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Sex disparities in salivary malignancies: Does female sex impact oncological outcome?

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ABSTRACT

Objective: Previous population-based studies in salivary gland carcinomas have described a relationship between female sex and superior oncological outcome.

Patients and methods: Our institutional database of 884 surgically treated patients with salivary gland malignancies from 1985 to 2015 was analyzed for the impact of sex on oncological outcomes. Histologies were classified in three risk groups, low, intermediate and high. Survival outcomes were determined using the Kaplan-Meier method. Hazard ratios for male sex were determined using the Cox proportional hazards model.

Results: Eight hundred sixty-seven patients were identified; median age was 59 years, and 51% had a minor salivary gland malignancy. Female patients were younger (58 versus 60 years; $p = 0.040$) and had a lower incidence of high-risk histologies (25% versus 40%, $p < 0.001$) and T3-T4 tumors compared to men (23% versus 31%, $p < 0.001$). With a median follow-up of 57 months, female patients had a superior 5-year disease-specific survival (DSS) (90% versus 79%; $p < 0.001$). The unadjusted hazard ratio showed male patients had a 2.15-fold increased risk of death (HR 2.15; 95% CI, 1.50–3.06, $p < 0.001$). After adjusting for Charlson co-morbidity index, tobacco use, histological risk group, and overall pathological stage, males still had a statistically significant increased risk of death (HR 1.48; 95% CI 1.05–2.17; $p = 0.047$). Subgroup analysis showed DSS for females was significantly better in the high-risk histological group (5-year 68% versus 49%, $p = 0.007$).

Conclusion: Our study shows that sex has an impact on cancer-specific survival and that female sex favors improved survival.

Introduction

Salivary gland malignancies are uncommon, comprising only 3%–6% of head and neck tumors. The reported incidence in the United States is 5.5 cases per 100,000 population [1]. The World Health Organization classification recognizes more than 20 different malignant histologies, each with specific features and outcomes.

In this group of tumors, stage, histological grade, and lymph node involvement have been reported as independent predictors of disease-specific survival (DSS) [2–4]. However, there is limited information available describing the relationship between sex and oncological outcomes in these patients [5]. In squamous cell carcinoma of the head and neck, sex differences in incidence and outcomes have been attributed to health-related behaviors such as tobacco and alcohol consumption. In salivary gland cancers, the impact of these risk factors is less evident.

In a recent population-based study of patients with major salivary gland cancer, it was reported that female sex was associated with superior oncological outcomes [6]. However, the clinical characterization of this cohort was limited, and no adjustment for other pathological prognostic factors was made.

Abbreviations: DSS, disease specific survival; SDC, salivary duct carcinoma; OS, overall survival; HR, hazard ratio; CI, confidence interval; PORT, post-operative radiation; SEER, Surveillance, Epidemiology, and End Results Program; RT, radiation therapy; CRT, chemoradiation therapy; AJCC, American Joint Committee on Cancer

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In the current study, we describe a large cohort of patients with major and minor salivary gland tumors treated in a single institution with comprehensive details on demographic, histopathology, treatment, and follow-up characteristics. The aim of our study was to evaluate the prognostic impact of sex on outcome in a large cohort of patients with salivary gland malignancies.

Methods

Patients

After obtaining approval from Memorial Sloan Kettering Cancer Center's Institutional Review Board, our database of 884 surgically treated patients with minor and major salivary gland malignancies from 1985 to 2015 was analyzed for the impact of sex on oncological outcomes. This database does not include patients with previous treatment or surgery at an outside institution. For this study, we excluded patients less than 18 years of age. This left 867 patients for analysis.

Data collection

Details regarding patient demographics, tumor characteristics, surgical treatment, adjuvant therapy, and oncological outcomes were recorded. The burden of concurrent patient disease status was assessed using the Charlson Comorbidity Index (CCI) [7]. Tumors were staged according to the 7th edition of the American Joint Committee on Cancer staging system for major salivary gland tumors. Minor salivary glands were staged using the mucosal tumor staging system according to the anatomical site of the tumor.

