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HEAD & NECK

Clinical behaviours and prognoses of high- and low-risk parotid malignancies based on histology

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Abstract

Purpose To report 5-year survival in patients with primary parotid malignant tumours and assess the impact of various factors on survival or local control among diverse histologic groups.

Methods A total of 65 patients with primary parotid malignant tumours who had surgery between 2003 and 2014 were identified. Demographic characteristics including age, T stage, N stage and clinical or pathological performance were analysed. According to risk stratification (based on pathology), 65 primary parotid malignant tumours were divided into high-risk (23, 35.38%) and low-risk (35, 53.85%) groups. Overall survival (OS) and disease-free survival (DFS) were recorded by the Kaplan–Meier methods.

Results The 5-year overall survival rate for primary parotid malignant tumours was 70.9%. Patients older than 60 years with fixed mass, pain, facial-nerve palsy and high-grade N stage had adverse OS and DFS. Upon multivariable analysis, facial-nerve palsy (HR 24.59; 95% CI 2.338–178.446; $P=0.002$) was the only independent predictive factor for OS. Patients with high-risk parotid malignant types were more likely to have tumour pain, facial-nerve palsy (Chi-square test: < 0.0001 and 0.02), lymphatic metastasis and local/regional recurrence (Chi-square test: 0.008 and 0.012).

Conclusions Compared with low-risk parotid carcinoma, tumours with high-risk histological features tend to need aggressive surgical extirpation, neck dissection and postoperative radiotherapy.

Keywords Primary parotid malignant tumour · Risk stratification · Prognosis · Overall survival (OS) · Disease-free survival (DFS)

Abbreviations

OS	Overall survival
DFS	Disease-free survival
WHO	World Health Organization
PPMT	Primary parotid malignant tumour
SPMT	Secondary parotid malignant tumour
HRs	Hazard ratios

Introduction

Parotid malignancies are relatively infrequent entities that account for less than 5% of all head and neck cancers presenting annually. Salivary-gland carcinomas comprise at least 20 distinct types recognized by the World Health Organization (WHO) [1, 2]. Their heterogeneous nature and rarity of occurrence have prevented a complete understanding of the clinical course and prognostic predictions related to parotid malignancies. As a result, treatment has to be tailored to each patient.

Many factors have been reported to be linked to outcomes, for example, tumour size, age, gender, clinical features (mobility, pain, facial-nerve palsy), T stage, N stage and pathologic types [3, 4]. Among these, histologic factors may be the most important predictors of outcome for parotid

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carcinoma. Compared with low- and intermediate-grade tumours (5-year survival 85–90%), high-grade salivary carcinoma has a 5-year survival of nearly 40% [5, 6]. As a result, the reliability of pre-treatment diagnosis is crucial in the era of multimodal treatment of parotid carcinoma, which is modulated according to histology and grading. However, the current salivary-gland tumour grading system is subject to many deficiencies and may not accurately predict outcome. Raja [7] divided all pathology types listed in the WHO classification scheme into low-risk and high-risk groups. This grading system should help to stratify patients into distinct management categories.

This study provides data relating to parotid malignant tumours in patients treated at our institution over a 10-year period. The study performs multivariate analyses on a broad range of histological and clinical factors at a single institution. We use OS and DFS as prognostic endpoints. In particular, we want to assess the impact of these factors on local control and among diverse histologic groups (high risk and low risk).

Methods

Patients

We identified 65 cases of primary parotid malignant tumours in our department dating from January 2003 to January 2014. Demographic data (age, sex, race), TNM stage (AJCC seventh edition [8]), clinical features, clinicopathologic data, survival data and corresponding surgical pathologic diagnosis were then obtained. According to the risk stratification (Table 1) [7], 65 primary parotid malignant tumours were identified as high-risk (23, 35.38%) or low-risk (35, 53.85%), while seven patients could not be stratified. Patients underwent a clinical analysis and subsequent surgery with or without postoperative radiotherapy (RT) or chemoradiotherapy (CRT).

