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Carcinoma ex pleomorphic adenoma: A review of incidence, demographics, risk factors, and survival☆,☆☆,☆☆☆

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ABSTRACT

Purpose: Identify variables that are independent predictors of survival in carcinoma ex pleomorphic adenoma (CXPA) of the major salivary glands using a population-based database and evaluate the incidence and management strategies for this rare malignancy.

Materials and Methods: The Surveillance, Epidemiology, and End Results (SEER) database was queried for all cases of major salivary gland CXPA from 1973 to 2015.

Results: Of the 619 patients identified, the parotid gland was the most common site of involvement (76.9%, 476/619). The reported incidence of CXPA has risen in the past decade (2005–2015, 0.24 to 0.63 per 1,000,000). The 2-year and 5-year disease-specific survival (DSS) rates were 90.3% and 80.4%, respectively. On univariate analysis, facial nerve sacrifice was not a statistically significant predictor of survival (HR = 1.213, 95% CI [0.588–2.058], P = 0.602). Patients with a tumor size > 4 cm, multiple positive lymph nodes, and distant metastatic disease had a 2 to 4-fold statistically significant increase in mortality using a multivariate analysis. Statistical significance was not demonstrated in the DSS of patients who underwent partial versus total parotidectomy procedures.

Conclusions: CXPA is a rare salivary malignancy that has a reported increased incidence in the last decade. Tumor size > 4 cm, multiple positive lymph nodes, and distant metastatic disease are predictors of disease-specific mortality. Further research should be conducted to improve early detection and survival strategies for this salivary cancer.

Level of Evidence: 4.

1. Introduction

Carcinoma ex pleomorphic adenoma (CXPA) is a rare malignant tumor of the salivary glands [1]. CXPA is part of the malignant mixed tumors category, which contains both benign and malignant components on histologic analysis. This malignant tumor arises from the epithelial component of either primary or recurrent pleomorphic adenoma (PA) [1]. Based on prior studies, the average prevalence of CPXA ranges from approximately 3% to 15% among all malignant salivary tumors [2–5].

CXPA most commonly presents as a firm mass in the parotid gland, although the submandibular and minor salivary glands may also be involved [6]. This presentation can be mistaken for a PA; however, a rapid increase in size observed in a previously slow growing mass should raise suspicion for CXPA. The gold standard for diagnosing CXPA is with histopathological evaluation of the suspected lesion [6]. Fine needle aspiration cytology is typically used for preoperative evaluation. Diagnosis can be challenging if the entire PA component is replaced by the malignant tumor. On the other hand, the malignant component may be sparse or scattered and missed when analyzing the pathological specimen [1]. Both scenarios can lead to misdiagnosis. As a result, this high-grade tumor can potentially lead to distant metastasis. In terms of prognosis, survival rates reported in previous literature range from 30% to over 70% [1–4,7].

Currently, there is limited body of evidence regarding the management of these malignant salivary tumors. The purpose of this study is to provide a current and comprehensive update on the management of these rare tumors by querying the Surveillance, Epidemiology, and

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End Results (SEER) database for incidence, demographic factors, treatment modalities, and determining predictors of survival in CXPA.

2. Materials and Methods

2.1. Data

Case-based data was obtained using the SEER database of the National Cancer Institute (NCI). Through data from population-based registries, around 34.6% of the population of the United States is included in the SEER Program. These registries obtain pertinent data regarding cancer, including but not limited to site, stage at diagnosis, initial treatment and survival [8]. In this study, the SEER 18 Registry Research Data (cases from 1973 to 2015, based on the November 2016 submission) was utilized with SEER*Stat Software Version 8.3.4 [9]. This study was deemed to be exempt from review by the Office of Research Integrity of the Medical University of South Carolina.

