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Clinicopathologic features are stronger prognostic factors than histology or grade in risk stratification of primary parotid malignancies

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Abstract

Objective—To determine the relative contribution of clinicopathologic risk factors versus low- and high-risk grade histologic groups to assist management of primary parotid cancers.

Study design—Retrospective chart review.

Methods—168 primary parotid malignancies were treated surgically at a tertiary care center from 1982 to 2005. Of these, 115 patients with complete follow up information were further analyzed. Pathologic updating and re-classification in 28% of cases enabled comparison of tumor histology or grade with current consensus criteria. Clinical outcomes of high- and low-risk histology and grade were compared with the influence of traditional clinicopathologic risk factors.

Results—Of 115 cases, the male: female ratio was equal and the median age was 63 years (range, 15 to 89 years). Mucoepidermoid carcinoma (n=28) was the most common histology. The median follow-up was 44 months (range, 0 to 278 months). 40% of low-risk histology patients who underwent neck dissection had pN+ disease. The median time to recurrence was not reached

for low-risk tumors as compared to 29 months for high-risk tumors ($p = .0001$). Interestingly, extracapsular spread (ECS) and margin status were independent prognostic factors and conferred significantly greater prognostic value than histologic grade risk group. Disease free survival (DFS) and overall survival (OS) at 5-years for the entire cohort was 51% and 57%, respectively. Risk group was a strong independent predictor of OS but not DFS.

Conclusions—Risk group defined by histology and grade was associated with disease-free survival. ECS and margin status were independent predictors of disease-free survival. Inclusion of ECS and margin status substantially improved the prediction of disease recurrence, supporting elective neck dissection and post-operative radiotherapy for high-grade tumors or low risk histologies with positive margins or ECS.

Keywords

Malignant parotid tumors; prognostic factors; neck dissection; neck metastasis

Introduction

The World Health Organization (WHO) in 2005 classified malignant salivary gland tumors into 24 different tumor types based on their cytological and architectural features^{1,2}. Due to their rarity and diverse histology, it is challenging to accrue adequate numbers of parotid tumors to study by individual histological subtypes at a single institution^{3,4}. In addition, a lack of consensus regarding the indications and extent of surgical management of the neck has made pooling of data difficult. Our aim was to study the large number of primary malignant tumors of the parotid gland⁵ treated at our institution in an effort to assist in loco-regional control since the latter remains one the most important predictors of long-term outcome and disease-specific survival⁶. A substantial evolution in diagnostic criteria and classification of tumors of the parotid gland over the 25 year period of this study necessitated a review of pathology to reclassify tumors based on the patterns of clinical behavior. Low- and high-risk group stratification was determined by histology and grade⁷ which are considered to be important factors influencing by local, regional or distant metastasis^{6,8-11}. We also identified clinical and pathologic factors, such as presence of nodal metastasis¹², predictive of loco-regional control, disease-free survival (DFS) and overall survival (OS). In addition, the study aimed at determining the relative contribution of these clinicopathologic risk factors versus stratification low- and high-risk grade histologic groups to assist management of primary parotid cancers.

Methods

A retrospective review was performed which identified 168 primary malignant tumors of the parotid gland treated surgically in the Department of Otolaryngology at the University of Pittsburgh between 1982 and 2005. The University of Pittsburgh Medical Center (UPMC) Cancer Network registry and the Head and Neck Oncology registry served as the data sources for the current study. Prior to embarking on this study an approval to conduct this study was obtained from the Institution Review Board (IRB.No.0610046). Tumors were staged according to the AJCC staging criteria (American Joint Committee on Cancer; 2002)¹³. Recurrent tumors, metastatic tumors to the parotid from cutaneous or mucosal

malignancies, and patients with a prior history of head and neck cancer treatment other than a diagnostic biopsy were excluded. Of the study population, 137 patients fulfilled our eligibility criteria. Histopathology was re-categorized as per current WHO classification for salivary tumors of head and neck ². This subset (62/137, 45.2%) included tumors which required re-evaluation of grading (mucoepidermoid carcinomas and adenoid cystic carcinomas) to bring current status to the cohort, where diagnosis was 'carcinoma' and required further classification, and diagnoses with potential for reclassification such as, adenocarcinoma-NOS (not otherwise specified), adenosquamous carcinoma, clear cell carcinoma, polymorphous low grade adenocarcinoma, and carcinoma ex-pleomorphic adenoma. One hundred and fifteen patients had complete risk data and follow-up were further analyzed.

