standard treatment with curative intent the 5-year recurrence-free survival in our patients was only 49%. We found that the single factor associated with both a higher risk of recurrence and death was advanced nodal stage. Our data also suggested that minor salivary gland location may have a better prognosis; however, this association was marginal and not statistically significant in univariate analysis when corrected for multiple testing. Moreover, our sample size did not allow for an evaluation of outcome by various histological subtypes.

Due to the rarity and diversity of salivary gland cancers, interpreting prognostic data is challenging. Prior retrospective reviews have shown that prognosis of patients with salivary gland cancers depends upon their histology, grade, and stage.^{3, 25} Other tumor characteristics which might affect prognosis include positive surgical margins, extracapsular extension, bone invasion, or perineural invasion. Overall, stage may be the most critical factor.¹⁰ However, the significance of the aforementioned unfavorable prognostic factors when patients are treated with postoperative radiotherapy is uncertain.

Retrospective data has shown that postoperative radiotherapy in locally advanced salivary gland cancers improves locoregional control.¹⁷⁻²² In patients with microscopic disease present at or close to the surgical margin postoperative radiotherapy reduced the incidence of local recurrence.²⁹ Renehan et al reported a trend towards a survival benefit for patients with high-grade tumors and tumors > 4 cm in size treated with postoperative radiotherapy.³⁰ In a series from the Dutch Head and Neck Oncology Cooperative Group, postoperative radiotherapy significantly improved 10-year local control compared with surgery alone in patients with T3–4 tumors (84% vs. 18%), close resection margins (95% vs. 55%), bone invasion (86% vs. 54%), and perineural invasion (88% vs. 60%)¹⁸. In our review, 9 of 37 patients with positive surgical margins were only positive at the facial nerve; however, the clinical impact of positive margins at the facial nerve only versus a positive margin is beyond the scope of this report. Nevertheless, margin status did not predict RFS in our patients who were all treated with postoperative radiotherapy.

A matched-pair analysis from Memorial Sloan-Kettering showed that the local control for stage III and IV disease in patients who received combined modality therapy (i.e. surgery followed by radiotherapy) versus patients who underwent surgery alone at 5 years was 51% versus 17%, respectively.¹⁷ A study from the University of Florida reported that the 10-year locoregional control in T4 tumors was 66% with surgery followed by radiation and 24% with radiotherapy alone.³¹ A retrospective review from Johns Hopkins University in patients with cancer of the major salivary glands who underwent surgery with or without radiation therapy showed that the local recurrence rates were significantly lower in patients who

received adjuvant radiotherapy (4% versus 26%).³² Five-year survival rates for patients treated with and without radiation therapy were 75% versus 59%, respectively, whereas the use of adjuvant radiotherapy was a significant predictor of survival on multivariate analysis. In a large series by Terhaard et al from the Dutch Head and Neck Oncology Cooperative Group, 498 patients with malignant salivary gland cancers were treated with (n = 386) or without (n = 112) adjuvant RT, and followed for a median of 76 months.¹⁸ Despite a greater frequency of poor prognostic features in the radiation therapy group (more positive neck nodes, more locally-advanced tumors) actuarial rates of local control were significantly higher with radiation therapy at both 5- and 10- years (94% versus 84%, and 91% versus 76%, respectively). Similar to our study, Teo et al who reviewed data on 50 patients with non-disseminated salivary gland carcinomas of whom 42 were treated with surgical resection followed by postoperative radiotherapy, noted that nodal stage was the main prognostic factor for overall and relapse-free survival.²⁶

In our series, patients with N2 disease had a median overall survival of only 2.8 years despite treatment with postoperative radiotherapy. It is possible that concurrent chemoradiotherapy will be beneficial in these patients as is in patients with locally advanced squamous cell carcinoma of the head and neck. However, there are no large prospective trials on the role of adjuvant concurrent chemotherapy radiotherapy for resected salivary gland cancers. In another retrospective study by Hocwald et al, patients who received adjuvant chemotherapy and radiation had a longer disease-free survival.²² We did not detect a benefit in a small number of our patients (17%) who received radiosensitizing chemotherapy concurrent with radiotherapy. However, a small sample size and selection bias could have accounted for the lack of observing a benefit with concurrent chemoradiotherapy as our patients treated with chemoradiotherapy had an increased nodal stage.

Our study has a number of limitations. A detailed analysis by histologic type was not possible due to the sample size. Also, our median follow-up is approximately 4 years, which may be relatively short for certain salivary gland cancers; however, given the aggressive nature of the selected salivary gland cancers many events occurred in the first 5 years of follow-up. Our observations can be potentially used in the design of prospective clinical trials in salivary gland cancers. The intent of the review was to identify patients who are at a greatest risk for recurrence of cancer after standard treatment. We noted that patients with advanced nodal stage have poorer survival. Other commonly seen pretreatment parameters, gender, positive margins, perineural invasion, extracapsular, grade or histology, did not influence outcome, possibly due to patient selection. In conclusion, the long-term outcome of patients with high-risk, locally advanced salivary gland cancers remains unsatisfactory. In order to improve treatment outcomes, we suggest the investigation of the addition of novel agents to postoperative radiotherapy in prospective clinical trials, especially in patients with advanced nodal stage disease.

