Prognostic indicators in clinically node-negative malignant primary salivary tumours of the parotid: A multicentre experience

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ABSTRACT

Objectives: Nodal metastasis is an important prognosticator in primary parotid cancers. The management of the clinically node-negative neck is an area lacking consensus. This study investigates the occult nodal metastasis rate, and prognostic indicators in primary parotid cancers.
Materials and methods: We performed a multicentre retrospective case note review of patients diagnosed and treated surgically with curative intent between 1997 and 2020. Demographic, clinic-pathological and follow-up data was recorded.
Results: After exclusions, 334 patients were included for analysis, with a median follow-up of 48 months. The overall rate of occult lymph node metastasis amongst patients undergoing elective neck dissection was 22.4%, with older age, high-grade and more advanced primary tumours being associated with higher rates. On multivariable analysis, age $\geq$ 60 years (HR = 2.69, p = 0.004), high-grade tumours (HR = 2.70, p = 0.005) and advanced primary tumours (pT3-4, HR = 2.06, p = 0.038) were associated with worse overall survival. Occult nodal metastasis on final pathology was associated with a close-to-significant reduction in regional recurrence free survival (HR = 3.18, p = 0.076).
Conclusion: This large series confirms the significant occult lymph node metastasis rate in primary parotid cancer, and demonstrates the importance of primary histology, tumour grade and stage in predicting survival outcome. This data supports the use of elective neck dissection in patients with high-risk tumours.

Introduction

Malignant primary salivary tumours are rare, making up approximately 1–3% of all head and neck cancers [1]. Around 53,000 new cases are diagnosed globally each year and it has been estimated that 8–9 new cases arise per million annually [2,3], with the parotid

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gland being most commonly affected [4]. They are a diverse group of tumours with many histological subtypes as classified by the World Health Organisation [5], and varying behaviour according to both subtype and grade. The management of these tumours is primarily surgical, with complete resection of the primary tumour with or without concurrent neck dissection and post-operative radiotherapy (PORT). Systemic therapy such as chemotherapy, androgen receptor therapy and tyrosine kinase inhibitor therapy have a role in selected cases only [6].

Whilst the biology and behaviour of primary salivary tumours differs from that of other head and neck cancers such as upper aerodigestive tract SCC, one similarity is the important effect on prognosis of regional nodal metastasis. For example, in the case of primary parotid cancers, the number, diameter and location (for example intra-parotid) of nodal metastases have been shown to be important prognosticators [7]. The management of nodal metastases is not controversial, with international guidelines recommending neck dissection [3,7]. However, the prognosis and elective management of the neck in clinically node-negative (cN0) primary parotid tumours is less clear, with various authors using different criteria to guide management of the neck [8–12].

The primary aim of this study is to report occult nodal metastasis rates in cN0 primary parotid cancers, with the secondary aim of investigating clinico-pathological predictors of outcome in a large series of carefully selected patients, in order to clarify the key prognostic indicators in this challenging clinical scenario.

Materials and methods

We performed a multi-centre retrospective record-based analysis, comprising patients affected by primary parotid malignant epithelial tumours diagnosed and treated at ten Departments of Otolaryngology – Head and Neck Surgery, in Italy (Brescia, Milan, Ferrara, Padova, Trieste and Treviso) Poland (Poznan), Greece (Larissa) and the United Kingdom (Birmingham and Nottingham).

Patients with a clinically and radiologically node-negative new primary epithelial malignancy of the parotid gland undergoing surgery ± adjuvant radiotherapy with curative intent were included. Patients with non-primary, non-epithelial or previously treated malignancies involving the parotid gland, and those with regional or distant metastasis at diagnosis were excluded. Anonymised demographic, clinical, radiological, histopathological and follow-up data for all selected consecutive patients treated from September 1997 to March 2020 were collected following local audit and governance department approval. The UK Health Research Authority decision tool was used to help ascertain that ethical approval was not required [13].

Variables were expressed in terms of median, interquartile range (IQR), and percentages. Staging is reported according to the 7th edition of the American Joint Committee on Cancer (AJCC) manual [14], and tumour grade is reported as low, intermediate and high where available from pathology reports. Where not otherwise specified, all cases of salivary duct carcinoma and carcinoma ex pleomorphic adenoma are assumed to be high grade. For the purpose of survival analysis, high grade tumour as a variable was compared with all non-high-grade tumours (including both low and intermediate grade).

To investigate whether a significant difference in the proportion of occult nodal metastasis was found according to age (cut-off 60 years), gender, histological grade, pT status, and histology, a Chi-square test was conducted.

Outcomes of interest for survival analysis were overall survival (OS), defined as the time from surgery to death from any cause, and regional recurrence-free survival (RRFS), defined as the time from surgery to first regional recurrence. For censored observations, the latest available clinical or radiological evaluation was considered. In addition, patient demographics, preoperative diagnostic studies, primary tumour, and treatment-related variables were analysed.