Definitions

Tumors were diagnosed according to criteria described by the World Health Organization classifications of head and neck salivary gland malignancies [8]. Because there are more than 20 histologies, we classified these histologies into 3 histological risk groups using the Kaplan-Meier survival plots for each histology: the high-risk group included salivary duct carcinoma (SDC), high-grade myoepithelial carcinoma, high-grade mucoepidermoid carcinoma, high-grade carcinoma ex pleomorphic adenoma, high-grade adenoid cystic carcinoma, high-grade adenocarcinoma, and high-grade acinic cell carcinoma. The intermediate risk group included low and intermediate-grade adenoid cystic carcinoma. The low-risk group included low- and intermediate-grade mucoepidermoid carcinoma, low-grade acinic cell carcinoma, low-grade adenocarcinoma, low-grade carcinoma ex pleomorphic adenoma, low-grade myoepithelial carcinoma, and all polymorphous adenocarcinomas and epithelial myoepithelial carcinomas. Forty (5%) patients with infrequent or single cases histologies were classified in the high or low risk group according to their grade.

Statistical analysis

Endpoints of interest were overall survival (OS) calculated from date of surgery to the date of last follow-up or death by any cause, and DSS, calculated from date of surgery to the date of last follow-up or death with disease. Calculations were made in months using the Kaplan-Meier method. Patients' last status was established by a member of the disease management team.

Variables were compared across sex. Categorical variables were compared using chi-square analysis or Fisher's exact test when appropriate, and continuous variables were compared using the Mann-Whitney *U* test. Any factor found to be statistically different between men and women was analyzed for impact on survival using the Kaplan-Meier method and the log-rank test. The unadjusted hazard ratio (HR) for the impact of sex on OS and DSS was determined by the Cox proportional hazard method. The adjusted HR for sex was then determined after adjusting for other prognostic variables. Lymphovascular invasion and perineural invasion were excluded from the multivariate model due to concordance with histological risk group. Survival outcomes stratified by sex were then determined individually for low-risk, intermediate-risk, and high-risk histologies. Based on the hypothesis that the main causal factor affecting DSS was the high incidence of SDC in men, we performed one planned analysis excluding patients with SDC, and one focused on the entire high-risk histological group. Statistical analyses were performed using SPSS Version 25.0 (IBM, Armonk, NY).

Results

Whole cohort

Of the 867 selected patients for analysis, 454 (52%) were female and 413 (48%) were male. The median age was 59 years (range 18–98). Fifty-one percent of patients reported a history of tobacco consumption and 468 (54%) of patients had a CCI of 2 or more. Tumors originated from a minor salivary gland in 446 (51%). Forty-nine percent of patients were classified as low risk and 32% were classified as high risk. The most frequent histologies were mucoepidermoid carcinoma (35%), adenoid cystic carcinoma (22%), and carcinoma ex-pleomorphic adenoma (8%).

Treatment was surgery alone for 477 (55%) patients, while 345 patients (40%) had surgery with postoperative radiation therapy (PORT). Chemoradiotherapy use was uncommon (5%). During the surgical resection, a therapeutic neck dissection was performed in 108 (12%) patients and a prophylactic neck dissection was done in 221 (25%) patients. The criteria for performing a prophylactic neck dissection were high-risk histology and advanced T stage.

On final pathological staging, there was a high incidence of T1-T2 lesions (70%), and 18% of the whole cohort had regional nodal metastasis. Perineural invasion and lymphovascular invasion was present in 37% and 16% of all cases, respectively. Three hundred seventy-seven (44%) patients had negative margins and 205 (24%) patients had close margins.

Comparison between men and women

Differences in clinical and pathological characteristics between men and women are shown in Table 1. Women were younger (58 versus 60 years; $p = 0.040$), had less tobacco consumption (44% versus 63%, $p < 0.001$) and had a lower CCI compared to men (CCI = 0–1 50% versus 42%, $p = 0.042$). At clinical presentation, women were more likely to present with earlier T stage (T1-T2 tumors 77% versus 69%, $p < 0.001$) and a negative N stage (clinically node negative: 91% versus 83%, $p < 0.001$). The incidence of high-risk histologies was significantly lower in women (25% versus 40%, $p < 0.001$).