Patients were included based on the following International Classification of Diseases for Oncology, Third Editions codes: 8941/3: Carcinoma in pleomorphic adenoma, C07.9, C08.0, C08.1, C08.8, C08.9 for major salivary glands occurring from 1973 to 2015. Demographic variables collected include age at diagnosis, sex, race, and ethnicity. Disease characteristics include tumor location and size, tumor extension, lymph node involvement, and presence of metastasis. Overall American Joint Commission on Cancer tumor stage was categorized to be either early stage (I-II) or late stage (III-IV) dichotomous variables for analysis. Tumor grade was also categorized into dichotomous variables as either low grade (well-to-moderately differentiated) or high grade (poorly-to-undifferentiated/anaplastic) disease. The American Head and Neck Society neck dissection guidelines were used to classify lymph nodes into corresponding cervical neck levels [10]. Treatment data included use of radiation or surgery. Surgically treated patients were categorized into total vs partial parotidectomy. Types of surgical procedures performed were ascertained by the SEER database coding classification of surgical procedures from 1998 to 2015. The number of patients with preserved or sacrificed facial nerve was also reported.

2.2. Statistical analysis

Data analyses were performed with SPSS 24.0 (SPSS Inc., IBM Corp., Armonk, NY), SigmaPlot 12.5 (Systat Software, Inc., San Jose, CA), and MedCalc 18.10.2 (Ostend, Belgium). Categorical variables were summarized by frequency and percentage. Continuous variables were summarized by mean ± standard deviation or median and interquartile range where appropriate. Two-year and Five-year Overall Survival (OS) and Disease Specific Survival (DSS) rates were calculated using Kaplan-Meier estimates of survival. Univariate and multivariate Cox proportional hazards regression analyses were performed to adjust for potential confounding variables. A Wald forward stepwise elimination method was used for the final multivariable model. A P value of < 0.05 was considered to indicate a statistically significant difference for all statistical tests.

3. Results

3.1. Incidence

The reported incidence of CXPA has been on the rise in the last decade (0.24 to 0.63 per 1,000,000 from 2005 to 2015), with an overall percent change of 163%. During the period of 1973 to 2015, 619 patients were identified using the aforementioned database search criteria (Fig. 1).

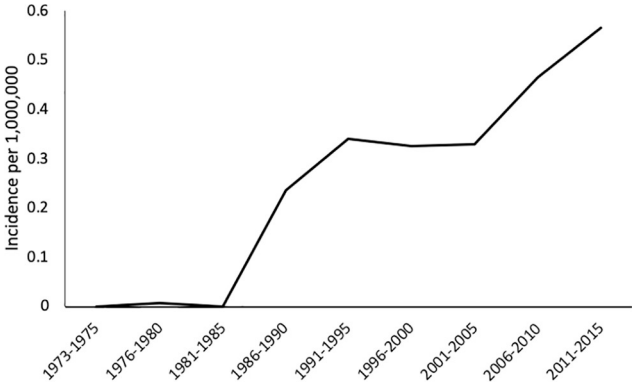

Fig. 1. Incidence of Carcinoma ex Pleomorphic Adenoma from 1973 to 2015 by 5-Year Average Interval.

3.2. Sociodemographic and tumor characteristics

Demographic data and tumor characteristics of these patients are located in Table 1. The mean age of the entire cohort was 62.1 years (17 to 97). Most patients were identified to be male (55.9%, 346),

Table 1
Carcinoma ex Pleomorphic Adenoma population characteristics.

Characteristics	Number of patients	
	$N = 619$[a] (SD)	%[a]
Sex		
Male	346	55.9
Female	273	44.1
Mean age in years	62.1 (14.6)	
Race		
Caucasian	449	72.5
African-American	61	9.9
Other	109	17.6
Ethnicity		
Non-Hispanic	574	92.7
Hispanic	45	7.3
Tumor location		
Parotid	476	76.9
Submandibular	110	17.8
Sublingual	1	0.2
Major Salivary Gland NOS	32	5.2
Tumor size		
≤ 2 cm	132	25.3
2–4 cm	214	41.1
≥ 4 cm	177	34.0
Mean tumor size	3.6 (2.4)	
Tumor extension		
None	401	67.3
Extraparenchymal extension	195	32.7
Lymph Nodes examined		
Not examined	229	39.1
One examined	62	10.6
Multiple examined	295	50.3
Mean no. of nodes examined	12.1 (22.2)	
Positive lymph nodes		
None	260	70.5
1	29	7.9
> 1	80	21.7
Distant metastases		
None	378	94.5
Distant metastases	22	5.5

