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Polymorphous adenocarcinoma of salivary glands

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ABSTRACT

Objective: Polymorphous adenocarcinoma of salivary gland (PAC) is rare. Despite being described as a low risk histology, some patients develop regional and distant metastasis. More aggressive behavior has been attributed to a PAC subcategory called cribriform adenocarcinoma of minor salivary glands (CAMSG). We examined oncological outcomes of PAC.

Patients and methods: Fifty-seven patients with PAC were identified from an institutional database of 884 patients surgically treated for salivary gland malignancies from 1985 to 2015. Detailed histopathological analysis was performed. Survival outcomes were calculated using the Kaplan-Meier method. Factors predictive of recurrence were identified using the Cox proportional hazard method.

Results: Fifty-four (95%) had tumors of minor salivary gland origin; the most frequent location was the oral cavity in 41 (76%), specifically the hard palate in 32 (55%). Forty-six patients (81%) were clinical T1-T2; 3 (5%) had a clinically positive neck. Thirty-two patients (56%) were classified as PAC and 14 (25%) as CAMSG. Forty-four patients (77%) had surgery alone; 13 (23%) had surgery and postoperative radiotherapy. The 5- and 10-year overall survival and disease-specific survival were 88% and 79% and 98% and 94%, respectively (median follow up 84 [1–159] months); 5- and 10-year recurrence-free survival were 93% and 88%, respectively. Univariate analysis showed male sex, III/IV stage, and CASMG variant had increased incidence of recurrence but were not statistically significant.

Conclusion: PAC of the salivary glands is an indolent disease with good survival outcomes. Recurrence is uncommon and tends to occur late. Long-term follow-up is indicated in patients with this disease.

Introduction

Polymorphous adenocarcinoma (PAC), previously called polymorphous low-grade adenocarcinoma (PLGA), of the salivary glands is a rare cancer. Population-based studies report an annual incidence of 0.051 cases per 100,000 individuals [1]. It is the second most common minor salivary gland tumor found in the oral cavity [2]; its incidence in a major salivary gland is much lower [3]. PLGA was initially described as a low-grade histology with low metastatic potential and excellent survival [4]. However, a recent update made by the salivary gland section of the World Health Organization (WHO) decided to remove the term low-grade due to emerging evidence showing recurrence rates of up to 19% and cases of transformation to high-grade malignancies [5,6].

Under the subheading of PAC, a distinctive type of cribriform adenocarcinoma of minor salivary gland (CAMSG) has been included. Despite studies showing a histologic overlap between classical PAC and CASMG, this update arose because each has a different pattern of

Abbreviations: PAC, polymorphous adenocarcinoma; CAMSG, cribriform adenocarcinoma of minor salivary gland origin; PORT, postoperative radiotherapy; OS, overall survival; DSS, disease-specific survival; RFS, recurrence-free survival; PLGA, polymorphous low-grade adenocarcinoma; WHO, World Health Organization; PNI, perineural invasion; LVI, lymphovascular invasion; LRFS, local recurrence-free survival; RRFS, regional recurrence-free survival; DRFS, distant recurrence-free survival; HR, hazard ratio; CI, confidence interval

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metastasis. CAMSG was first described as a distinctive cribriform adenocarcinoma of the tongue, associated more frequently with nodal metastases even at presentation [7–9]. Although clinicopathological differences exist between them, survival differences have not yet been established. The aim of this study is to examine the oncological outcomes of PAC and the impact of CAMSG within this group.

Materials and methods

Patients

After obtaining approval from Memorial Sloan Kettering Cancer Center's Institutional Review Board, 57 patients with PAC were identified from an existing database of 884 patients with minor and major salivary gland malignancies surgically treated from 1985 to 2015. This study excludes patients with previous treatment or surgery at an outside institution.

Data collection

Details on patients' demographics, tumor characteristics, surgical treatment, adjuvant therapy, and oncological outcomes were recorded. Detailed histopathological analysis was conducted by a head and neck pathologist (NK) with special expertise in salivary gland tumors. Tumors were staged according to the seventh edition of the American Joint Committee on Cancer for major salivary gland tumors [10]. Minor salivary glands were staged using the mucosal tumor staging system according to the anatomical site of the tumor.