Univariate analyses were conducted with the Cox proportional hazard model and log-rank test. Results were expressed in terms of hazard ratio (HR) and 5-year OS estimates, respectively, with relative 95% confidence intervals (CI). The Kaplan-Meier method was used to graphically represent the outcomes under investigation, with relative 95% CI.

A multivariable Cox proportional hazard model was conducted considering relevant prognosticators at univariate analysis. Multicollinearity between covariates was tested through variance inflation factors (vif); vif < 5 was considered acceptable. Schoenfeld residuals test was performed to assess the proportional hazards assumptions. Statistical analysis was performed using R (version 4.0.4, R Foundation for Statistical Computing, Vienna, Austria). P values < 0.05 were considered statistically significant.

Table 1
Patient and tumour characteristics. * Applied for patients undergone elective neck dissection (N = 134).

Variable		N.	%
Gender	Male	156	46.7%
	Female	178	53.3%
Median age at diagnosis (IQR) - yr	59 (25.25)		
Histology	Mucoepidermoid carcinoma (MEC)	81	25.0%
	Acinic cell carcinoma (AcCC)	80	24.7%
	Adenoid-cystic carcinoma (AdCC)	33	10.2%
	Salivary duct carcinoma (SDC)	27	8.3%
	Carcinoma ex-pleomorphic carcinoma (CEPA)	26	8.0%
	Adenocarcinoma non otherwise specified (ADC NOS)	17	5.3%
	Basal cell adenocarcinoma	16	4.9%
	Myoepithelial carcinoma	12	3.7%
	Epitethelial-myoepithelial carcinoma	8	2.5%
	Poorly differentiated carcinoma	6	1.9%
	Oncocytic carcinoma	5	1.6%
	Mammary analogue secretory carcinoma (MASC)	3	0.9%
	Clear cell carcinoma	2	0.6%
	Lymphoepithelial carcinoma	2	0.6%
	Intraductal carcinoma	2	0.6%
	Polymorphous low-grade adenocarcinoma	2	0.6%
	Carcinosarcoma	1	0.03%
	Sebaceous adenocarcinoma	1	0.03%
	Missing	(10)	
Tumour grade	Low-grade	154	48.4%
	Intermediate-grade	47	14.8%
	High-grade	117	36.8%
	Not specified	(16)	
pT classification (TNM 8th edition)	pT1	116	34.9%
	pT2	113	34.0%
	pT3	60	18.1%
	pT4	43	13.0%
	Missing	(2)	
pN classification (TNM 8th edition)*	pN0	104	77.6%
	pN+ (occult metastasis)	30	22.4%
	- pN1	8	6.0%
	- pN2a	1	0.7%
	- pN2b	17	12.7%
	- pN2c	0	0%
	- pN3	4	3.0%

Results

A total of 383 patients were identified, of which 49 were excluded due to insufficient follow-up data either due to being followed up at a different centre, or difficulty obtaining historical clinicopathological data from historical medical records. This left 334 patients meeting the inclusion criteria, with a median follow up of 48 months. There was a slight female preponderance (53.3%) and the median age at diagnosis was 59 years. Mucoepidermoid carcinoma and acinic cell carcinoma

Table 2
Treatment and follow-up

Variable		N.	%
Surgery performed	Extracapsular excision	13	4.0%
	Partial superficial parotidectomy	15	4.6%
	Superficial parotidectomy	170	52.0%
	Total parotidectomy	93	28.4%
	Radical parotidectomy	36	10.8%
	Parotidectomy non otherwise specified	(7)	
Elective neck dissection	Not performed	198	59.6%
	Performed	134	40.41313
	Missing	(2)	
Neck dissection performed	ND II + frozen section	34	25.4%
	ND I-III	7	5.2%
	ND I-IV	9	6.7%
	ND I-V	12	9.0%
	ND IIA, III	30	22.4%
	ND IIA, III, IV	7	5.2%
	ND IIA,B, III, IV	27	20.1%
	ND IIA,B, III, IV, VA	6	4.5%
	ND IIA,B, III, IV, VA, VB	2	1.5%
	Missing	(2)	
Surgical margins	R0	189	56.8%
	R1-2	144	43.2%
	Missing	(1)	
Adjuvant radiotherapy	No	149	44.9%
	Yes	183	55.1%
	Missing	(2)	
Median follow-up (IQR) - months	48 (64.75)		
Status at last follow-up	Alive	270	82.3%
	Dead (any cause)	58	17.7%
	Missing	(6)	
Regional recurrence	No	311	95.7%
	Yes	14	4.3%
	Missing	(9)	
Median disease-free interval for regional recurrence (IQR) - months	23.5 (15.75)		
Median survival after regional recurrence (IQR) - months	34.5 (27.25)		

were the most common diagnoses, making up 25.0% and 24.7% of cases respectively. Patient and tumour characteristics are displayed in Table 1. Elective neck dissection (END) was performed in 134 (40.4%) cases. PORT was delivered in 55.1% of cases. Most patients with pT3 (81.4%), pT4 (86.0%) lesions and nodal metastasis (86.7%) were irradiated. PORT followed END in 67.4% of patients, whereas only 44.5% of patients who did not undergo END received adjuvant treatment. Details of treatment and follow-up are shown in Table 2.