Abbreviations: SD, standard deviation; NOS, not otherwise specified.
[a] Total number of cases for certain variables may be less than N because of missing values.

Table 2
Carcinoma ex Pleomorphic Adenoma treatment modalities.

Treatment	Number of Patients	
	$N = 619$[a]	%
Surgery[b]		
No surgery	17	2.8
Surgery	600	97.2
Type of surgery		
Partial parotidectomy	273	52.5
Total parotidectomy	213	42.3
Facial nerve[b]		
Spared	181	68.8
Sacrificed	82	31.2
Radiation		
None	240	38.7
External beam	379	61.2
Chemotherapy		
None/Unknown	549	88.7
Chemotherapy	70	11.3

[a] Total number of cases for certain variables may be less than *N* because of missing values.
[b] Surgery type and facial nerve were identified for patients from 1998 to 2015.

Caucasian (72.5%, 449), and Non-Hispanic (92.7%, 574). The parotid gland was noted to be the most common site (76.9%, 476) of involvement. Mean tumor size was noted to be 3.6 (2.4) cm, and extra-parenchymal extension was observed in 32.7% (195) of patients. The majority of patients had at least one node examined (60.9%, 357). The mean number of nodes examined was 12.1 (22.2). Among cases with reported data, 5.5% (22) had distant metastatic disease.

3.3. Management strategies

The primary method of treatment of this tumor was surgical resection (97.2%, 600). Among those that underwent parotid gland resection, 273 (52.5%) patients had partial parotidectomy and 42.3% had total parotidectomy procedures. The facial nerve was sacrificed in 31.2% (82) of cases. Within the entire cohort of patients, the majority (61.2%) received external beam radiation. Only a small minority (11.3%) received chemotherapy. Table 2 provides data on the various treatment modalities for CXPA patients.

3.4. Survival analyses

The overall 2-year and 5-year survival rates were noted to be 84.6% and 68.5%, respectively. Overall rates of DSS at 2-year and 5-year intervals were 90.3% and 80.4%, respectively. Survival analysis of those who underwent partial or total parotidectomy demonstrated no significant differences in survival using a log-rank test (P = 0.278) (Fig. 2). Stratification of DSS by tumor size demonstrated a decreased DSS with an increased tumor size. There was a significant difference in survival among patients with tumors of 4 cm or greater and those with a tumor size of < 4 cm using a log-rank test ($P < 0.001$) (Fig. 3).

3.5. Predictors of survival

The following tumor characteristics were demonstrated to be statistically significant ($P < 0.05$) predictors of mortality by univariate analyses: high grade, late stage, distant metastasis, tumor size, extra-parenchymal extension, multiple lymph node involvement (lymph node levels I–V), and partial parotidectomy (Table 3). Notably, distant metastasis was associated with a 13-fold increase in mortality (hazard ratio (HR) = 12.984, 95% CI [6.926–24.338]). High grade tumors