Treatment and follow-up

All patients underwent tumour excision, and 18 patients underwent lymph-node dissection. Twenty-four patients underwent partial parotidectomy, and 41 patients underwent total parotidectomy. The modified radical neck dissection was commonly performed in patients with clinical nodal metastasis, while elective neck dissection was preferred in patients without clinical nodal metastasis. Of 65 patients, 24 patients received postoperative radiotherapy, of whom three underwent concurrent chemotherapy. Head and neck examination were scheduled every 3 months in the first year and every 6 months in subsequent years. The median follow-up time of patients alive at the last follow-up was 55.8 months. Outcome variables were 5-year OS and 5-year DFS. Nine patients had local/regional recurrence, four of whom had lung metastasis. DFS is the percentage of individuals in the treatment group who were likely to be free of recurrence (local/regional/distant metastasis) after the duration of follow-up.

Ethical considerations

This study was approved by the ethics boards of Eye and ENT Hospital of Fudan University and conducted in line with the principles of the Declaration of Helsinki.

Statistical analysis

OS and DFS were recorded by the Kaplan–Meier method. The impact of prognostic factors on OS and DFS was evaluated through univariate and multivariable hazard ratios

Table 1 Risk stratification of WHO recognized salivary-gland malignancies

Low risk	High risk
Acinic cell carcinoma	Sebaceous carcinoma and lymphadenocarcinoma
Low-grade mucoepidermoid carcinoma	High-grade mucoepidermoid carcinoma
Epithelial–myoepithelial carcinoma	Adenoid cystic carcinoma
Polymorphous low-grade adenocarcinoma	Mucinous adenocarcinoma
Clear cell carcinoma	Squamous cell carcinoma
Basal cell adenocarcinoma	Small cell carcinoma
Low-grade salivary duct carcinoma	Large cell carcinoma
Myoepithelial carcinoma	Lymphoepithelial carcinoma
Oncocytic carcinoma	Metastasizing pleomorphic adenoma
Carcinoma ex pleomorphic adenoma (intracapsular/minimally invasive or with low-grade histology)	Carcinoma ex pleomorphic adenoma (widely invasive or high-grade histology)
Sialoblastoma	Carcinosarcoma
Adenocarcinoma NOS and Cystadenocarcinoma, low grade	Adenocarcinoma NOS and cystadenocarcinoma, high grade

(HRs) with 95% confidence intervals (CIs). Statistical analysis was carried out using the SPSS statistics package (IBM Corp., Armonk, NY). A *P* value of less than 0.05 was considered statistically significant.

Results

Patients and treatment characteristics

Table 2 shows 65 primary malignancies in parotid glands. The median age was 49.3 years (range 8–78), and 32 patients (49.23%) were female. Forty-two patients were at clinical stage T1/T2, and nine patients had clinical nodal disease. The study included 12 (18.46%) patients with mucoepidermoid carcinoma, 11 (16.92%) with polymorphous low-grade adenocarcinoma, 9 (13.85%) with acinic cell carcinoma, 9 (13.85%) with squamous cell carcinoma, 6 (9.23%) with adenoid cystic carcinoma, 5 (7.69%) with adenocarcinoma, 5 (7.69%) with lymphoma, 3 (4.62%) with lymphoepithelial carcinoma, 1 (1.54%) with myoepithelial carcinoma and 2 (3.08%) with other types.