Occult cervical nodal metastasis

Considering only patients undergoing an elective neck dissection (n = 134), the overall rate of occult cervical nodal metastasis was 22.4%. Most of these patients were staged pN2b (12.7%), followed by pN1 (6.0%), pN3 (3.0%) and pN2a (0.7%). No cases of pN2c disease were registered (Table 1).

Chi-square analysis revealed that older patients (>60 years) showed a significantly ($p = 0.020$) higher proportion of occult nodal metastasis (31.2%), compared to younger patients (11.8%), whereas no difference was found according to gender. In addition, chi-square analysis revealed a significant difference in the proportion of occult nodal metastasis according to tumour grade ($p < 0.001$), pT status ($p < 0.001$) and histology ($p = 0.006$). Higher histological grade (2.3% low-grade, 5.0% intermediate, 41.9% high-grade), and pT status (3.0% pT1, 10.3% pT2, 34.5% pT3, 46.9% pT4) increased the risk of occult disease in the neck. Salivary duct carcinoma (56.5%) and adenocarcinoma not-otherwise specified (41.7%) were at highest risk of occult nodal spread, whereas a lower risk was observed for acinic cell (9.5%) and mucoepidermoid carcinoma (12.9%). Occult metastasis was observed in 23.5% of patients undergoing elective neck dissection for adenoid cystic carcinoma.

Overall survival

Overall survival was 96.7% (95 %CI, 94.7–98.7%), 93.6% (95 %CI, 90.8–96.5%), 84.1% (95 %CI, 79.6–89.0%) at 1-, 2- and 5-year follow-up, respectively (Fig. 1).

At univariate analysis, older (≥60-years, HR = 3.26, $p < 0.001$), male (HR = 2.02, $p = 0.009$) patients, treated with radical parotidectomy (HR = 3.20, $p = 0.002$) and neck dissection (HR = 3.97, $p < 0.001$) for high-grade (HR = 4.46, $p < 0.001$) lesions with occult cervical metastasis (HR = 3.79, $p < 0.001$) and positive surgical margins (HR = 1.91, $p = 0.016$) showed a significant reduction in OS (Table 3).

In this setting of cN0 lesions, adenocarcinoma (HR = 4.94, $p = 0.017$), salivary duct carcinoma (HR = 11.68, $p < 0.001$) and adenoid cystic carcinoma (HR = 4.01, $p = 0.028$) were significantly associated with worse OS when compared to acinic cell carcinoma. OS was

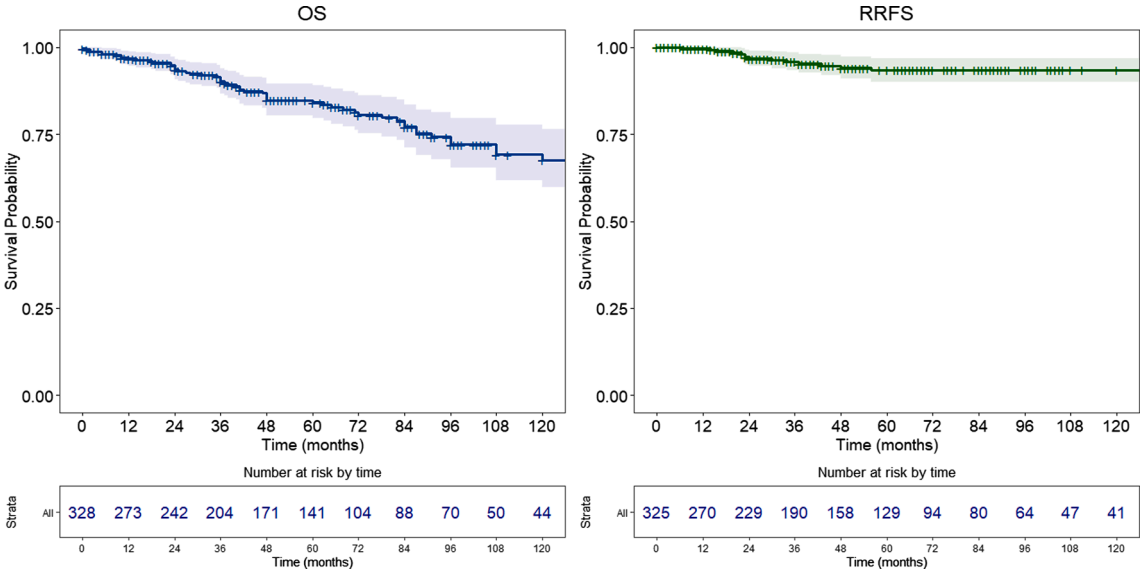

Fig. 1. Kaplan Meier survival curves with relative 95% confidence interval and table of patients at risk according to OS and RFS.