Statistical Analysis

The endpoints for evaluation of clinical outcome were overall survival and disease-free survival measured from the date of surgery. Disease-free survival was counted from the day of surgery till disease recurrence. Estimates of survival statistics were calculated with the Kaplan-Meier method with Greenwood confidence intervals. Group differences were tested with the log rank test. Effects of prognostic covariates were evaluated with Cox proportional hazards models. Models were checked for additivity, linearity and proportional hazards. Association between risk group and clinical and pathologic characteristics were tested with the Wilcoxon test or Fisher's exact test.

Results

Demographics and Clinicopathological Datas

There were 57 men and 58 women with a median age of 63 years (range, 15-89 years). Tumors were classified as T1 in 23%, T2 in 33%, T3 in 21%, T4 in 12%, and Tx in 11%. Twenty-five patients (22%) were treated with surgery alone while 85 (74%) patients received surgery and postoperative radiation therapy (RT). In five patients, information on post-operative therapy was not found. Our indications for adjuvant RT were positive margins, nodal metastasis, extra-capsular spread (ECS), perineural invasion (PNI), and advanced T class (T3 and T4). The main trunk of facial nerve was sacrificed in 8 (6%) cases. 69 patients (60%) underwent neck dissection. The incidence of pathologic nodal disease, extracapsular nodal spread (ECS), positive margins, and positive intraparotid nodes was 30% (35/115), 20.8% (24/115), 33% (40/115), and 16% (8/115). Among the 115 patients analyzed, the distribution of pathological disease was mucoepidermoid carcinoma in 24% (28), squamous cell carcinoma in 15% (17), acinic cell carcinoma in 12% (14), salivary duct carcinoma 9% (10), adenocarcinoma, NOS in 17% (20), carcinoma ex-pleomorphic adenoma in 5% (6), adenoid cystic carcinoma in 8% (9), NS and others in 10% (11).

Mucoepidermoid carcinoma (MEC) was the most common histological subtype (24%), followed by squamous cell carcinoma (15%), (Table 2). Tumors were then classified by grade and histology into high- and low-risk groups (Table 1), using established criteria ¹⁰. The risk classification was found to be strongly associated with well known clinical and pathologic features of prognostic importance for primary parotid cancers (Table 2). The high

risk group patients were characterized as older, more likely to have larger tumors (T3/T4), have positive margins and ECS. Furthermore these patients were much more likely to be selected for neck dissection and adjuvant radiotherapy.

Partial parotidectomy was performed in 57 (49.6%) cases and 58 (50.4 %) underwent a total parotidectomy. Forty-nine patients (37%) had positive surgical margins. Among 108 patients evaluated for margin status, 33% (18/54) of patients who underwent a partial parotidectomy and 41% (22/54) who with a total parotidectomy had positive surgical margins. Sixty-nine patients (60%) had a simultaneous ipsilateral neck dissection.

The incidence of pathological nodal metastasis was 15% in the low-risk group and 44% in the high-risk group ($p = .0034$). Among the low-risk group patients who underwent neck dissection, five patients were clinically node-positive. Of these, all five had evidence of nodal metastasis on pathology. The incidence of extracapsular spread among high-risk tumors was 36% (22/61).

Survival Analysis and Tumor Recurrence

The median follow-up for patients who were alive was 44 months (range, 0 to 278 months). The OS and DFS for the cohort at 5-years was 51% (95% CI – 41% - 64%) and 57%, respectively (95% CI = 47% - 68%). We examined the covariates age, margin status, ECS, grade pathologic node and tumor stage, intra-parotid node status and risk group along with the treatment variables radiation therapy and neck dissection. In the univariate analysis, all factors except intra-parotid node status were marginally associated with OS (Table 3). All factors except age and intra-parotid node status were associated with DFS (Table 4).

In a multivariate proportional hazards regression analysis, four of the covariates emerged as independently associated with overall survival: margin status, ECS, pathologic T classification and histologic grade risk group (all covariates had $p < .05$) (Table 5). In a multivariate model for disease-free survival, margin status, ECS and neck dissection independently predicted disease-free survival (Table 6). Interestingly, when margin status and ECS were considered, risk group was only weakly associated with DFS (hazard ratio 2.1, 95% CI = 0.95 – 4.47).