Pathology review

Tumors were classified as PAC and CAMSG according to WHO data from 2017 and prior publications of Michal et al. and Skalova et al. [7,11] PAC is an infiltrative tumor that displays histologic diversity with different histologic pattern including tubular, fascicular, cribriform, papillary and solid with fascicular and targetoid features [12]. CAMSG displayed architectural uniformity with a predominant cribriform and solid growth pattern, sometimes demonstrating peripheral palisading, peripheral clefting, and glomeruloid appearance [7]. Fig. 1 shows representative histology of PAC and CAMSG. Pathology characteristics reviewed were size, mitotic index, necrosis, perineural invasion (PNI), lymphovascular invasion (LVI), percentage of cribriform, and papillary pattern.

Statistical analysis

Univariate analysis of clinical, pathological, and treatment factors was performed. Bivariate analysis was conducted using the chi-square test to compare PAC and CAMSG histological groups. Endpoints of interest included overall survival (OS) calculated from date of surgery to date of last follow-up or death of any cause, disease-specific survival (DSS) calculated from date of surgery to date of last follow-up or death with disease, recurrence-free survival (RFS) calculated from date of surgery to date of first recurrence (local, regional, or distant); local recurrence-free survival (LRFS), regional recurrence-free survival (RRFS), and distant recurrence-free survival (DRFS) all were calculated in months from the date of surgery. All outcomes were calculated in months using the Kaplan-Meier method. Patients' last status was established by a member of the disease management team. The unadjusted hazard ratio (HR) for the impact of clinicopathological factors on OS and RFS was determined by the Cox proportional hazard method. Statistical analysis was carried out using SPSS Statistics software, version 25 (IBM).

Results

Clinical and pathological characteristics

During the study period, 57 patients with the diagnosis of PAC were identified. Patient characteristics are shown in Table 1. In this cohort, the median age at diagnosis was 61 years (22–83 years), and 65% of patients were female. Thirty-nine patients (68%) had a history of tobacco consumption. Fifty-four patients (95%) had tumors of minor salivary gland origin, and 3 tumors arose in the parotid gland. The most frequent location of tumors was the oral cavity for 41 patients (76%), specifically the hard palate in 32 patients (55%). Forty-six patients (81%) were staged T1–T2, and 3 (5%) patients had regional disease diagnosed on imaging. Histology review classified 32 (56%) patients as PAC and 14 (25%) as CASMG; in 11 cases, material was not available for review. Comparison of clinical and pathological characteristics between PAC and CAMSG are shown in Table 2. There was no significant difference between PAC and CAMSG regarding age at diagnosis, sex, and tobacco consumption. For both categories, more than 80% of patients presented with early T stage and clinically negative neck. Comparison of pathological factors revealed no differences in overall staging, margin status, LVI, or PNI.

Treatment characteristics

In this cohort, surgical treatment was as follows: 34 (60%) patients were treated with a partial maxillectomy, 17 (30%) with wide local excision, 1 (2%) with transoral robotic surgery, 1 (2%) with craniofacial resection, and 1 (2%) with mandibulectomy. Of the 3 cases that presented in the parotid gland, 2 (3%) patients had a total