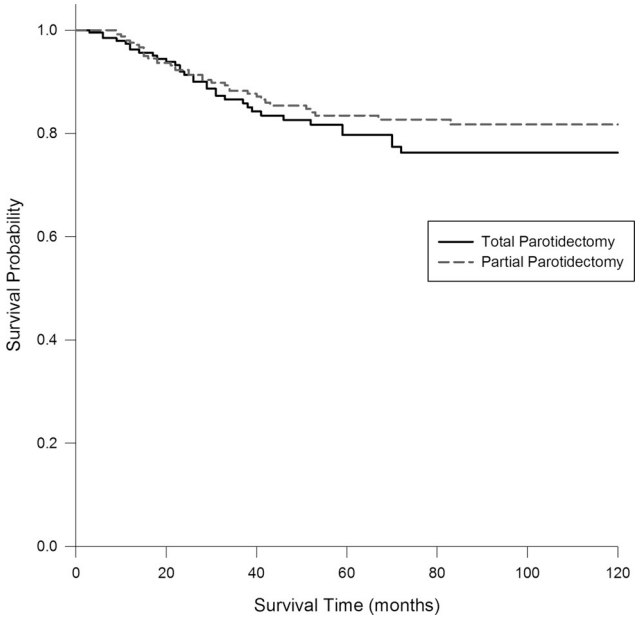

Fig. 2. Partial versus Total Parotidectomy Kaplan-Meier Disease Specific Survival Comparison.

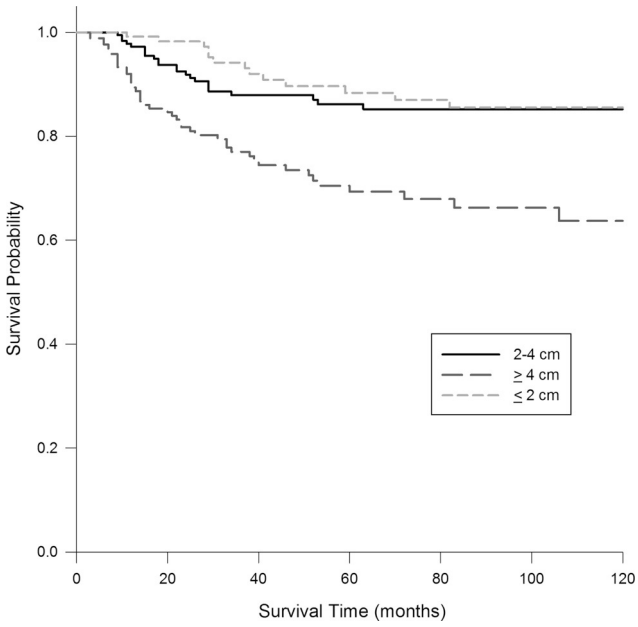

Fig. 3. Kaplan-Meier Disease Specific Survival Stratified by Tumor Size.

(HR = 5.313, 95% CI [2.424–11.647]), late stage tumors (HR = 5.678, 95% CI [2.562–12.583]), and multiple lymph node involvement (HR = 5.411, 95% CI [3.374–8.677]) were associated with a > 5-fold increase in mortality. On the other hand, partial parotidectomy was associated with decreased mortality (HR = 0.636, 95% CI [0.413–0.979]). Of note, facial nerve sacrifice was not a demonstrated to be a statistically significant predictor of survival (HR = 1.213, 95% CI [0.588–2.058], P = 0.602).

After adjusting for relevant covariates using multivariable analysis, tumor size of 4 cm or greater (HR = 2.394, 95% CI [1.121–5.113]), multiple positive lymph nodes (HR = 3.886, 95% CI [1.806–8.364]), and distant metastatic disease (HR = 3.661, 95% CI [1.352–9.915]) were found to be significant ($P < 0.05$) independent predictors of mortality (Table 4).

Table 3
Univariate analyses of disease-specific survival.