Final pathological staging showed that fewer women had T3-T4 tumors compared to men (24% versus 34%, $p < 0.001$), and that women had lower rates of positive lymph nodes (12% versus 24%, $p < 0.001$). There was no significant difference in margin status between women and men (negative margin: 45% versus 46%, $p = 0.947$). Due to lower stage disease and more frequent low-risk histology, the use of PORT and chemoradiation therapy (CRT) was lower in women compared to men (PORT, 38% versus 42%, and CRT, 3% versus 8%, $p < 0.001$).

Impact of sex on survival

With a median follow-up of 57 months (1–364), the 5-year OS and DSS for the entire cohort was 78% and 84%, respectively. Women had a superior DSS compared to men (5-year DSS 90% versus 79%; 10-year DSS 81% versus 65%, $p < 0.001$) (Fig. 1). There were 133 disease-specific deaths: 85 in men and 48 in women.

The unadjusted and adjusted HRs for sex on DSS are shown in

Table 1
Patients and pathological variables stratified by sex.

	Total (n = 867)	Women (n = 454; 52.4%)	Men (n = 413; 47.6%)	p-value
Age, n (%)				
< 60 years	445 (51.3)	245 (54.0)	200 (48.4)	0.103
≥60 years	422 (48.7)	209 (46.0)	213 (51.6)	
CCI				
0	233 (26.9)	130 (28.6)	103 (24.9)	
1	166 (19.1)	97 (21.4)	69 (16.7)	0.042
≥2	468 (54.0)	227 (50.0)	241 (58.4)	
Tobacco, n (%)				
Never	387 (44.6)	243 (55.9)	144 (36.6)	< 0.001
Ever	441 (50.9)	192 (44.1)	249 (63.4)	
Unknown	39 (4.5)			
Alcohol, n (%)				
Never	259 (29.9)	172 (40.8)	87 (22.8)	< 0.001
Ever	545 (62.9)	250 (59.2)	295 (77.2)	
Unknown	63 (7.3)			
Site, n (%)				
Major	421 (48.6)	207 (45.6)	214 (51.8)	0.067
Minor	446 (51.4)	247 (54.4)	199 (48.2)	
Clinical T[a] stage, n (%)				
TX	3 (0.3)			
T1	338 (39.0)	211 (46.6)	127 (30.9)	< 0.001
T2	293 (33.8)	136 (30.0)	157 (38.2)	
T3	103 (11.9)	49 (10.8)	54 (13.1)	
T4	130 (15.0)	57 (12.6)	73 (17.8)	
Clinical N[b] stage, n (%)				
N0	756 (87.2)	415 (91.4)	341 (82.6)	
N1	40 (4.6)	19 (4.2)	21 (5.1)	< 0.001
N2	69 (8.0)	20 (4.4)	49 (11.9)	
N3	2 (0.2)	0 (0.0)	2 (0.5)	
Risk Histology, n (%)				
Low	426 (49.1)	238 (52.8)	188 (45.5)	
Intermediate	158 (18.2)	99 (22.0)	59 (14.3)	< 0.001
High	280 (32.3)	114 (25.3)	166 (40.2)	
Unknown	3 (0.3)			
Pathological T Stage, n (%)				
TX	11 (1.3)			
T1	393 (45.3)	240 (53.6)	153 (37.5)	
T2	215 (24.8)	99 (21.1)	116 (28.4)	< 0.001
T3	57 (6.6)	27 (6.0)	30 (7.4)	
T4	191 (22.0)	82 (18.3)	109 (26.7)	
Pathological N Stage, n (%)				
N0/NX	710 (82.1)	398 (87.7)	314 (76.0)	
N1	32 (3.7)	18 (4.0)	14 (3.4)	< 0.001
N2	121 (14.0)	38 (8.4)	83 (20.1)	
N3	2 (0.2)	0 (0.0)	2 (0.5)	
AJCC[c] Stage (7th Edition), n (%)				
Stage I	364 (42.0)	226 (50.4)	138 (33.8)	
Stage II	174 (20.1)	85 (19.0)	89 (21.8)	< 0.001
Stage III	61 (7.0)	35 (7.8)	26 (6.4)	
Stage IV	257 (29.6)	102 (22.8)	155 (38.0)	
Unknown	11 (1.3)			
Perineural Invasion, n (%)				
No	317 (36.6)	170 (51.8)	147 (47.4)	
Yes	321 (37.0)	158 (48.2)	163 (52.6)	0.266
Unknown	229 (26.4)			
Lymphovascular Invasion, n (%)				
No	465 (53.6)	248 (82.4)	217 (72.1)	
Yes	137 (15.8)	53 (17.6)	84 (27.9)	0.003
Unknown	265 (30.6)			
Margins, n (%)				
Negative	377 (43.5)	195 (44.7)	182 (45.8)	
Close	205 (23.6)	108 (24.8)	97 (24.4)	0.947
Positive	251 (29.0)	133 (30.5)	118 (29.7)	
Unknown	34 (3.9)			
Treatment, n (%)				
Surgery alone	477 (55.0)	270 (59.5)	207 (50.1)	
Surgery + RT[d]	345 (39.8)	172 (37.9)	173 (41.9)	< 0.001
Surgery + CRT[e]	44 (5.1)	12 (2.6)	32 (7.7)	
Surgery + Chemotherapy	1 (0.1)	0 (0.0)	1 (0.2)	