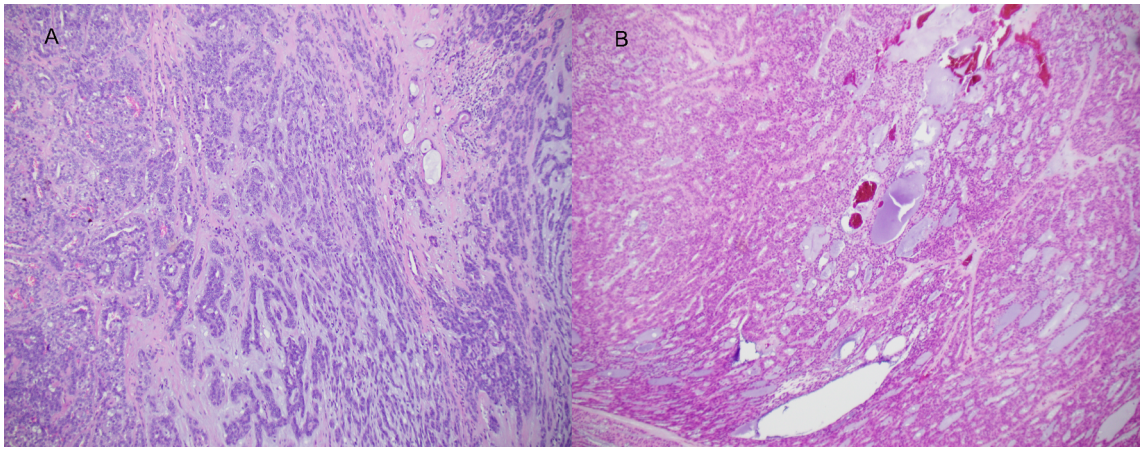

Fig. 1. Histologic Features (A) Polymorphous adenocarcinoma. (B) Cribriform adenocarcinoma of minor salivary gland.

Table 1
Clinicopathological data of patients included in this study.

Characteristics	No. of patients (%)
Total	57 (100)
Age	
Median	61 (22–83)
< 60	24 (42)
≥60	33 (58)
Sex	
Male	20 (35)
Female	37 (65)
Tobacco*	
Yes	39 (68)
No	18 (32)
Alcohol*	
Yes	38 (67)
No	19 (33)
Tumor site	
Minor salivary	
Hard palate	31 (54)
Buccal mucosa	5 (9)
Retromolar trigone	2 (4)
Gum	2 (4)
Upper lip	1 (2)
Base of tongue	6 (11)
Soft palate	5 (9)
Nasal/paranasal	2 (4)
Major salivary	
Parotid	3 (5)
Clinical T[a] Status	
T1	24 (42)
T2	22 (39)
T3	1 (2)
T4	10 (18)
Clinical N[b] Status	
N0/NX	54 (95)
N1	1 (2)
N2	2 (4)
Pathological T Status	
T1	35 (61)
T2	16 (28)
T3	0 (0)
T4	6 (11)
Pathological N Status	
N0/NX	51 (89)
N1	2 (4)
N2	4 (7)
Overall stage	
Stage I	33 (58)
Stage II	14 (25)
Stage III	1 (2)
Stage IV	9 (16)
Vascular invasion	
No	53 (93)
Yes	2 (4)
Unknown	2 (4)
Perineural invasion	
No	18 (32)
Yes	37 (65)
Unknown	2 (4)
Margins	
Negative	27 (47)
Close	16 (28)
Positive	13 (23)
Unknown	1 (2)
Histological variant	
PAC[c]	32 (56)
CAMSG[d]	14 (25)
Unknown	11 (19)

Note: Some percentages do not sum to 100 due to rounding.

[a] T, tumor.
[b] N, nodal.
[c] PAC, polymorphous adenocarcinoma.
[d] CAMSG, cribriform adenocarcinoma of minor salivary gland origin.
* Patients who had a history of tobacco or alcohol consumption were coded as Yes. Patients who had never smoked or drank alcohol were coded as No.

Table 2
Comparison of patients with PAC[a] and CAMSG[b].

	PAC (n = 32) n (%)	CAMSG (n = 14) n (%)	p-value
Age			
< 60	15 (47)	7 (50)	0.845
≥60	17 (53)	7 (50)	
Sex			
Male	10 (31)	5 (36)	0.511
Female	22 (69)	9 (64)	
Tobacco			
No	9 (28)	5 (36)	0.427
Yes	23 (72)	9 (64)	
Alcohol			
No	5 (16)	7 (50)	0.021
Yes	27 (84)	7 (50)	
Tumor site			
Minor salivary			
Hard palate	19 (60)	6 (43)	
Buccal mucosa	4 (13)	0 (0)	
Retromolar trigone	0 (0)	1 (7)	
Gum	1 (3)	1 (7)	
Base of tongue	3 (9)	3 (21)	
Soft palate	2 (6)	2 (14)	
Nasal/paranasal	1 (3)	0 (0)	
Major salivary			
Parotid	2 (6)	1 (7)	
Clinical T[c] Status			
T1–T2	26 (82)	12 (86)	0.537
T3–T4	6 (19)	2 (14)	
Clinical N[d] Status			
N0/NX	30 (94)	13 (93)	0.673
N+	2 (6)	1 (7)	
Pathological T Status			
T1–T2	29 (91)	13 (93)	0.646
T3–T4	3 (9)	1 (7)	
Pathological N Status			
N0/NX	27 (84)	12 (86)	0.642
N+	5 (16)	2 (14)	
Overall stage			
Stage I–II	27 (84)	11 (79)	0.463
Stage III–IV	5 (16)	3 (21)	
Vascular invasion			
No	32 (100)	14 (100)	–
Yes	0	0	
Perineural invasion			
No	8 (25)	6 (43)	0.193
Yes	24 (76)	8 (57)	
Margins			
Negative	12 (38)	8 (57)	0.216
Close/Positive	20 (63)	6 (43)	