Table 3
Uni- and multi-variable analysis of the most influential demographics, clinicopathological and treatment related variables in terms of OS and RRFS. AcCC, acinic cell carcinoma; ADC NOS, adenocarcinoma non-otherwise specified; AdCC, adenoid-cystic carcinoma; G1, low-grade; G2, intermediate grade; G3, high-grade; SDC, salivary duct carcinoma; R0, negative surgical margins; R1-2, positive surgical margins.

		Overall Survival						**Recurrence Free Survival**					
		Univariate analysis				**Multivariable analysis**		**Univariate analysis**				**Multivariable analysis**	
		Log-rank test		**Cox Proportional-Hazard model**		**Cox Proportional-Hazard model**		**Log-rank test**		**Cox Proportional-Hazard model**		**Cox Proportional-Hazard model**	
Variable		**5-year OS**	**p-value**	**HR (95% CI)**	**p-value**	**HR (95% CI)**	**p-value**	**5-year OS**	**p-value**	**HR (95% CI)**	**p-value**	**HR (95% CI)**	**p-value**
Age at diagnosis - yr	<60-year-old	90.4% (85.2–95.8%)	**<0.001**	Reference	**<0.001**	Reference	**0.032**	95.0% (91.1–99.0%)	0.550	Reference	0.550		
	≥60-year-old	77.5% (70.1–85.7%)		3.26 (1.85–5.77)		1.96 (1.06–3.64)		92.1% (86.3–98.1%)		1.39 (0.47–4.15)			
Gender	Female	87.4% (81.7–93.5%)	**0.007**	Reference	**0.009**	Reference	*0.053*	95.9% (92.3–99.6%)	*0.090*	Reference	0.105		
	Male	80.2% (72.9–88.1%)		2.02 (1.19–3.41)		1.82 (0.99–3.34)		90.2% (84.2–96.7%)		2.47 (0.83–7.38)			
Tumor grade of differentiation	G1	90.3% (84.9–96.0%)	**<0.001**	Reference		Reference		97.0% (93.6–100%)	**0.001**	G1–G2: Reference		G1–G2: Reference	**0.005**
	G2	88.5% (78.4–99.9%)		1.78 (0.73–4.37)	0.208	1.36 (0.52–3.51)	0.530	100%			**0.002**		
	G3	72.4% (63.0–83.0%)		4.54 (2.45–8.46)	**<0.001**	2.57 (1.20–5.51)	**0.016**	84.8% (76.7–93.8%)		G3: 7.53 (2.09–27.1)		G3: 6.74 (1.80–25.3)	
Histology	AcCC	98.2% (94.7–100%)	**<0.001**	Reference				91.9% (84.6–99.9%)	**0.050**	Non–SDC: Reference	**0.017**		
	MEC	86.3% (77.7–95.8%)		2.31 (0.78–6.75)	0.127			100%					
	AdCC	77.3% (59.5–100%)		4.01 (1.16–13.88)	**0.028**			91.1% (79.9–100%)					
	ADC NOS	71.9% (51.6–100%)		4.94 (1.33–18.40)	**0.173**			90.9% (75.4–100%)					
	Other histology	80.4% (71.6–90.4%)		3.98 (1.50–10.56)	**0.055**			94.4% (89.2–99.9%)					
	SDC	60.8% (41.4–89.4%)		11.68 (4.10–33.29)	**<0.001**			75.8% (54.6–100%)		4.75 (1.32–17.1)			
Surgical margins	R0	88.2% (82.9–93.9%)	**0.010**	Reference	**0.016**	Reference	0.176	96.1% (92.7–99.6%)	0.120	Reference	0.130		
	R1-2	79.0% (71.4–87.4%)		1.91 (1.13–3.23)		1.54 (0.82–2.88)		89.9% (83.7–96.7%)		2.33 (0.78–6.94)			
pT classification	pT1	97.1% (94.0–100%)	**<0.001**	Reference		Reference		96.5% (92.6%–100%)		Reference		pT1–3: Reference	**0.027**
	pT2	83.5% (75.2–92.7%)		4.08 (1.61–10.32)	**0.003**	pT2: 2.63 (0.99–6.95)	*0.051*	96.6% (91.8–100%)		0.75 (0.12–4.48)	0.750		
	pT3	68.1% (55.8–83.0%)		7.56 (3.03–18.91)	**<0.001**	pT3–4: 3.08 (1.14–8.33)	**0.027**	89.9% (80.7–100%)		2.83 (0.63–12.67)	0.173		
	pT4	75.8% (62.6–92.4%)		7.32 (2.77–19.30)	**<0.001**			77.7% (61.9–97.6%)		6.59 (1.57–27.61)	**0.010**	pT4: 4.50 (1.18–17.10)	
Presence of occult nodal metastasis	cN0-pN0	87.1% (82.5–91.8%)	**<0.001**	Reference				94.4% (91.1–97.7%)	*0.062*	Reference	*0.076*		
	pN+	53.5% (53.1–81.6%)		3.79 (1.98–7.24)	**<0.001**			83.5% (67.4–100%)		3.18 (0.88–11.47)			
pN classification	cN0-pN0	87.1% (82.5–91.8%)	**<0.001**	Reference		Reference							
	pN1	64.3% (33.8–100%)		3.53 (1.09–11.46)	**0.036**	1.05 (0.30–3.69)	0.936						
	pN2	57.4% (36.9–91.9%)		3.42 (1.53–7.65)	**0.003**	0.95 (0.37–2.44)	0.910						
	pN3	0%		7.58 (1.80–31.92)	**0.006**	1.66 (0.36–7.64)	0.518						
Adjuvant RT	Not performed	92.1% (87.5–96.9%)	**<0.001**	Reference		Reference	0.224	93.9% (89.2–98.9%)	0.640	Reference	0.646	Reference	0.353
	Performed	77.4% (70.2–85.3%)		3.04 (1.64–5.66)	**<0.001**	1.58 (0.76–3.27)		93.0% (88.4–97.9%)		1.28 (0.44–3.70)		0.54 (0.14–1.99)	

