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Acinic Cell Carcinoma of the Major Salivary Glands: Analysis of Prognostic Factors in 2,950 Patients

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Abstract

Background: *Acinic cell carcinoma (ACC) is an uncommon salivary gland neoplasm. The purpose of this study was to evaluate the prognostic factors that influence survival.*

Methods: *From the National Cancer Data Base (NCDB), 2,950 cases of ACC of the major salivary glands from 2004-2013 with primary surgical management and documented treatment course were identified. Kaplan-Meier and multivariate Cox regression analysis was used to evaluate survival outcomes and prognostic factors.*

Results: *1,960 patients (66.4%) had some extent of regional lymph node sampling, with 453 patients (15.3%) having ≥ 10 lymph nodes removed. Multivariate analysis demonstrated that tumor size ≥3cm and the number of positive lymph nodes had the strongest association with decreased survival ($p<0.001$). Advanced age, male sex and positive surgical margins also negatively impacted survival($p<0.001$).*

Conclusions: *While ACC is considered a low-grade neoplasm with good overall prognosis, tumor size and lymph node involvement have a strong negative impact on outcomes.*

Keywords: *parotid gland, acinic cell carcinoma, survival, prognosis, treatment*

Introduction

Acinic cell carcinoma (ACC) is a rare neoplasm of the major salivary glands that is typically categorized as a low-grade, highly differentiated tumor[1,2,3,4]. Acinic cell carcinoma makes up approximately 11-18% of salivary gland malignancies and occurs most commonly in the parotid gland [1,5]. Average incidence rate is 0.13 per 100,000 patients per year [4] with females exhibiting a slightly higher incidence than males. ACC tumors are composed mainly of serous acinar cells with several histological subtypes [6]. Despite the generally favorable long-term prognosis associated with this diagnosis, certain subsets of patients have poor outcomes[1,4,6,7].

Like other salivary gland malignancies, it is widely accepted that primary surgical resection is the preferred treatment modality for ACC when the patient's condition permits. However, debate persists regarding the role for elective neck dissection and adjuvant radiotherapy (RT). Due to its general acceptance as being a low grade tumor, prophylactic treatment of the neck is typically not recommended unless in very advanced cases. Adjuvant radiation is

often performed for more advanced-stage tumors as well, in addition to those with lymph node involvement, positive margins, or recurrent tumors [3,8]. Yet, there are currently no well-defined treatment guidelines for the use of adjuvant radiation with this specific disease.

Existing literature and population-based studies are limited due to the rarity of this diagnosis. Previous studies completed have explored prognostic factors through single institution[8] and national database retrospective reviews using both the Surveillance, Epidemiology, and End Results (SEER) [1, 4] and the National Cancer Database (NCDB) databases [2,7]. The purpose of this study was to examine the prognostic factors that influence survival for ACC, with an emphasis on clinical factors that may assist the clinician in patient counseling and treatment decision-making.

Methods

Data was obtained using the NCDB, which identified 3,100 cases of ACC of the major salivary glands for the years 2004-2013 based on the histologic type (ICD-O-03 8550). 2,950 cases met inclusion criteria and had primary surgical management with documented treatment course as well as comprehensive follow-up data. Using SPSS version 24.0 (IBM Corp, New York, NY), Kaplan-Meier analysis was then used to evaluate survival outcomes stratified by sex, age, race, insurance status, facility type, Charlson-Deyo Comorbidity Code (CDCC), tumor size, positive lymph nodes, and surgical margins, with statistical significance denoted for $p<0.05$. The role of adjuvant radiation therapy was not evaluated due to absence of local control data in the database, and a portion of those receiving radiation not having adequate dose information. Multivariate Cox regression analysis with 95% confidence intervals was then used to identify prognostic factors associated with survival.

Results

Demographics. This NCDB data set included 3,100 cases of ACC of the head and neck that were diagnosed between 2004 and 2013 with 2950 of those cases having received primary surgical management with documented treatment course and follow-up data. Females accounted for 1793 (60.8%) cases and males accounted for 1157 (39.2%) cases, with a 1.6:1 female to male prevalence ratio. The vast majority of cases were white/Caucasian with the mean age at diagnosis being 53.5 years. Most patients were insured, with nearly two-thirds of patients having private insurance. The vast majority of this patient cohort was considered relatively healthy as represented by nearly 87% of patients having a Charlson-Deyo comorbidity score of zero. (**Table I**).

Tumor characteristics. 2,857 cases (96.8%) were parotid gland tumors, with the majority being grade I tumors when grade was reported (**Table II**). 2023 (68.6%) primary site tumors were <3cm at diagnosis. 1190 patients (40.3%) were pathologically staged T1, 927 (31.4%) T2, 324 (11.0%) T3 and 126 (4.3%) T4 (**Table II**).

Treatment and Outcomes. Data regarding extent of the surgical management was available for 2942 patients (99.7%). Most patients received a parotidectomy as initial management with 1448 (49.1%) receiving a partial parotidectomy, 1196 (40.5%) a total parotidectomy, and 64 (2.2%) a radical parotidectomy. 1,960 patients (66.4%) had some extent of regional lymph node sampling during primary surgery, with 453 patients (15.3%) having ≥ 10 lymph nodes removed. Available surgical data show that 270 patients (9.2%) were found to have node positive disease. 750 patients (25.4%) had reported positive surgical margins 1,239 patients (42.0%) received adjuvant radiation. 2537 (86.0%) patients were alive 90 days following initial surgery and 2324 patients (78.8%) were alive at last known contact. (**Table III**). The results of the nodal evaluation is shown in Table IV.