[a] PAC, polymorphous adenocarcinoma.
[b] CAMSG, cribriform adenocarcinoma of minor salivary gland origin.
[c] T, tumor.
[d] N, nodal.

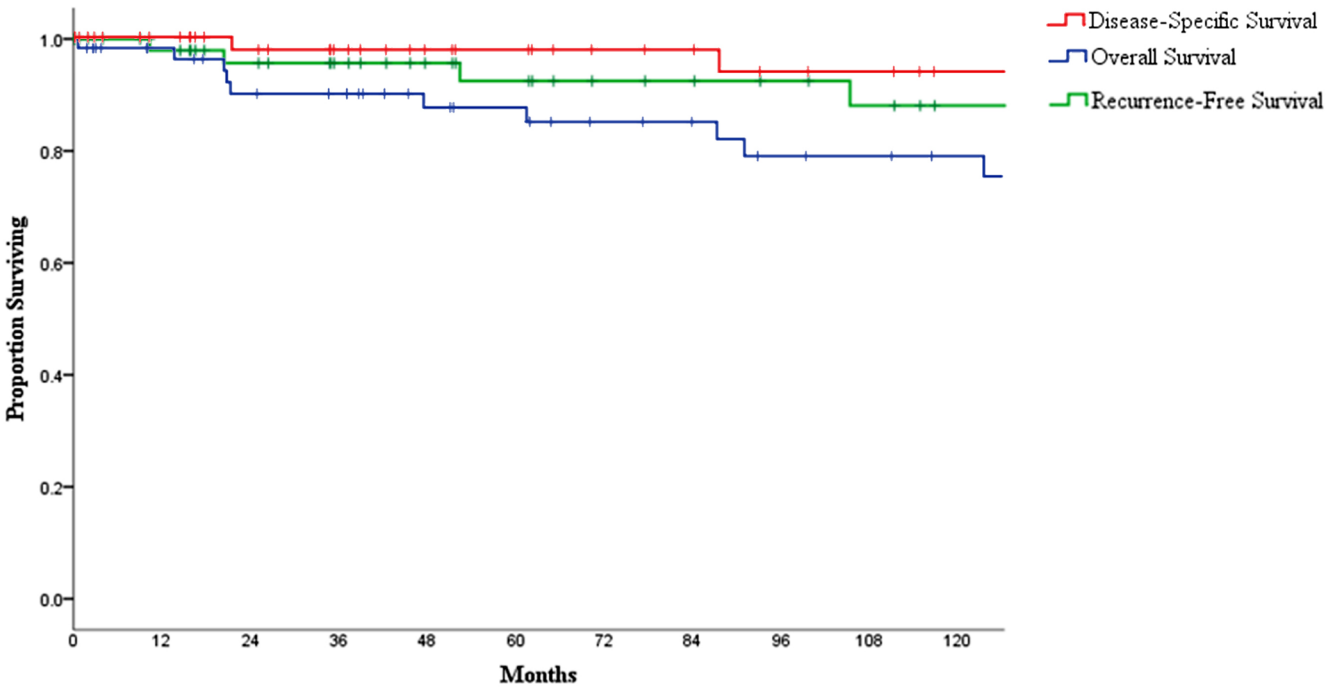

Fig. 2. Overall survival, Disease-specific survival and Recurrence-free survival in patients with PAC.

parotidectomy and 1 (2%) a partial parotidectomy. Eleven (19%) patients had a neck dissection, which was therapeutic in 3 (5%) and elective in 8 (14%). All were unilateral, except for 1 patient with a tumor on the base of the tongue. The decision for elective neck dissection was based on advanced T stage (T4) and the location of the primary in the oropharynx. In this cohort, 13 (23%) patients received PORT. In general, patients treated with PORT had positive or close margins, N+ disease, and advanced overall stage.