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Figure 1. Kaplan-Meier overall survival (OS) with 95% CI (shaded gray). Median overall survival was 5.5 years (95% CI, 4.1-10.3).

Figure 2. Kaplan-Meier recurrence-free survival (RFS) with 95% CI (shaded gray). Median recurrence-free survival was 4.5 years (95% CI, 3.6-NA).

Figure 3.

Kaplan-Meier overall survival (OS) by nodal stage with 95% CI (shaded gray). The median overall survival for patients with N0-1 stage was 6.6 years and for the ones with N2 stage was 2.8 years ($p=0.003$).

Table 1

Clinicopathologic parameters and univariate analysis for overall and recurrence-free survival

Parameter		N=74 (% of total)	Median OS (years)	P	Bonferroni adjusted P	Median RFS (years)	P	Bonferroni adjusted P
Age			HR=1.04	0.001	0.01	HR=1.01	0.23	1.00
Gender	Female	34 (46%)	6.4	0.19	1.00	8.8	0.15	1.00
	Male	40 (54%)	4.1			4.4		
Year of Diagnosis	1990-1995	17 (23%)	6.4	0.50	1.00	8.8	0.22	1.00
	1996-2000	15 (20%)	4.6			4.4		
	2001-2006	42 (57%)	4.7			4.1		
Primary Site	Minor	15 (20%)	10.3	0.04	0.30	NR	0.02	0.22
	Major	59 (80%)	4.7			3.8		
Pathologic T-stage	1	11 (15%)	5.8	0.80	1.00	4.5	0.79	1.00
	2	15 (20%)	4.7			NR		
	3	22 (30%)	6.2			8.8		
	4	25 (34%)				4.4		
	Unknown	1 (1%)						
Pathologic N-stage	0-1	43 (58%)	6.6	0.003	0.03	7.6	0.0004	0.004
	2	29 (39%)	2.8			2.0		
	Unknown	2 (3%)						
Histology	Adenoid Cystic	17 (23%)	10.3	0.15	1.00	10.3	0.20	1.00
	Mucoepidermoid	10 (14%)	6.6			NR		
	Salivary Duct	18 (24%)	4.7			2.7		
	Adenocarcinoma	14 (19%)	5.5			8.8		
	Carcinoma ex pleomorphic	6 (8%)	3.9			1.8		
	Other *	9 (12%)	3.5			NR		
Grade	High	49 (66%)	4.1	0.41	1.00	3.6	0.63	1.00
Risk Group	Low	7 (10%)	4.7			NR		
	Unknown	18 (24%)						
Perineur. Invasion	Yes	50 (67%)	5.5	0.78	1.00	4.5	0.37	1.00
	No	12 (16%)	5.3			NR		
	Unknown	12 (16%)						
Surgical Margins	Positive	37 (50%)	6.4	0.50	1.00	4.5	0.84	1.00
	Negative	33 (45%)	4.7			4.4		
	Unknown	4 (5%)						
Adjuvant	Yes	14 (19%)	3.5	0.19	1.00	4.1	0.13	1.00

Parameter		N=74 (% of total)	Median OS (years)	<i>P</i>	Bonferroni adjusted <i>P</i>	Median RFS (years)	<i>P</i>	Bonferroni adjusted <i>P</i>
chemotherapy	No	57 (77%)	6.2			8.8		
	Unknown	3 (4%)						

Abbreviations: NR, not reached; OS, overall survival; RFS, recurrence-free survival

High risk grade group includes the following histologic types: Squamous cell carcinoma; salivary duct carcinoma; carcinoma ex pleomorphic adenoma; carcinosarcoma; high-grade adenocarcinoma, non otherwise specified; high-grade mucoepidermoid carcinoma; adenoid cystic carcinoma, solid.

* include acinic-cell carcinoma (5), myoepithelial carcinoma (2), polymorphous adenocarcinoma (1), carcinoma (1)

Table 2

Multivariate analysis model for overall survival and recurrence-free survival

	P value	Hazard Ratio	Standard Error
OVERALL SURVIVAL			
Age at diagnosis	0.001	1.04	0.01
Primary site (parotid and submandibular vs. minor)	0.603	1.31	0.51
Pathological nodal stage (N0-1 vs. N2)	0.001	3.11	0.35
RECURRENCE FREE SURVIVAL			
Primary site (parotid and submandibular vs. minor)	0.082	2.91	0.61
Pathological nodal stage (N0-1 vs. N2)	0.002	3.05	0.36