[a] T, tumor.
[b] N, nodal.
[c] AJCC, American Joint Committee on Cancer.
[d] RT, radiation therapy.
[e] CRT, chemoradiation therapy.

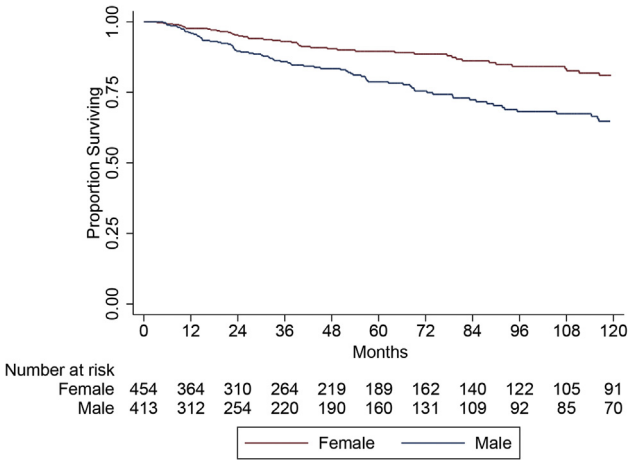

Fig. 1. Disease-specific survival stratified by sex.

Table 2. Factors predictive of worse DSS on univariate analysis were CCI, sex, tobacco use, lymphovascular invasion, perineural invasion, histological risk group, and overall pathological stage. The unadjusted HR showed male patients had a 2.15-fold increased risk of death (HR 2.15; 95% confidence interval CI 1.50–3.06; p < 0.001). After adjusting for CCI, tobacco use, histological risk group, and overall pathological stage, male patients still had a statistically significant increased risk of death (HR 1.59; 95% CI 1.07–2.37; p = 0.022).

Impact of sex on survival stratified by histological risk group

On analysis of the impact of sex on DSS for each histological risk group, stratified for histological risk, we found that 8 deaths were in the low-risk group, 27 were in the intermediate-risk group, and 98 were in the high-risk group.

The DSS for the histological low-risk group is shown in Fig. 2A. The DSS did not differ between women and men. Patients with low-risk disease had a 5-year DSS of 99%, irrespective of sex. At 10 years, women had a DSS of 98%, while men had a DSS of 95% (p = 0.338).

The DSS for the histological intermediate-risk group is shown in Fig. 2B. There was no significant difference in DSS between men and women, although there was a trend to lower survival in men at 10 years. In the intermediate-risk group, women had a 5- and 10-year DSS of 92% and 74%, respectively, while men had a 5- and 10-year DSS of 100% and 59%, respectively (p = 0.200).