Outcomes

The outcome data are presented in Table 3. The median follow-up was 49.56 months. The OS rate for parotid malignant tumours was 70.88%, while the DFS rate was 70.81%. For primary parotid malignant tumour, data analysis demonstrated a significant difference in age and clinical features. In terms of age, OS percentages for patients older than 60 compared with their younger counterparts were 41.54% and 78.49%, respectively ($P=0.0059$). Clinical characteristics of tumour pain, fixed mass and facial-nerve palsy were associated with worse OS and DFS. Patients with pain mass had an OS of 21.36% and a DFS of 21.38% as compared with 84.96% and 85.21%, respectively, for those with no pain mass (OS, $P=0.0008$; DFS, $P=0.0026$). Patients with a fixed mass had an OS of 53.75% and a DFS of 53.02% as compared with 89.42% and 89.29% respectively, for those with no fixed mass (OS, $P=0.0085$; DFS, $P=0.0072$). Patients with facial-nerve palsy had an OS of 15.54% and a DFS of 15.54% as compared with 84.10% and 84.40%, respectively, for those with no facial-nerve palsy (OS, $P<0.0001$; DFS, $P<0.0001$). Upon multivariable analysis, facial-nerve palsy (HR = 24.59; 95% CI, 2.338–178.446; $P = 0.002$) was the only independent predictive factor for OS (Table 4).

By contrast, histopathologic features of extracapsular invasion and perineural invasion were not poor prognostic factors. No significant difference was observed between partial and total parotidectomy among T1/T2-stage patients.

Patients who did or did not receive postoperative radio therapy (RT) did not significantly differ in terms of DFS and

Table 2 Clinical characteristics of malignant tumour of parotid gland

Characteristics	No. of patients, %
Gender	
Male	33 (50.77)
Female	32 (49.23)
Age	
≥60	17 (26.15)
<60	48 (73.85)
Pain	
Yes	16 (24.62)
No	49 (75.38)
Mobile tumour	
Yes	30 (46.15)
No	35 (53.85)
Facial-nerve palsy	
Yes	13 (20.00)
No	52 (80.00)
T classification	
T_1	23 (35.38)
T_2	29 (44.62)
T_3	5 (7.69)
T_4	8 (12.31)
N classification	
N_0	56 (86.15)
N_1	2 (3.08)
N_2	7 (10.77)
Tumour size	
≥4 cm	9 (13.85)
<4 cm	56 (86.15)
Pathology type	
Mucoepidermoid carcinoma (low grade)	11 (16.92)
Mucoepidermoid carcinoma (high grade)	1 (1.54)
Polymorphous low-grade adenocarcinoma	11 (16.92)
Acinic cell carcinoma	9 (13.85)
Squamous cell carcinoma	9 (13.85)
Adenoid cystic carcinoma	6 (9.23)
Adenocarcinoma	5 (7.69)
Lymphoma	5 (7.69)
Lymphoepithelial carcinoma	3 (4.62)
Other types	2 (3.08)
Basal cell adenocarcinoma	2 (3.08)
Myoepithelial carcinoma	1 (1.54)
Perineural invasion	
Yes	11 (16.92)
No	54 (83.08)
Recurrence	
Yes	9 (13.85)
No	56 (86.15)
Treatment	
Surgery	38 (58.46)
Surgery + PORT	24 (36.92)
Surgery + POCRT	3 (4.62)

Table 2 (continued)

Characteristics	No. of patients, %
Surgical therapy	
Partial parotidectomy + tumour excision	24 (36.92)
Total parotidectomy + tumour excision	41 (63.08)
Lymph-node dissection	
Yes	18 (27.69)
No	47 (72.31)

OS ($P > 0.05$). To further investigate the role of postoperative radiotherapy, we divided the patients into high-risk and low-risk groups according to histology. However, patients in the postoperative radiotherapy group and those in the postoperative non-radiotherapy group did not differ significantly ($P > 0.05$).

All patients were then categorized into high-risk or low-risk categories according to pathology. Overall, compared with low-risk types, patients with high-risk pathology types