When a modified risk category was created for DFS according to the multivariate Cox model, we found that ECS and margin status were strongly associated with DFS, but risk group (based only on histology and grade) was not statistically correlated with DFS ($p < 0.05$) and was only marginally important. We classified all patients having ECS, positive margins or falling into the high risk category ($N = 79$) into one group comparing them to patients who had none of those factors ($N = 34$). Figure 1 shows the improvement in association with DFS when these overriding prognostic factors are added to the prediction. Only 2 patients recurred within 10 years out of the 34 patients at low risk in this modified classification. Only one patient had an event beyond 10 years. Figure 2 further clarifies that ECS and positive margins are important predictors of disease-free survival as compared to high/low risk groups. In order to facilitate integration of this information into clinical practice as prognostic variable, we developed a nomogram with relative risk quantified (Figure 3).

For overall recurrences, the median time to recurrence was not reached for low-risk tumors, as compared to 29 months for high-risk tumors ($p = .0001$). The incidence of distant metastasis was 14% (16/115). Two were derived from the low-risk group (12.5%) and 87.5% (14/16) from the high risk group. Distant metastasis was most commonly seen in the lung (25%) followed by the liver (25%) and bone (18%), respectively. None of the distant failures could be salvaged.

Discussion

Varied histology, lack of consensus on the pathological diagnosis and extent of surgery across centers, and a low incidence of primary cancers of the parotid gland (2%) have resulted in current literature being limited to studies that lack the numbers to provide strong recommendation for managing individual histological subtypes^{10,14,15}. In the last two decades salivary gland tumors have been re-classified histopathologically with new guidelines in the literature favored by better consensus². These factors could be limit prognostic studies of parotid gland cancers. Furthermore, there is a general phenomenon that prognostic models used to determine patient outcome do not always work as well in populations different from those in which the index was developed. Takahama (2009), compared 2 prognostic scores that were previously published for patients with parotid carcinoma in a retrospective series of 175 patients treated in their institution and found that both scores were not completely reproducible for their patient cohort.¹⁶ In a distinction from current published studies, we reanalyzed pathological records and reevaluated slides to ensure that accurate and contemporary diagnoses were considered prior to analysis of our data. We performed this study to directly compare, in a multivariate analysis, the relative risk of clinicopathologic factors such as nodal disease, ECS and margin status, with accepted high- and low-risk histologic grading classifications. This information is expected to contribute to prognostic evaluation of parotid cancer patients in the clinic and to guide treatment decisions, such as the application of elective neck dissection, since the information provided by status of nodal disease and ECS is much more prognostically important than histologic risk group of the primary tumor..

In our study, risk classification was independently associated with clinical outcome and independently affected overall survival and to a lesser extent, disease free survival. The high risk group patients were characterized as older, larger tumors (T3/T4), had positive margins and ECS. Furthermore these patients were much more likely to be selected for neck dissection and adjuvant radiotherapy having a greater incidence of nodal metastasis (44% vs. 6%) with a high frequency of ECS (36% vs. 2%) as compared to the low-risk group. Among thirty clinically node positive patients who had neck dissections, 27 (90%) had nodal metastasis. In our observed cohort, clinically palpable neck disease correlated with pathological node positivity. Although, the overall incidence of nodal metastasis in low-risk patients was 15%, all five low-risk, clinically node-positive patients having a neck dissection had evidence of nodal metastasis on pathology (100%). The high incidence of pathological node positivity within high risk patients and the overall clinically node positive group justifies elective neck dissection for clinically node-positive patients (low and high risk groups). The need for elective neck treatment for low-risk tumors with clinically node-negative necks needs further investigation. Currently, we do not recommend elective neck

dissection in low-risk patients with clinically N0 necks. Adjuvant radiotherapy is known to improve local tumor control^{17,18} (Terhaard 2004; Zbaren P 2003) and we recommend it for any salivary cancer with poor histopathological features (advanced T stage, facial nerve infiltration, positive margins, PNI, nodal metastasis, or ECS).