The DSS for the histological high-risk group is shown in Fig. 2C. In the high-risk group, there was a significant difference in DSS between women and men, with women having superior survival compared to men (5-year DSS, 68% versus 49%; 10-year DSS, 55% versus 34%, p = 0.007).

Table 2
Unadjusted and adjusted hazard ratios for sex on disease-specific survival.

Factor	Variable	n	Univariate			Multivariate		
			HR[a]	95% CI[b]	p-value	HR	CI	p-value
Sex	Female	454						
	Male	413	2.150	1.509–3.064	< 0.001	1.590	1.068–2.366	0.022
CCI	0	233						
	1	166	1.875	1.072–3.278		2.211	1.217–4.018	
	≥ 2	468	2.832	1.764–4.546	< 0.001	1.974	1.174–3.320	0.019
Alcohol	Never	259						
	Ever	545	1.394	0.938–2.070	0.099			
Tobacco	Never	387						
	Ever	441	1.755	1.215–2.535	0.002	1.211	0.823–1.783	0.331
Lymphovascular Invasion	No	465						
	Yes	137	7.007	4.608–10.654	< 0.001			
Perineural Invasion	No	317						
	Yes	321	5.233	3.102–8.829	< 0.001			
Histological Risk Group	Low	426						
	Intermediate	158	8.401	3.816–18.495		3.299	1.445–7.533	
	High	280	26.756	12.995–55.089	< 0.001	8.739	4.070–18.790	< 0.001
AJCC Stage	I	364						
	II	174	14.417	4.222–49.230		9.359	2.712–32.300	
	III	61	41.075	12.024–140.312		23.445	6.704–81.988	
	IV	257	65.501	20.717–207.096	< 0.001	21.217	6.521–69.034	< 0.001

[a] HR, hazard ratio.
[b] CI, confidence interval.