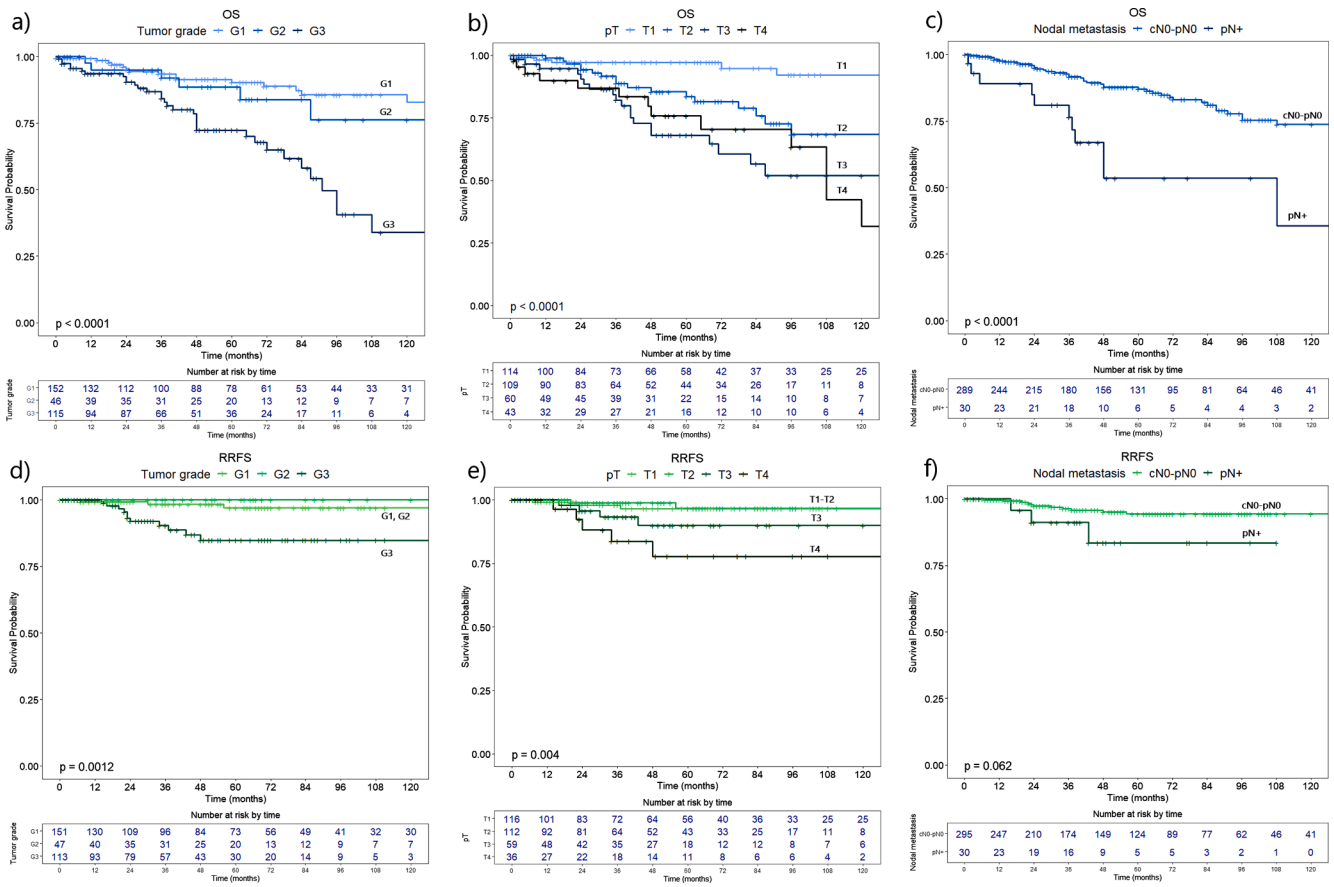

Fig. 2. Kaplan Meier plots with relative table of patients at risk showing overall survival curves according to (a) tumour grade of differentiation, (c) pT status, (d) presence of occult nodal metastasis, and regional recurrence free survival curves according to (d) tumour grade of differentiation, (e) pT status, (f) presence of occult nodal metastasis. G1, low-grade; G2, intermediate grade; G3, high grade.

significantly influenced by pT status as well, with a progressive increase in the HR, reaching a plateau for pT3 and pT4 lesions (HR = 7.56, and HR = 7.32, respectively, p < 0.001). Kaplan-Meier plots for OS according to grade, pT status and occult nodal metastasis on OS are shown in Fig. 2a-c. On univariate analysis, PORT was associated with a reduced OS (HR = 3.04, p < 0.001) (Fig. 3).

At multivariable analysis (Table 3), age ≥ 60 years (HR = 1.96, p = 0.032), high-grade (HR = 2.57, p = 0.016) and high-stage lesions (pT3-4, HR = 3.08, p = 0.027) played an independent negative prognostic role in terms of OS. Male gender, margin status, pN status and PORT did not independently affect OS.

Regional recurrence free survival

Regional recurrence free survival was 99.6% (95 %CI, 99.0–100%), 96.8% (95 %CI, 94.6–99.0%), 93.4% (95 %CI, 90.1–96.9%) at 1-, 2- and 5-year follow-up, respectively (Fig. 1). Among patients who recurred in the neck (n = 14), 3 (21.4%) previously showed occult nodal metastasis. Regarding treatment, 3 (21.4%) did not underwent END nor PORT, 2 (14.3%) received only PORT, 6 (42.8%) underwent both END and PORT, and 3 (21.4%) END without PORT.

At univariate analysis (Table 3), patients undergoing nodal dissection were at higher risk of regional recurrence (HR = 3.97, p = 0.104). Similarly, patients undergoing radical as opposed to superficial parotidectomy, had an increased risk of regional recurrence (HR = 6.59, p = 0.005). Salivary duct carcinoma (HR = 4.75, p = 0.017), high-grade features (HR = 7.53, p = 0.002) and