Risk factor	Hazard ratio	95% CI	*P* value
Female	1.213	0.826–1.782	0.325
Age	1.012	0.998–1.026	0.086
African-American	0.724	0.318–1.652	0.444
High grade	5.313	2.424–11.647	< 0.0001*
Late stage	5.678	2.562–12.583	< 0.0001*
Distant metastasis	12.984	6.926–24.338	< 0.0001*
Tumor size			
≤2 cm	0.511	0.288–0.908	0.022*
2-4 cm	0.589	0.366–0.946	0.029*
≥4 cm	2.642	1.714–4.073	< 0.0001*
Extraparenchymal Extension	3.677	2.423–5.579	< 0.0001*
Number of positive nodes			
One	1.347	0.645–2.812	0.428
Multiple	5.411	3.374–8.677	< 0.0001*
Lymph node level			
Level 1	4.041	2.204–7.410	< 0.0001*
Level 2	4.707	4.707–7.648	< 0.0001*
Level 3	6.785	3.984–11.555	< 0.0001*
Level 4	5.463	2.365–12.618	< 0.0001*
Level 5	7.688	3.675–16.080	< 0.0001*
Surgery			
Partial Parotidectomy	0.636	0.413–0.979	0.040*
Total Parotidectomy	1.035	0.666–1.606	0.879
Facial Nerve Sacrifice	1.213	0.588–2.503	0.602
Adjuvant Radiotherapy	1.361	0.900–2.058	0.144

Abbreviation: CI, confidence interval.
Referents: Male, Caucasian, low grade, early stage, no distant metastatic disease, no extraparenchymal extension, node-negative disease, no surgery, facial nerve sparing, no external beam radiation.
* Denoted values achieved significance with $P < 0.05$.

Table 4
Multivariate analysis of disease-specific survival.

Risk factor	Hazard ratio	95% CI	*P* value
Tumor size ≥ 4 cm	2.394	1.121–5.113	0.024*
Multiple positive nodes	3.886	1.806–8.364	0.001*
Distant metastasis	3.661	1.352–9.915	0.011*

Abbreviation: CI, confidence interval.
Referents: tumor size ≤2 cm, node-negative disease, no distant metastatic disease.
* Denoted values achieved significance with $P < 0.05$.

4. Discussion

4.1. Importance

To the best of our knowledge, this study represents the largest the cohort of major salivary gland CXPA patients in the literature using a population-based database. Previous works on this topic have been limited and have not provided a comprehensive analysis of the prognostic factors and treatment modalities for this malignant salivary gland tumor. Chen et al. [11] conducted a population-level analysis of CXPA using the SEER database; however, their study included patients from 1988 to 2009, had a smaller population size (278 patients), and was solely limited to the parotid gland. Other attempts to quantify the burden of this disease have been conducted at an institutional level and in case reports, highlighting the paucity of literature regarding the management of this malignancy.

4.2. Incidence and prevalence

Malignant salivary gland tumors represent approximately 5% of head and neck malignancies [12]. The previous incidence of CXPA was noted to be 0.68 per 1,000,000 by Rebhun et al. [8] using population-based data through 2011. Based upon our study, the reported incidence of CXPA has been rising, especially in the last decade (0.24 to 0.63 per 1,000,000 from 2005 to 2015). A possible interpretation of this result may arise from the increased recognition and awareness of CXPA as a specific diagnostic entity by pathologists that specialize in salivary gland malignancies. The pathological diagnosis of CXPA can prove to be difficult in unusual cases and lead to potential misclassifications. Differential diagnoses for CXPA include, but are not limited to, benign pleomorphic adenomas, metastatic mixed tumors, high grade salivary adenocarcinomas, and other salivary gland malignancies.

The pathogenesis of this disease is poorly understood, but geographical differences in the prevalence of this tumor have been previously described. In the United Kingdom, Malata et al. [9] demonstrated that CXPA represents 25% of all primary parotid malignancies. In contrast, CXPA had a prevalence of 14% of primary parotid malignancies in Switzerland [4], and only 10% in Japan [13]. In the United States, a study by Byrne and Spector [14] noted CXPA to represent 12% of primary parotid cancers. Further work is necessary to understand the burden of disease, risk factors of pathogenesis, geographical differences, and this phenomenon of a reported rising incidence in the United States.