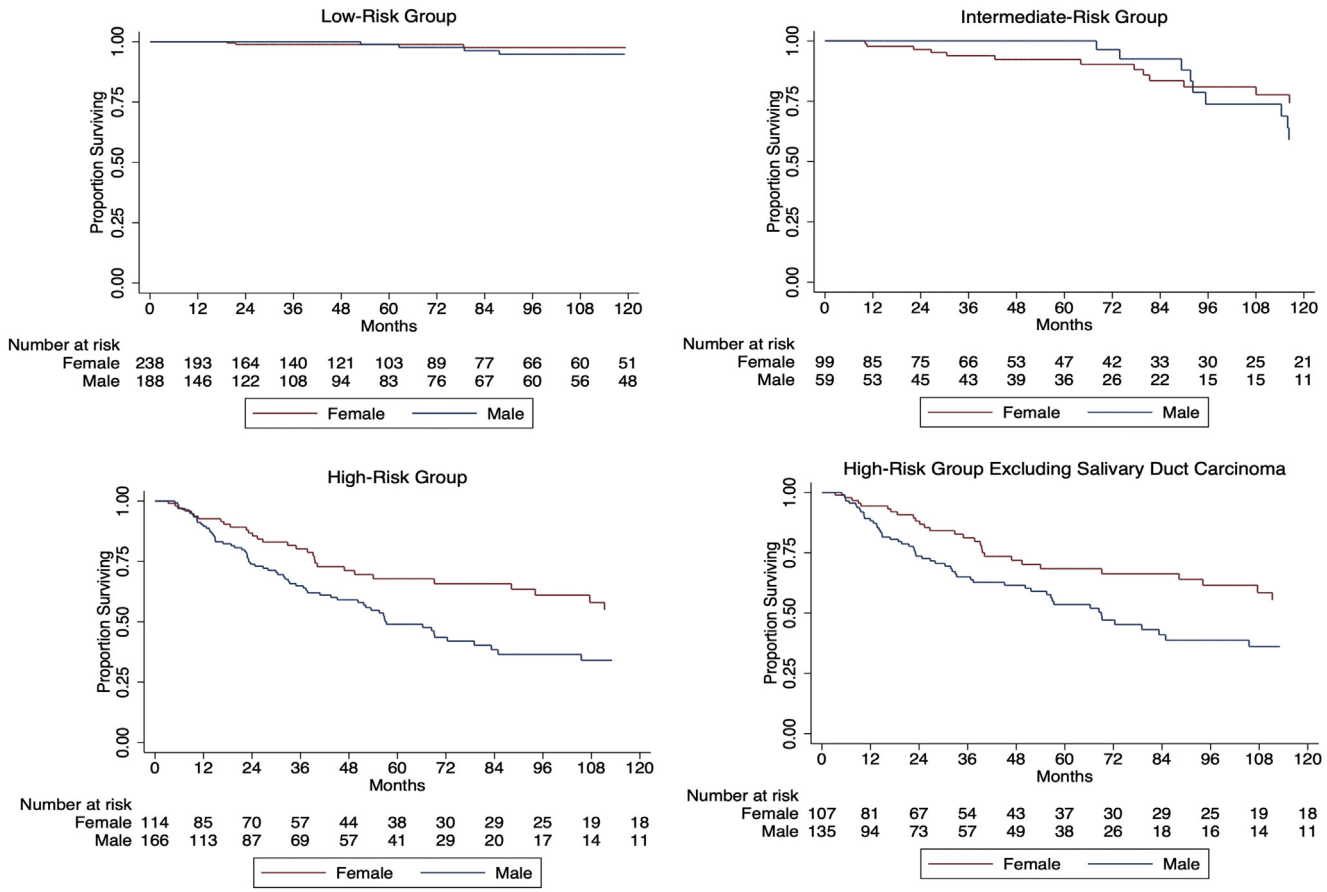

Fig. 2. Disease-specific survival stratified by histological risk group and sex. (A) Disease-specific survival for the low-risk group stratified by sex. (B) Disease-specific survival for the intermediate-risk group stratified by sex. (C) Disease-specific survival for the high-risk group stratified by sex. (D) Disease-specific survival for the high-risk group excluding salivary duct carcinoma stratified by sex.

Table 3
Patient characteristics and pathological variables stratified by sex in the high-risk histological group.

	Female (n = 114; 40.7%)	Male (n = 166; 59.3%)	p-value
Age, n (%)			
< 60 years	43 (37.7)	60 (36.1)	0.788
≥60 years	71 (62.3)	106 (63.9)	
CCI			
0	18 (15.8)	29 (17.5)	0.133
1	23 (20.2)	19 (11.4)	
≥2	73 (64.0)	118 (61.1)	
Tobacco, n (%)			
Never	62 (59.0)	47 (29.7)	< 0.001
Ever	43 (41.0)	111 (70.3)	
Alcohol, n (%)			
Never	43 (41.3)	34 (22.1)	0.001
Ever	61 (58.7)	120 (77.9)	
Previous RT[a], n (%)			
No	110 (96.5)	161 (97.0)	0.536
Yes	4 (3.5)	5 (3.0)	
Site, n (%)			
Major	62 (54.4)	117 (70.5)	0.006
Minor	52 (45.6)	49 (29.5)	
cT[b] Stage, n (%)			
T1	29 (25.4)	26 (15.9)	0.250
T2	35 (30.7)	56 (34.1)	
T3	24 (21.1)	36 (22.0)	
T4	26 (22.8)	46 (28.0)	
cN[c] Stage, n (%)			
N0	93 (81.6)	103 (62.0)	
N1	9 (7.9)	17 (10.2)	0.001
N2	12 (10.5)	44 (26.5)	
N3	0 (0.0)	2 (1.2)	
cM[d] Status n (%)			
M0	113 (99.1)	162 (97.6)	0.651
M1	1 (0.9)	4 (2.4)	
pT[e] Stage, n (%)			
T1	35 (31.8)	26 (15.8)	
T2	24 (21.8)	46 (27.9)	0.019
T3	11 (10.0)	19 (11.5)	
T4	40 (36.4)	74 (44.8)	
pN[f] Stage, n (%)			
N0/Nx	79 (69.3)	81 (48.8)	
N1	8 (7.0)	6 (3.6)	< 0.001
N2	27 (23.7)	77 (46.4)	
N3	0 (0.0)	2 (1.2)	
AJCC[g] Stage (7th Edition), n (%)			
Stage I	27 (24.5)	15 (9.1)	
Stage II	15 (13.6)	25 (15.2)	< 0.001
Stage III	13 (11.8)	9 (5.5)	
Stage IV	55 (50.0)	116 (70.3)	
Histology, n (%)			
Acinic Cell Carcinoma	5 (4.4)	5 (3.0)	
Adenocarcinoma	17 (14.9)	31 (18.7)	
Adenoid Cystic Carcinoma	17 (14.9)	16 (9.6)	
Carcinoma Ex-Pleomorphic Adenoma	24 (21.1)	29 (17.5)	0.094
Mucoepidermoid Carcinoma	31 (27.2)	36 (21.7)	
Myoepithelial carcinoma	6 (5.3)	5 (3.0)	
Poorly Differentiated Carcinoma	3 (2.6)	6 (3.6)	
Salivary Duct Carcinoma	7 (6.1)	31 (18.7)	
Other	4 (3.5)	7 (4.2)	
Margin, n (%)			
Negative	45 (40.9)	57 (36.8)	0.783
Close	26 (23.6)	38 (24.5)	
Positive	39 (35.5)	60 (38.7)	
Lymphovascular Invasion, n (%)			
Absent	39 (54.9)	51 (43.2)	0.119
Present	32 (45.1)	67 (56.8)	
Perineural Invasion, n (%)			
Absent	26 (33.8)	39 (31.0)	0.677
Present	51 (66.2)	87 (69.0)	