In addition to risk stratification by histology and grade, it is important to consider other factors of prognostic importance such as stage, age, pre-operative facial weakness, positive margins, perineural invasion and ECS^{9, 10,19}. In our study, ECS and margin status were associated with overall and disease free survival independently of high/low risk stratification. ECS is only reliably detected using neck dissection and this further validates the need for elective neck dissection in patients at risk for nodal metastasis. Our results agree with others studies that have shown ECS is an independent predictor for survival in parotid tumors²⁰ (Klussman 2008). We adjusted our risk categories to include these two factors and found that adding ECS status and margin status to grade and histology substantially improves the prediction of disease recurrence by these modified risk categories (see Figures 1 and 2). We created a predictive model for relative risk, disease-free survival, and median interval to recurrence based on margin status, ECS, and risk stratification. Such a predictive model can help plan adjuvant treatment, follow-up, and define prognosis based on histopathological staging. Although, this proposed model is accurate for our study population, it would need external validation before it can be extrapolated for use in clinical practice.

Distant metastasis signifies a dismal prognosis with death occurring within months of detection. The incidence of distant metastasis in our series was 14%. In the literature, this can vary according the histology being extremely rare for mucoepidermoid carcinoma to as high as 50% in salivary duct carcinoma^{21,22} (Zbaren P 2003). The commonest sites for distant metastasis in our series was lung (25%), liver (25%), and bone (18%) which is similar to other reports²³ (Terhaard Head Neck 2004). Interestingly, 12.5 percent (2/16) were derived from the low-risk group. In the high-risk group, 90 percent of the patients recurred within 29 months. The comparable figure in the low risk group was observed at five years, suggesting that long-term follow up for at least 5 years is warranted for patients with low-risk tumors to improve the prospects of identifying distant failures.

Conclusions

ECS and margin status were much stronger predictors of disease-free survival than histologic grade risk group. Inclusion of ECS and margin status substantially improved the prediction of disease recurrence, supporting elective neck dissection and postoperative radiotherapy for high-grade tumors or low risk histologies with positive margins or ECS. Low-risk tumors with clinically palpable lymphadenopathy also had a high incidence of nodal metastasis and can benefit from elective neck dissection to identify ECS. A predictive model based on margin status, ECS, and risk groups can help in counseling patients regarding prognosis, planning adjuvant treatment, and follow up. Follow up to identify distant failures can be recommended for at least 5 years in low-risk patients and at least 29 months for high risk tumors. The conclusions of this study are valid for our patient cohort

but need to be validated in large multicenter prospective trials for more generalized applicability.

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Clinicopathologic features as stronger prognostic factors than histology or grade in risk stratification of primary parotid malignancies

Figure 1.

A. Disease-free survival by high risk/low risk group. Dotted lines indicate the 95% confidence interval. The number of patients at-risk for recurrence is shown above the X-axis at the beginning of each 2 year interval.

B. Disease-free survival by modified risk group (Negative margins, No ECS, Low risk vs. Positive margins, ECS, High risk). Dotted lines indicate the 95% confidence interval. The number of patients at-risk for recurrence is shown above the X-axis at the beginning of each 2 year interval. Inclusion of ECS and margin status substantially improves the prediction of disease recurrence.

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Figure2. Disease free survival curves demonstrating the effect of ECS and positive margin on disease recurrence within high/low risk groups

The number of patients at-risk for recurrence is shown above the X-axis at the beginning of each 2 year interval. Inclusion of ECS and positive margin status worsens prognosis within high/low risk groups ($p < 0.001$). Exclusion of ECS and positive margins makes high and low risk groups more comparable in terms of disease-free survival ($p < 0.001$).

Clinicopathologic features as stronger prognostic factors than histology or grade in risk stratification of primary parotid malignancies

Figure 3. Nomogram showing predictive model for relative risk, disease-free survival at 2 and 3 years, and median disease free survival

The risk for recurrence is compared to patients with least risk of failure (i.e. low risk group + negative margin + no ECS). Margin status, ECS, and risk groups are assigned points based on observed results. Risk factors above the line are scored clinically. For example, patient A after surgical treatment who is low risk (0), has positive margins (100), and ECS (90) would score 190 points. The total score (190) then can be plotted against relative risk, disease-free survival at 2 and 3 years, and median disease-free survival (190 points~ 12.5, 35%, 20%, 14 months, respectively) that are below the dividing line to predict outcome.