pT4 lesions (HR = 5.19, p = 0.003) were significantly associated with reduced RRFS (Fig. 2d-f). Age ≥ 60 years (p = 0.550), gender (p = 0.105), resection margins (p = 0.130) and PORT (p = 0.646) did not significantly influence RRFS. Presence of occult nodal metastasis was a close-to-significant risk factor for regional failure (HR = 3.18, p = 0.076). At multivariable analysis (Table 3), pT4 (HR = 4.50, p = 0.027) and high-grade features (HR = 6.74, p = 0.005) were independent prognosticators for RRFS.

Discussion

Primary malignant parotid tumours are a rare group of cancers and single institution series are rarely large enough to provide meaningful data on prognostic factors and outcomes following treatment, especially in subgroups such as clinically node-negative tumours. Here we report a large multicentre series of cN0 primary malignant parotid tumours. Our results show 5-year overall survival of 84.1%, and 5-year recurrence free survival of 93.4%. Amongst those who underwent elective neck dissection, the rate of occult nodal metastasis was 22.4%, although this varied significantly according to tumour histology, with a rate of 56.5% in salivary duct carcinoma. The decision to undertake END was taken on a case-by-case basis, with various centres and different clinicians within centres using different criteria, so this is a diverse group in terms of pre-operative clinicopathological characteristics, however our occult nodal metastasis rate is comparable to other reports [8,15,16], and perfectly in keeping with a recent *meta*-analysis which reported an overall rate of 22% [10], although some authors have reported much higher rates, including in patients with small primary tumours and low-grade tumours [17,18], prompting calls for elective neck dissection even in those with low-risk tumours. Another recent *meta*-analysis of occult nodal metastasis in parotid cancers focussed on the anatomical levels involved, and found that level 2 was most frequently involved (16.5%), but all