[a] RT, radiation therapy.
[b] cT, clinical tumor.
[c] cN, clinical nodal.
[d] cM, clinical metastatic disease.
[e] pT, pathologic tumor.
[f] pN, pathologic nodal.
[g] AJCC, American Joint Committee on Cancer.

Impact of sex in the histological high-risk group

A subgroup analysis was performed in the histological high-risk group (Table 3). Out of 280 patients, 114 (41%) were women, and 166 (59%) were men. There was no difference between women and men in terms of age or CCI (age, p = 0.557 and CCI, p = 0.133). Women had a higher incidence of early-stage T1/T2 tumors (54% versus 44%; p = 0.019) and less regional nodal metastasis (31% versus 51%; p = 0.001). Postsurgical margin status, lymphovascular invasion, and perineural invasion did not differ between women and men. Frequent histologies in this group were mucoepidermoid carcinoma (n = 67), carcinoma ex-pleomorphic adenoma (n = 53), adenocarcinoma (n = 48), and SDC (n = 38). A higher incidence of SDCs was observed in men (19% versus 6%; p < 0.001). After excluding patients with SDC, there was still a significant difference in DSS between women and men (the 5-year DSS was 68% for women and 54% for men; p = 0.013) (Fig. 2D).

Discussion

This retrospective study clearly shows that sex is an important prognostic factor in patients with salivary gland malignancies based on the superior DSS observed in female patients. Even after adjusting for the other relevant covariates such as CCI, tobacco use, stage, and histology risk group, sex remained an independent prognostic factor for survival in the multivariable analysis.

Female sex as a favorable prognostic factor has previously been described in many other neoplasms using cancer registries. Using the Surveillance, Epidemiology, and End Results Program (SEER) database, Cook et al. reported that for most cancers, survival was worse for males compared to females [9]; consistently, the EUROCARE-4 project reported that women had a lower relative excess risk of death in 17 of 26 cancer sites, a finding especially pronounced in younger patients [10]. Another registry-based publication from Canada reported that women had a significantly improved survival in 13 of 18 cancers, most evident in thyroid cancer and melanoma [11]. Finally, Afshar et al. reported an excess mortality rate for men in 11 cancers, including head and neck neoplasms, melanoma, lung, and colorectal [12]. These differences in overall survival are largely attributed to the fact that men are older and have more comorbidities [13–15], whereas differences in cancer-specific survival can be attributed to the fact that men tend to present with more advanced-stage disease due to delay in presentation [16,17].