Table 3 Survival analysis of malignant tumour of parotid gland for 5-years

Variable	OS. %	*P* value	HR (95% CI)	DFS. %	*P* value	HR (95% CI)
Age (year)						
< 60	78.49			79.37		
≥ 60	41.54	0.0059	0.1 (0.03–0.6)	43.98	0.0032	0.1 (0.03–0.5)
Pain						
Yes	21.36			21.38		
No	84.96	0.0008	0.08 (0.02–0.4)	85.21	0.0026	0.1 (0.03–0.5)
Mobile mass						
Yes	89.42			89.29		
No	53.75	0.0085	0.2 (0.08–0.7)	53.02	0.0072	0.2 (0.07–0.7)
Facial-nerve palsy						
No	84.10			84.40		
Yes	15.54	< 0.0001	0.01 (0.002–0.06)	15.54	< 0.0001	0.02 (0.004-0.1)
T stage						
T1 or T2	71.97			71.66		
T3 or T3	66.46	0.5258	0.6 (0.1–2.7)	66.46	0.6276	0.7 (0.2-3.0)
N stage						
N0	74.23			74.06		
N1 or N2	57.14	0.0007	0.009 (0.001-0.1)	64.82	0.0012	0.01 (0.001-0.2)
Tumour size						
< 4	72.04			71.95		
≥ 4	58.33	0.6741	0.7 (0.1–3.8)	58.33	0.7570	0.8 (0.1-4.0)
Margin status						
−	73.06			76.66		
+	53.47	0.1509	0.3 (0.08–1.5)	55.56	0.1816	0.4 (0.09–1.6)
Extracapsular spread						
Yes	75.00			75.00		
No	70.08	0.9193	1.0 (0.2–5.2)	69.97	0.9809	1.0 (0.2–4.5)
Perineural invasion						
Yes	71.11			71.34		
No	71.55	0.5148	0.5 (0.09–3.4)	74.07	0.5974	0.6 (0.1–3.7)
Recurrence						
No	81.35			81.353		
Yes	18.75	0.0031	0.08 (0.01–0.4)	0.000	< 0.0001	0.01 (0.002-0.1)
Treatment						
Surgery	74.522			73.46		
Surgery + radiotherapy	69.213			68.46		
Surgery + chemotherapy	100.00	0.8890	–	80.00	0.9754	–
Surgery for T1/T2 patients						
Partial parotidectomy	70.72	0.7142	0.78 (0.21–2.93)	79.12	0.9400	0.93 (0.18–4.81)
Total parotidectomy	73.68			74.44		

Table 4 Multivariable analysis for overall survival and disease-free survival

Variable	OS		DFS	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Age	5.606 (1.003–31.347)	0.050	5.974 (1.106–32.279)	0.038
Fixed max	1.308 (0.214–8.005)	0.771	1.683 (0.290–9.764)	0.562
Pain	1.113 (0.254–4.870)	0.887	0.370 (0.067–2.054)	0.256
Facial-nerve palsy	24.586 (3.388–178.446)	0.002	21.519 (2.921–158.535)	0.003
T stage (T1-2/T3-4)	0.537 (0.084–3.413)	0.510	0.351 (0.065–1.893)	0.223
N stage (N0/N+)	0.119 (0.015–0.972)	0.047	0.069 (0.008–0.577)	0.014
Recurrence	4.664 (0.904–24.073)	0.066	–	–

had worse OS and DFS (OS, $P=0.007$; DFS, $P=0.0059$) (Fig. 1). Perineural invasion occurred significantly more often (Chi-square test: $P=0.02$, $P=0.014$) in the high-risk malignant tumour types. Moreover, patients with high-risk parotid malignant types were more likely to have tumour pain, facial-nerve palsy (Chi-square test: <0.0001 and 0.02), lymphatic metastasis and recurrence (Chi-square test: 0.008 and 0.012) (Table 5).