Table 1

Risk stratification of tumors by histology and grade

HIGH RISK	LOW RISK
<ul style="list-style-type: none"> • SCC • Salivary Duct Carcinoma • Carcinoma Ex-Pleomorphic Adenoma • Carcinosarcoma • High Grade Carcinoma • Variants – Adenocarcinoma, NOS; Mucoepidermoid carcinoma (high grade) ; Solid Adenoid Cystic Carcinoma 	<ul style="list-style-type: none"> • Acinic Cell Carcinoma • Myoepithelial Carcinoma • Polymorphous Low Grade Adenocarcinoma • Low to Intermediate Grade Carcinoma • Variants – Adenocarcinoma, NOS; Mucoepidermoid carcinoma (low and intermediate grade) ; Tubular or Cribriform Adenoid Cystic Carcinoma

Table 2

Distribution of clinical and pathological features by histologic grade risk groups

	Low-Risk N = 54	High-Risk N = 61	P value for test of equality *
Median Age	54	68	.0002
T3/T4	13 (24%)	25 (41%)	.0737
Neck Dissection	21 (39%)	48 (79%)	<.0001
pN+	158 (15%)	27 (44%)	.001
Margins+	16 (30%)	24 (39%)	.2336
ECS	2 (4%)	22 (36%)	<.0001
Radiation Therapy	31 (57%)	53 (87%)	.0001
Intra parotid node+	6 (11%)	12 (20%)	.304

* Wilcoxon test for age; Fisher's exact test for all others.

Table 3

Individual covariates and overall survival

Covariate	P	Level	Reference	Hazard Rate	95% CI
ECS	<.0001	Yes	No	3.71	2.05 – 6.71
Risk Group	<.0001	High	Low	4.41	2.31 – 8.43
pNstage	<.0001	N1	N0	1.78	0.58 – 5.50
		N2	N0	5.37	2.61 – 11.06
Age	.0001	75	49	1.47	0.45 – 4.83
pTstage	.0047	TX	T1	2.90	1.12 – 7.46
		T2	T1	4.18	1.68 – 10.35
		T3/T4	T1	6.17	2.37 – 16.09
Grade	.002	Intermediate	Low	2.55	0.95 – 6.80
		High	Low	5.14	2.13 – 12.40
Radiation Therapy	.0015	Yes	No	4.51	1.62 – 12.57
Neck Dissection	.0028	Yes	No	2.59	1.39 – 4.84
Margins	.0077	Positive	Negative	2.27	1.24 – 4.14
Intra Parotid Node	.8368	Positive	Negative	1.09	0.49 – 2.43

Table 4

Individual covariates and disease-free survival

Covariate	P	Level	Reference	Hazard Rate	95% CI
ECS	<.0001	Yes	No	4.0	2.19 – 8.33
pNstage	<.0001	N1	N0	2.38	0.75 - 7.62
		N2	N0	7.53	3.45 – 16.41
Margins	.0002	Positive	Negative	3.24	3.24 – 6.09
Risk Group	.0003	High	Low	3.28	1.73 – 6.20
Grade	.0007	Intermediate	Low	3.75	1.36 - 10.36
		High	Low	4.88	1.87 – 12.76
Neck Dissection	.0008	Yes	No	2.71	0.76 – 9.64
pTstage	.0039	TX	T1	3.50	1.16 – 10.60
		T2	T1	5.49	1.87 – 16.10
		T3/T4	T1	5.62	1.84 – 18.18
Radiation Therapy	.0032	Yes	No	5.74	1.78 – 18.59
Intra Parotid Node	0.79	Positive	Negative	0.89	0.38 – 2.10
Age	.184	75	49	1.34	0.87 – 2.05

Table 5

Joint covariates and overall survival

Covariate	P	Level	Reference	Hazard Rate	95% CI
Margins	.0001	Positive	Negative	2.76	1.44 – 5.32
ECS	.0015	Yes	No	2.53	1.23 – 5.20
Risk Group	.0047	High	Low	3.01	1.40 – 6.45
pTstage	.0001	TX	T1	2.18	0.60 – 7.89
		T2	T1	1.66	0.67 – 5.20
		T3/T4	T1	4.11	1.25 – 9.27

Table 6

Joint covariates and disease-free survival

Covariate	P	Level	Reference	Hazard Rate	95% CI
Margins	.0001	Positive	Negative	3.61	1.90 – 6.88
ECS	.0022	Yes	No	3.15	1.51 – 6.55
Risk Group	.0668	High	Low	2.06	0.95 – 4.47