OS and DSS

With a median follow-up of 84 months (1–159 months), the 5- and 10-year OS and DSS were 88% and 79% and 98 and 94%, respectively (Fig. 2). On univariate analysis, age, pathological T stage, and overall stage were predictors of OS. Patients older than 60 years of age had a 15-fold increased risk of death ($p = 0.001$), and patients with stage III/IV disease had a 4-fold increase risk of death ($p = 0.013$). CAMSG histology did not show a worse outcome in terms of OS (Table 3).

Two patients had a disease-specific death, both of whom presented initially with an advance T stage tumor. The first patient had a tumor located in the retromolar trigone and had presented with trismus. He required a craniofacial resection with an infratemporal approach, ipsilateral neck dissection, and free-flap reconstruction. Final pathology confirmed a T4 tumor with negative margins. PORT was delivered to the primary site. At 20 months, he was found to have lung metastases and eventually died at 87 months.

The second patient had a clinical T4a tumor of the hard palate treated with a partial maxillectomy; pathology showed a pT1 cancer. Ten months later, she developed bone metastases and had a pathologic fracture of the hip requiring a hip replacement and radiation. Although she received further treatment, the disease progressed. She died 21 months after being diagnosed.

RFS

The 5- and 10-year RFS were 93% and 88%, respectively (Fig. 2). The median time to recurrence for the six patients who recurred was 79 months (10–232 months). The 10-year LRFS, RRFS, and DRFS was 97%, 92%, and 96%, respectively. Details of the 6 patients who experienced recurrence are shown in Table 4. Of the 6 patients who had a recurrence, 3 of them were identified as CAMSG; 67% had stage I–II disease, all of them had close negative margins, and 2 received PORT. Distant disease was the most frequent event.

Factors predictive of recurrence by univariate analysis are shown in Table 5. Univariate analysis of margins showed that the close and positive margin groups had similar outcomes ($p = 0.175$). Therefore, close and positive margins were combined for analysis. Due to small sample size and limited number of events, no variable was statistically significant. Male patients had a 5-fold increased incidence of recurrence ($p = 0.057$), and patients with advanced overall stage had a 4-fold increased incidence of recurrence ($p = 0.087$). Patients with the CAMSG pathology variant had a 3-fold increased incidence of recurrence compared to the PAC variant, but this was not significant ($p = 0.228$).

Discussion

In this study, we report our experience in the management of 57 patients diagnosed with PAC of the salivary glands treated at a single institution over a 30-year period. Our aims were to report recurrence and survival outcomes and to identify factors predictive of outcome. We were interested to determine if outcomes were poorer in patients with CAMSG.

The small number of patients treated over a long period illustrates how rare this cancer is. A summary of the main studies reporting PAC in the literature is shown in Supplementary Table 1. In relation to the literature, the demographics and clinical characteristics in our cohort are comparable; most of the patients were female, with a median age of 61 years, and 55% of tumors were located in the hard palate. As reported by the largest study, based on the Surveillance Epidemiology and End Results (SEER), most of the cases (81%) presented with early disease (T1–T2) [1]. The incidence of regional disease was 11% in our study, a lower rate than the SEER report (25%), but in agreement with most of the studies, which report rates from 5% to 15% [13–15].

Twenty-three percent of our patients had positive margins, which correlated with the 22% reported by Elhakim et al. [16]. It has been suggested that 1 in 3 patients will have positive margins, even after

Table 3
Factors predictive of OS[a].

Factor	Variable	No. of Patients	5-year OS	Univariate		
				HR[b]	CI[c]	p-value
Age	≤60	27	100%			
	> 60	30	77%	15.47	1.99–120.92	0.001
Sex	Female	37	91%			
	Male	20	83%	2.67	0.884–8.12	0.071
Alcohol	Never	18	83%			
	Ever	38	89%	0.549	0.176–1.715	0.295
Tobacco	Never	17	94%			
	Ever	39	85%	0.763	0.330–4.535	0.763
Site	Minor	54	87%			
	Major	3	100%	—	——	0.585
pT[d] Status	T1/T2	51	91%			
	T3/T4	6	67%	6.64	1.91–23.07	0.001
pN[e] Status	N0/X	51	91%			
	N+	6	67%	1.798	0.391–8.263	0.444
Overall pathological stage	I/II	47	93%			
	III/IV	10	69%	3.91	1.227–12.478	0.013
Vascular invasion	No	53	89%			
	Yes	2	100%	1.552	0.192–12.518	0.678
Perineural invasion	No	18	89%			
	Yes	37	89%	0.567	0.182–1.766	0.321
Histology	PAC[f]	32	88%			
	CAMSG[g]	14	92%	0.793	0.160–3.935	0.776