Discussion

Parotid tumours are the most common salivary-gland tumours. Histological examination of most parotid tumours shows them to be benign, while 20% are malignant. The prognosis of parotid malignancies depends on many factors, including tumour size, age, sex, tumour histology and presence of pain or facial-nerve paralysis [9]. In our study, we report an OS rate 70.88% for primary parotid malignancy at 5 years. These findings are similar to other epidemiologic findings, in which approximately 84% of malignant salivary-gland carcinomas were in the parotid gland [10]. Mucoepidermoid carcinoma (18.46%) and polymorphous low-grade adenocarcinoma (16.92%) were the most common tumour types. We confirmed that clinical factors (fixed mass, pain, facial-nerve palsy) and histologic factors (high N stage, high-risk pathology types) were independent predictors for poorer clinical outcomes. The above clinical characteristics of parotid carcinoma were associated with tumour-aggressive features such as facial-nerve infiltration and tumour-surrounding tissue invasion (fixed mass). Perineural growth has been identified in multivariate analysis as a prognostic factor for survival of patients with parotid malignancies. What we observed was consistent with previously results [11]. Vincent et al. found that facial-nerve dysfunction, perineural growth and positive surgical margins acted as major factors predicting recurrence, while Eitan et al. [12] found that the presence of positive lymph nodes and perineural invasion was an important independent predictor of disease-free survival. Vander et al. [11] developed a prognostic model for disease-free survival in parotid carcinoma. They found that sex, tumour size, N stage and metastasis, localization, comorbidity, skin involvement and pain were predictive. This information can help physicians provide patients with more detailed information regarding expected prognoses.

Only 25–30% of parotid carcinomas showed clear clinical manifestation of malignancy, such as pain, fixed mass and facial-nerve palsy. All other cancers more or less presented

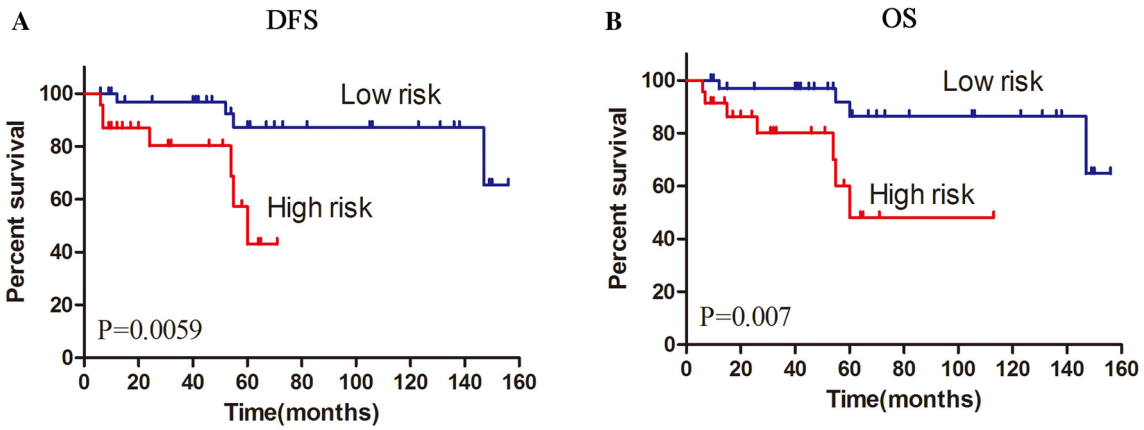

Fig. 1 Influence of risk categories on overall and disease-free survival

Table 5 Clinical characteristics of high-risk and low-risk parotid malignancies according to pathology

Characteristics	Risk stratification		
	Low risk	High risk	Chi-square test
Facial-nerve palsy			
Yes	2 (5.71%)	9 (39.13%)	0.02
No	33 (94.29%)	14 (60.87%)	
Pain			
Yes	2 (5.71%)	11 (47.83%)	< 0.0001
No	33 (94.29%)	12 (52.17%)	
Fixed mass			
Yes	16 (45.71%)	14 (60.87%)	0.263
No	19 (54.29%)	9 (39.13%)	
Perineural invasion			
Yes	3 (8.57%)	8 (34.78%)	0.014
No	32 (91.43%)	15 (65.22%)	
Margin status			
Positive	6 (17.14%)	6 (26.09%)	0.415
Negative	29 (82.86%)	17 (73.91%)	
N stage			
N0	34 (97.14%)	17 (73.91%)	0.008
N1–N2	1 (2.86%)	6 (26.09%)	
T stage			
T1–T2	28 (80%)	19 (82.61%)	0.806
T3–T4	7 (20%)	4 (17.39%)	
Recurrence			
Yes	2 (5.71%)	7 (30.43%)	0.012
No	33 (94.29%)	16 (69.57%)	