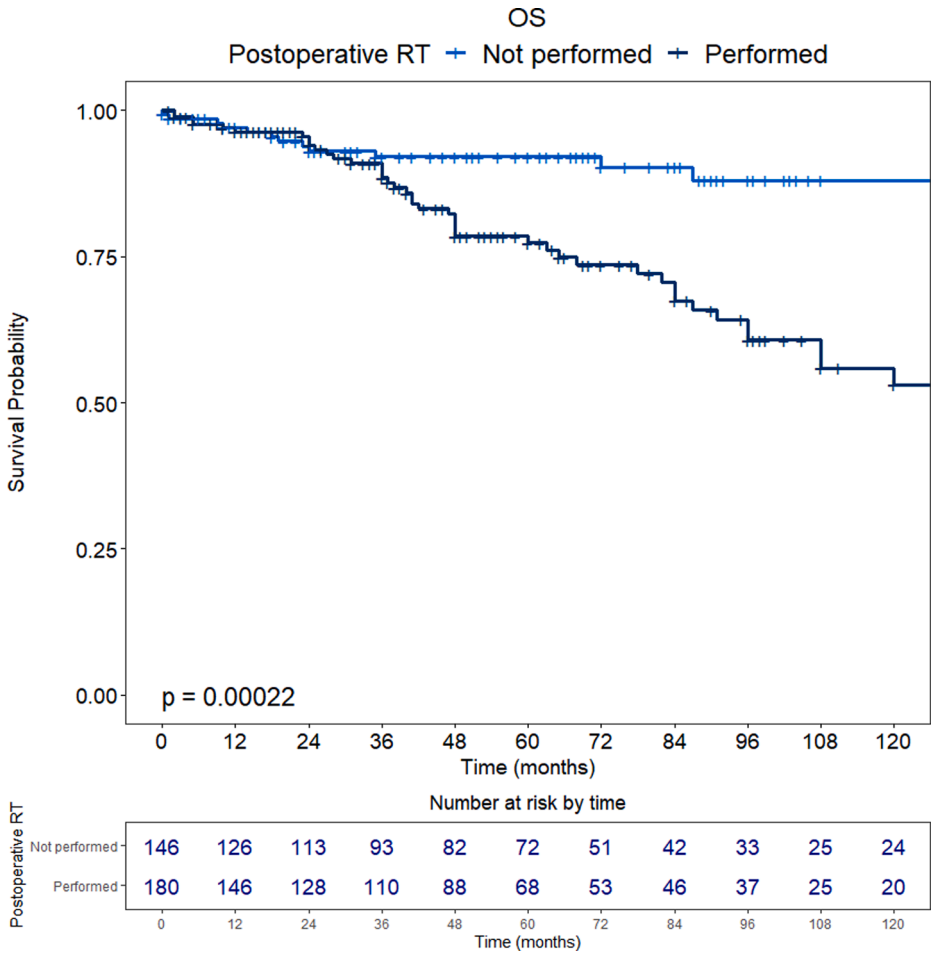

Fig. 3. Kaplan Meier plot showing overall survival curve according to post-operative radiotherapy.

other levels were rarely involved [19]. It is worth noting the substantial rate of occult metastasis from adenoid-cystic carcinoma (23.5%), a tumour which has classically been considered poorly lymphotropic and known for its predilection for haematogenous metastasis. This is in keeping with reports from other authors, citing nodal metastasis rates of 14.5–24% [20,21]. The clinical benefit of elective dissection in adenoid-cystic carcinoma is however unclear, with no survival benefit demonstrated by the large multicentre study of Amit *et al.* [21].

Our findings support those of other groups regarding the effect of age, primary tumour status, grade and histology on OS [15,22,23]. Whilst univariable analysis identified a negative prognostic role of radical parotidectomy, elective neck dissection and PORT on OS, this is likely to reflect the more aggressive treatment of tumours of higher stage and grade and more aggressive histological subtypes. Indeed, on multivariable analysis, only age, pT status and grade showed significant negative associations with OS. In the current series there was no evidence that pathological nodal status (pN) nor the prescription of PORT impacted OS. Other authors have demonstrated a negative impact on OS of cervical lymph node metastasis [24], and the discrepancy here may be due to the relatively low numbers of pN + cases in our series due to the focus on cN0 patients, with 77.6% being pN0 after END. The results for the effect of PORT on OS is interesting, as the Kaplan-Meier plot (Fig. 3) shows that despite the poorer prognostic factors necessitating PORT, for the first 36 months the OS for PORT patients remains comparable to those who did not receive PORT. However, after 36 months the OS declined in the PORT group as compared to the no-PORT group. This suggests that the benefits of PORT may not be sustained, perhaps due to distant metastasis despite locoregional control. Indeed, most of the evidence in favour of PORT in primary malignant salivary gland tumours stems from its effects on locoregional control rather than survival [25].