In salivary gland malignancies, few studies have addressed the prognostic impact of sex, and those reported have shown mixed results. While most cancer registry studies do not consider relevant covariates in their analyses, a SEER database study analyzed data of 9661 patients with minor and major salivary tumors and showed a HR of 1.27 for men compared to women after adjusting for age and stage. This finding is consistent with our study, although adjustment by grade was not

possible because of a lack of grade information in SEER [9].

In our study, male patients were older, presented with more advanced disease (T3-T4), had higher comorbidity and had more high-risk histologies. Given histology is one of the most important prognostic factors in salivary gland malignancies [18–20], we stratified our cohort by histological risk categories. We found that the difference in prognosis between sex groups was most evident in the patients with high-risk histologies which included cancers which express androgen receptors such as salivary duct cancer. In contrast, in low-risk and intermediate-risk histologies, no difference was appreciated. A comparable study was published by Cheung et al using the Florida cancer registry in which male sex, high-grade histology, and advanced stage correlated with a worse OS [5]. Similarly in a Danish study, which included 871 patients diagnosed with primary major or minor salivary gland carcinomas, male sex was associated with worse DSS, but this was not significant in the multivariable analysis.[4]

In our cohort, surgical treatment to the primary site did not differ between the groups, and similar rates of close and positive margins were observed. However, because of the more advanced stage at presentation in males, men had higher rates of neck dissection and were more frequently treated with postoperative radiation and chemotherapy in concordance with National Comprehensive Cancer Network guidelines.

In our high-risk histological group, 14% of the patients had an SDC and 82% of them were men. SDC is known to be one of the most aggressive types of salivary gland carcinomas, and SDC patients frequently develop distant metastasis even after curative resection [21,22]. Considering that SDC was more frequent in men, a difference in survival between women and men in the high-risk group might be expected. However, when we removed SDC from the high-risk group, the DSS was still superior in the female cohort compared to the male cohort. This suggests that there is an inherent sex disparity in outcomes in high-risk histologies.

The underlying reasons for poorer survival in men is not clear, and several theories for this have been proposed. Female patients tend to seek medical attention and therefore receive earlier diagnoses, which can have a profound impact on prognosis [23]. However, in our study, even after controlling for comorbidity status, smoking, stage, and histology, we still observe a superior survival in females. It has been suggested that sex hormones may influence cancer growth when cancers express sex hormone receptors. In a study of SDC cell lines, it was shown that androgens could enhance cell growth. Moreover, proliferation could be mitigated by inhibition or knockdown of androgen receptors [24]. Small series and several single-case reports have shown responses in patients with metastatic SDC treated with androgen receptor inhibitors [25,26]. In our study, this would explain the negative effect that SDC has on sex since SDC is more common in men. However, even after removing SDC from the high-risk cohort, we still observed superior survival in females. One possible explanation for this could be that other high risk histologies may be expressing androgen receptors. Alternatively, an interaction between sex hormones and the immune system may be responsible. It is now recognized that androgens play an important role in immunomodulation, acting as an immunosuppressive agent affecting the innate and adaptive response in men [27–29]. This could potentially have a negative impact on survival in males. Further studies to investigate the role of the immune system in patients with high-risk pathology are therefore warranted.

There are several limitations to our study, mainly related to the biases associated with retrospective data collection. Patient-, physician-, and treatment-related biases can never be adequately accounted for. Although pathological review of slides was carried out, there were many slides which were unavailable for review due to the long time period over which the study was done. Salivary carcinomas are an infrequent disease, comprised of an unparalleled variety of histologies in which classification has continuously evolved. Therefore, the collection of a large number of cases spanning decades may have resulted in misclassification bias. Despite these limitations, our study is one of the largest cohorts reported with comprehensive details on clinical, pathological, treatment, and outcome information from a single institution with a homogeneous philosophy on treatment.

Conclusion

In our study, female sex is an independent prognostic factor of superior outcome in patients with salivary tumors. Future research is now required to investigate the factors responsible for the sex disparity in outcomes in salivary gland malignancies.

Declaration of Competing Interest

None declared.

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