[a] OS, overall survival.
[b] HR, hazard ratio.
[c] CI, confidence interval.
[d] pT, pathological tumor.
[e] pN, pathological nodal.
[f] PAC, polymorphous adenocarcinoma.
[g] CAMSG, cribriform adenocarcinoma of minor salivary gland origin.

radical resection. This finding is possibly attributable to the classic infiltrative morphology of PAC [17]. PNI was frequently identified, but LVI was rarely encountered.

Standard treatment for patients with PAC is complete surgical resection with negative margins. The use of adjuvant radiation in salivary gland tumors is based on the recommendations made by the National Comprehensive Cancer Network, which consider risk factors like intermediate- or high-grade, close or positive margins, PNI, lymph node metastasis, and T3–T4 tumors. For PAC, there is no clear evidence that the use of PORT correlates with better RFS. In our study, 25% of patients received PORT, which is in concordance with rates reported from other institutions that range from 19% to 30% [1,13,16]. Patients selected for PORT had regional disease and advanced overall stage.

In line with previously published studies, our cohort has excellent survival, with a 5- and 10-year OS of 88%–79%, and a 5- and 10-year DSS of 98% and 94%. The survival difference between OS and DSS highlight the indolent behavior of this carcinoma, as the majority of deaths are not cancer related. Because of the low number of disease-specific deaths, we assessed factors predictive of OS. On univariate analysis, age, advanced T, and overall pathological stage were predictive of worse OS outcome. The influence of age on the survival of patients with major and minor salivary gland tumors was previously addressed, with survival decreasing with older age [18]. Pathological T3–T4 classification was correlated with an unadjusted HR of 6.64 and

Table 4
Clinical and pathological characteristics of patients who experienced recurrence.

Sex	Age	Primary site	cTN	Treatment	pTN	Histologytype	Margin	PNI[a]	LVI[b]	Time to first recurrence	Site recurrence	Time to death
Male	53	Oral cavity	T[c]1N[d]0	Surgery	T1NX	CAMSG[e]	Negative	No	No	232 months	Local	
Male	54	Oral cavity	T4N0	Surgery + RT[f]	T4N0	Unknown	Negative	No	No	20 months	Local/lung	87 months
Female	70	Oral cavity	T4aN0	Surgery	T1NX	PAC[g]	Close	Yes	No	10 months	Bone (hip)	21 months
Female	48	Oral cavity	T2N0	Surgery	T1NX	PAC	Close	Yes	No	52 months	Neck	
Male	22	Pharynx	T2N0	Surgery + RT	T1N2b	CAMSG	Negative	No	No	160 months	Bone (sacrum)	
Male	63	Oral cavity	T2N0	Surgery	T2NX	CAMSG	Negative	No	No	105 months	Neck	

[a] PNI, perineural invasion.
[b] LVI, lymphovascular invasion.
[c] T, tumor.
[d] N, nodal.
[e] CAMSG, cribriform adenocarcinoma of minor salivary gland origin.
[f] RT, radiotherapy.
[g] PAC, polymorphous adenocarcinoma.

Table 5
Factors predictive of recurrence-free survival.