4.3. Prognostic predictors of survival

The rates of 5-year survival of CXPA have been quite variable in the previous literature, ranging from 25% to 75% [1,2,4,6,15]. Overall survival at 5 years was 68.5% using Kaplan-Meier analysis in our study, whereas 5-year DSS was demonstrated to be 80.4% using our reported data that represents the United States population. Our study suggests that the DSS of CXPA of the SEER database is not as poor as previously published reports. However, this result should be cautiously interpreted with the understanding of possible misclassifications of the tumor pathologies as previously mentioned.

Based on univariate regression analyses, patients with larger tumor size (≥4 cm), high grade disease, late stage disease, extraparenchymal extension, multiple lymph node involvement, and distant metastatic disease were found to have an increased Cox proportional HR for disease specific mortality. These predictors of survival have been previously reported in the literature, highlighting the need to focus upon these risk factors for pursuing aggressive treatment [11].

Most commonly, lymphatic spread of parotid malignancies occurs from intraparotid nodes to level I and II cervical nodes of the neck. Of note, patients with cervical neck level involvement had a 2 to 5-fold increase risk of mortality as compared to patients without cervical nodal involvement in our study. Elective surgical management of the cervical neck should be considered for high-grade CXPA based on a large database study by Xiao et al. [16] of 22,653 patients with parotid malignancies. However, there is no consensus statement from the American Head and Neck Society regarding the role of elective neck dissection for occult nodal disease in parotid malignancies, but this warrants further investigation [16,17].

In our study, multivariate analysis revealed that patients with a tumor size of 4 cm or greater, multiple positive nodal involvement, and distant metastatic disease had a 2 to 4-fold increase in the HR for disease-specific mortality. These results are consistent with previous literature demonstrating that patients with late stage disease have lower rates of 5-year survival [16].

4.4. Treatment modalities

Although there is no well-established standard of care for this tumor, surgical resection is the mainstay treatment. Our study demonstrated that almost all patients with CXPA had some type of surgical procedure performed (97%). Options for surgical resection of the parotid site include partial or superficial parotidectomy when the disease is superficial to the facial nerve. In more involved cases, facial

nerve sacrifice may be necessary to perform a total or radical parotidectomy.

Based on our data, statistical significance was not demonstrated in DSS on Kaplan-Meier survival analysis comparing patients who underwent partial parotidectomy versus total parotidectomy procedures. Of the 31.2% of patients having facial nerve sacrifice as part of their surgical procedure, this variable did not achieve statistical significance in the univariate model as a risk factor for DSS. At our institution, every effort is made to preserve the facial nerve function unless there is a possibility that the tumor could have replaced the nerve. Patients in our study that had partial parotidectomy procedures were demonstrated to have a significantly decreased risk of disease-specific mortality. It is possible that patients undergoing partial parotidectomy procedures had less initial disease-burden as an inherent cause of this result, but nevertheless statistical significance was achieved on univariate analysis.

Radiation and chemotherapy are adjuvant treatment options for CXPA, but these were not found to be statistically significant risk factors of survival in the univariate regressions in our study. These results are limited by sample size and possible discrepancies in coding of these adjuvant therapies in the database. Further research should be conducted to understand the role of radiotherapy and possible chemotherapy for this tumor.

4.5. Limitations

There is a reliance on accurate diagnosis, coding, and reporting of this tumor in a retrospective national database. Due to the nature of this study, we could not assess and review pathologic specimens to confirm diagnoses and grades. The SEER database has a limitation of information, including possible discrepancies in the reported use of adjuvant therapies [18], the lack of clinical staging, comorbid conditions, and recurrence of disease. However, the database is monitored on a regular basis to provide the most accurate and reliable data possible.

5. Conclusions

CXPA is a difficult entity to properly diagnose preoperatively and surgery is the mainstay treatment for this malignancy. Based upon data in our study, patients with a tumor size of 4 cm or greater, multiple positive nodes, and distant metastatic disease had a 2 to 4-fold increase in the hazard ratio for disease-specific mortality. Further evidence-based research regarding the management of this tumor should be conducted to understand its pathophysiology, disease burden, nodal involvement, extent of surgical resection, and role of adjuvant therapies.

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