with benign performance, i.e. were slowly growing, mobile lumps [13]. Parotid carcinomas are the most diverse, with at least 20 distinct types. This variance in histology and grade of malignancy may account for the varieties in clinical features and prognoses of parotid malignancies. Their rarity and heterogeneity present clinical challenges when determining appropriate treatments [14]. Although the American Joint Committee on Cancer (AJCC) staging system remains the most practical and reliable system for staging parotid malignancies, doctors should pay close attention to histologic and grading information when they determine management strategies for patients [15]. Roberto et al. [6] found that patients with high-grade tumours and high-stage tumours had the worst prognoses according to multivariate analysis. In our analysis, we used the pathological type of parotid tumour to determine tumour grade (high or low), which has been reported previously [7]. Facial-nerve palsy and perineural invasion occurred significantly more often (Chi-square test: $P=0.02$, $P=0.014$) in the high-risk malignant types; adenoid cystic malignant types (50%) were mainly responsible for perineural invasion. In our study, patients with high-risk pathology types had worse OS and DFS (OS, $P=0.007$; DFS, $P=0.0059$). The OS and DFS for the low-risk group were 86.38% and 87.24%, respectively, while the OS and DFS for the high-risk group were 48.04% and 43%, respectively. Moreover, high-risk parotid malignant tumours were more likely to have perineural invasion, lymphatic metastasis and local/regional recurrence. As a result, for low-risk tumours, a single parotidectomy (partial or total) is likely to yield an ideal locoregional disease control. By contrast, tumours with high-risk histological features tend to need aggressive surgical extirpation, neck dissection and postoperative radiotherapy, and their five-year survival rate is much lower. Histological type is a significant predictor of outcome in parotid carcinomas. As a result, tissue diagnosis before preceding to the operating room for parotidectomy is important. For patients with less clear manifestations of malignancy, such as slow-growing or mobile lumps, fine-needle aspiration cytology (FNAC) or intraoperative frozen section could be used to define histological types and risk groups through the predictive grading scheme above. FNAC is a globally accepted method in the preoperative evaluation of head and neck tumours. However, it has many limitations, which means that a definitive diagnosis may not be established until therapeutic surgery [16]. A frozen section may provide an opportunity to refine or clarify the presurgical diagnosis. It can also determine whether nerve involvement is present, which would help in deciding for or against facial-nerve sacrifice [17].

Postoperative radiotherapy was verified to be important for reducing tumour recurrence rate, especially in cases of advanced T stage, pathological results and lymph-node metastasis. However, some investigators have found that the prognosis of parotid cancer is no different with or without radiotherapy [14]. In this study, 27 of 65 patients (41.5%) received postoperative radiotherapy, which did not significantly change the DFS or OS for parotid carcinoma. To avoid the effects of pathological risk factors, we divided the patients into high-risk and low-risk groups. We then analysed the treatment results in each group with and without radiotherapy. Notably, no significant difference was observed between the low-risk or high-risk groups.

This study had many limitations inherent in its retrospective design, including a limited number of cases and various histological subtypes. Of 65 parotid malignant tumours, the pathological degree of seven patients could not be stratified. The overall survival rate in this study was lower than previously reported in the literature, which may be influenced by the relatively limited number of cases.

Conclusion

This study demonstrated that patients older than 60 years with a fixed mass, facial-nerve paralysis and tumour pain showed adverse OS and DFS. Compared with patients having low-risk tumour types, patients with high-risk malignant

types experienced significantly more perineural invasion, lymphatic metastasis and local/regional recurrence.

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Compliance with ethical standards

Conflict of interest The authors have no conflict of interest concerning the study.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of Eye & ENT Hospital of Fudan University and with the 1964 Helsinki Declaration and its later amendments.

Informed consent Informed consent was obtained from all individual participants included in the study.

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