We found that high grade tumours and pT4 tumours were associated with a poorer RRFS, thus supporting international guidelines recommending elective neck dissection and PORT in patients with locally advanced, high-grade tumours [3,6]. However, PORT itself was not an independent prognostic factor for regional recurrence. This is at odds with the findings of other authors, who have demonstrated improved regional control with PORT in patients with high-risk features [26], perhaps due to differing indications for PORT between centres, and the relatively low number of patients suffering regional recurrence in our series. It is also possible that the fact that 67.4% of patients undergoing END also received PORT masks the true effect of PORT alone on regional control in our results.

In addition to the controversy surrounding the indications for elective neck dissection in primary malignant salivary gland tumours, there is significant variation in practice regarding the extent of neck dissection when it is performed. Our results show considerable variation between centres, with some clinicians offering level 2 neck dissection and frozen section, with further neck dissection depending on positive occult nodal metastasis in level 2, and others offering a variety of levels, from limited (levels 2 and 3) to more extensive (levels 1–5). Levels 2 and 3 have been reported to be the most commonly affected by occult nodal metastasis [8,18,19,27], and therefore dissection of at least these levels in patients with high-risk features for occult metastasis and regional recurrence as described here and elsewhere is appropriate. Lombardi *et al.* have proposed three scenarios for the management of the cN0 neck in primary salivary gland cancers: first, that either surveillance or END is acceptable for young patients with low grade T1-T2 tumours. Second, that if risk factors for occult nodal metastasis are discovered only upon final

histology, then elective irradiation of the neck should be considered. Third, when risk factors for occult nodal disease are known to be present preoperatively then END levels 2–4 or 1b-4 is considered with the alternative option of elective neck irradiation if radiotherapy is planned for the primary site, or END dictated by intraoperative frozen section of lymph nodes from levels 2 or 3 and comprehensive neck dissection only of occult disease is confirmed [28].

In the setting of cutaneous squamous cell carcinoma of the head and neck, intraparotid nodal metastasis has long been recognised as a negative prognostic indicator, having been described by O'Brien *et al.* in 2002 [29]. There are numerous lymph nodes within both the superficial and deep lobes of the normal parotid gland [30], and a recent systematic review has identified a pooled prevalence of intraparotid nodal metastasis in primary parotid cancers of 24.1% [31]. In addition, the authors identified a significant negative prognostic effect of intraparotid nodal metastases. This raises important questions about the adequacy of the current nodal staging system for parotid cancers, and lends weight to the argument in favour of total parotidectomy in cases of known high-grade malignancy [32], both to maximise regional control and to aid prognostication and planning of adjuvant therapy.

Limitations

We have reported a large series of clinically node-negative primary parotid tumours with stringent inclusion criteria and extensive clinicopathological and follow-up data. However, the retrospective nature of the data collection inevitably introduces a source of bias. Furthermore, although multicentre studies are required in order to achieve high case numbers of these rare tumours, the variation in treatment and follow-up practices between centres means that the current series are not entirely homogeneous; moreover, the low number of regional recurrence events limited the relative multivariable analysis. This is further compounded by the wide variation in tumour behaviour and treatment paradigms for different histological subtypes and tumour grades. Another limitation of the use of retrospective multicentre study design is the difficulty in standardising the classification of parotidectomy as recommended by the European Salivary Gland Society [33]. This classification should be utilised in future research on primary parotid cancers in order to standardise definitions of the extent of parotidectomy. Unfortunately, even using large datasets from multicentre studies, meaningful subgroup analysis according to histological subtype is limited by series size. Finally, as the current staging system does not distinguish between intraparotid and cervical lymph node metastasis, the data presented here do not allow us to comment on the rate and role of intraparotid occult nodal metastasis on oncological outcomes.

Conclusions

Primary malignant parotid tumours are a diverse group with differing behaviour and outcomes. Clinically node-negative cases represent a particular treatment challenge due to uncertainty as to the appropriate extent of surgical and adjuvant treatment. This large multicentre series confirms the importance of histological subtype, and primary tumour extent and grade in predicting occult nodal metastasis, OS and RRFS, with higher pT status, high-grade tumours of unfavourable histological subtype such as salivary duct carcinoma being poor prognostic indicators. Our findings support the use of elective neck dissection in patients aged over 60 years, and those with T3/4 tumours, or high-grade lesions. Large scale collaborative prospective research is required to investigate the locoregional control and survival benefit attributable to elective neck dissection and PORT, respectively.

Declaration of Competing Interest

The authors declare that they have no funding, known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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