Factor	Variable	No. of Patients	5-year RFS[a]	Univariate		
				HR[b]	CI[c]	p-value
Age	≤60	27	90%			
	> 60	30	96%	0.831	0.147–4.714	0.834
Sex	Female	37	92%			
	Male	20	94%	4.589	0.826–25.487	0.057
Alcohol	Never	18	100%			
	Ever	38	89%	2.725	0.317–23.402	0.341
Tobacco	Never	17	83%			
	Ever	39	94%	0.604	0.109–3.332	0.558
Site	Minor	54	92%			
	Major	3	100%	—	—	0.751
pT[d] Status	T1/T2	51	94%			
	T3/T4	6	75%	6.419	0.545–75.592	0.091
pN[e] Status	N0/X	51	91%			
	N+	6	100%	1.994	0.222–17.924	0.530
Overall pathologic stage	I/II	47	94%			
	III/IV	10	88%	4.308	0.701–26.484	0.087
Vascular invasion	No	53	92%			
	Yes	2	100%	—	—	0.588
Perineural invasion	No	18	86%			
	Yes	37	97%	0.267	0.048–1.472	0.104
Histology	PAC[f]	32	92%			
	CAMSG[g]	14	100%	2.926	0.473–18.080	0.228
Margin	Negative	27	95%			
	Close /Positive	29	89%	0.596	0.108–3.270	0.547
PORT[h]	No	44	92%			
	Yes	13	92%	1.921	0.316–11.666	0.471

[a] RFS, recurrence-free survival.
[b] HR, hazard ratio.
[c] CI, confidence interval.
[d] pT, pathological tumor.
[e] pN, pathological nodal.
[f] PAC, polymorphous adenocarcinoma.
[g] CAMSG, cribriform adenocarcinoma of minor salivary gland origin.
[h] PORT, postoperative radiotherapy.

a 67% 5-year OS. This finding differs from the literature. A Danish study based on 73 patients with PAC showed that T stage was not a predictor of worse OS and neither was an advanced overall stage [16]. In our cohort, advanced overall pathological stage was also a predictor of worse OS.

Despite good survival outcomes, PAC patients do experience recurrence. According to the literature, local recurrence rates range from 10% to 33% [4,13], while regional recurrence ranges from 9% to 13% [13,19]. However, in our study, only 2 (4%) local and 2 (4%) regional recurrences were identified. It is possible these differences may be related to different treatments, but it may also be related to cases in the literature being wrongly classified as PAC. In terms of distant disease, 2 of the 3 PAC patients presented with symptoms, which prompted specific imaging.

Three of the 6 patients who experience a recurrence, had their recurrence diagnosed more than 10 years after the initial surgery, indicating the importance of long-term follow-up in these patients. A minimum of 15–20 years has been suggested [14,20].

Because of the ongoing debate related to the differences between PAC and CAMSG in terms of site distribution, histological characteristics and regional metastasis were compared in both groups. We carried out a detailed pathology review of 46 of the 57 patients and classified 14 with CAMSG and 32 with PAC. The literature describes patients with CAMSG as being younger, having a female:male ratio of 1:1, commonly developing early cervical lymph node metastases, and having a higher propensity for LVI [21]. Molecular differences have also been reported. PACs are characterized by *PRKD1* mutation, whereas CAMSGs are characterized by *PRKD1–3* translocation. Nevertheless, in cases with mixed PAC and CAMSG features, molecular overlapping exists [22,23]. In our study, no differences were found between PAC and CAMSG with regards to demographics, stage of disease, and pathological characteristics such as PNI and LVI. In agreement with the literature, CAMSG was not a predictor of worse OS [9]. However, in terms of recurrence, patients with CAMSG histology did have a 2.9-fold increased incidence, though this was not statistically significant. Of the 6 patients who recurred in our cohort, 3 of them were listed as CAMSG, which tends to suggest a tendency to more frequent recurrence. Importantly, in this group, recurrences were late, occurring after 8 years. Late recurrences in CAMSG have been described in the literature [7,24].

There are limitations to our study related to the biases associated with retrospective data collection. Selection bias associated with patient-, physician-, and treatment-related biases can never be fully accounted for. However, the strengths of our study are that all patients were treated with a uniform treatment philosophy by a multidisciplinary management team at a single institution. Importantly, all slides were reviewed by a pathologist specializing in salivary gland tumors. These differences may account for the superior recurrence and survival rates that we report in our cohort, compared with the literature. With regards to the debate about the CAMSG variant being more aggressive, our study does lend some evidence that these patients may have increased probability of recurrence, but due to small sample size and number of events, we were not able to show this to be significant or perform a multivariable analysis.

Conclusion

PAC of the salivary gland is a rare disease with excellent survival outcomes. Recurrence is not common and tends to occur late. Long-term follow-up is indicated in patients with this pathology.

Declaration of Competing Interest

None declared

Acknowledgements

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.oraloncology.2019.06.002.

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