Survival analysis. Kaplan-Meier survival analysis indicated that sex, age, race, insurance status, CDCC comorbidity score, tumor size, lymph node status, and surgical margins all had a significant impact on overall survival ($p<0.05$), (**Figure 1**).

Multivariate analysis demonstrated that tumor size ≥3cm (hazard ratio 2.057, $p<0.001$, CI 1.541- 2.747) and the number of positive lymph nodes (1 positive node hazard ratio 3.063, $p<0.001$, CI 2.046 – 4.586; >1 positive node hazard ratio 6.320, $p<0.001$, CI 4.363 – 9.156) had the strongest association with decreased five-year survival (**Table V**). More advanced age (hazard ratio 1.050, $p<0.001$, CI 1.037 – 1.063), male sex (hazard ratio 1.485, $p=0.011$, CI 1.095 – 2.013), and positive surgical margins (hazard ratio 1.508, $p=0.010$, CI 1.102 – 2.064) were also associated with decreased five-year survival.

Table I. *Patient demographics*

Variable	n	%	p
Gender			<0.001
Male	1157	39.2%	
Female	1793	60.8%	
Race			<0.001
White	2504	84.9%	
Black	281	9.5%	
Other	165	5.6%	
Age at diagnosis (yr)			<0.001
<40	660	22.4%	
40-49	513	17.4%	
50-59	663	22.5%	
60-69	556	18.8%	
≥70	558	18.9%	
Mean	***53.47 yrs***		
Range	***18-90 yrs***		
Insurance Status			<0.001
Uninsured	112	3.8%	
Private	1831	62.1%	
Government	926	31.4%	
Unknown	81	2.7%	
Facility Type			0.106
Community	1119	37.9%	
Academic	992	33.6%	
Unknown	839	28.4%	
Charlson-Deyo Comorbidity (CDCC)			<0.001
0	2564	86.9%	
1	321	10.9%	
2	65	2.2%	

Table II. *Tumor Characteristics*

Variable	n	%
Anatomic site		
Parotid	2857	96.8%
Submandibular	44	1.5%
Sublingual	6	0.2%
Unknown	43	1.5%
Grade		
I	824	27.9%
II	287	9.7%
III	132	4.5%
IV	37	1.3%
Unknown	1670	56.6%
Tumor Size		
<3 cm	2023	68.6%
≥3 cm	757	25.7%
Unknown	170	5.8%

pT Stage		
T0	9	0.3%
T1	1190	40.3%
T2	927	31.4%
T3	324	11.0%
T4	126	4.3%
Unknown	374	12.6%
pN Stage		
N0	1971	66.8%
N1	136	4.6%
N2	113	3.8%
Unknown	730	24.7%

Table III. *Treatment characteristics*

Variable	n	%
Surgical treatment		
Local excision	234	7.9%
Partial parotidectomy	1448	49.1%
Total parotidectomy	1196	40.5%
Radical parotidectomy	64	2.2%
Unknown	8	0.3%
Surgical margins		
Negative	2038	69.1%
Positive	750	25.4%
Unknown	162	5.5%
Adjuvant Radiation		
No radiation	1658	56.2%
Radiation	1239	42.0%
Unknown	53	1.8%
Chemotherapy		
No chemotherapy	2765	93.7%
Chemotherapy given	54	1.83%
Unknown	131	4.44%
Regional Nodes Examined		
0	972	32.9%
1	408	13.8%
>1	1483	50.3%
≥10	453	15.3%
Unknown	87	2.9%
Regional Nodes Positive		
0	1686	57.2%
1	149	5.1%
2	41	1.4%
≥3	80	2.7%
No nodes examined	972	32.9%
Unknown	22	0.7%

Days to tx initiation from dx *Mean* *Range*	 *14.33* *0 – 609*	
Days to first surgical procedure from dx *Mean* *Range*	 *14.45* *0 – 609*	
Status at last contact Dead Alive Unknown	 316 2324 310	 10.7% 78.8% 10.5%

Table IV. *Nodal evaluation, positive nodes, probability of additional positive nodes and impact on survival*

Nodes Evaluated	n	Positive nodes	% with at least 1 positive node	Percent yield (+nodes/nodes evaluated)	Probability of having additional +nodes if 1 node +	5-year OS Whole cohort	5-year OS Node +
1 node	347	39	11.2%	11.2%	NA	89.6%	65.4%
2 nodes	234	17	7.3%	4.48%	23.5%	92.6%	86.7%
3 nodes	189	13	6.9%	3.88%	46.2%	95.1%	84.6
4 nodes	154	15	9.7%	4.38%	53.3%	86.8%	71.1%
5 nodes	102	8	7.8%	1.76%	12.5%	94.5%	83.3%
6-10 nodes	229	32	14.0%	3.54%	37.5%	91.1%	63.6%
11-15 nodes	102	22	21.6%	6.92%	45.4%	89.4%	71.6%
>15 nodes	231	86	37%	6.21%	73.2%	62.1%	32.4%

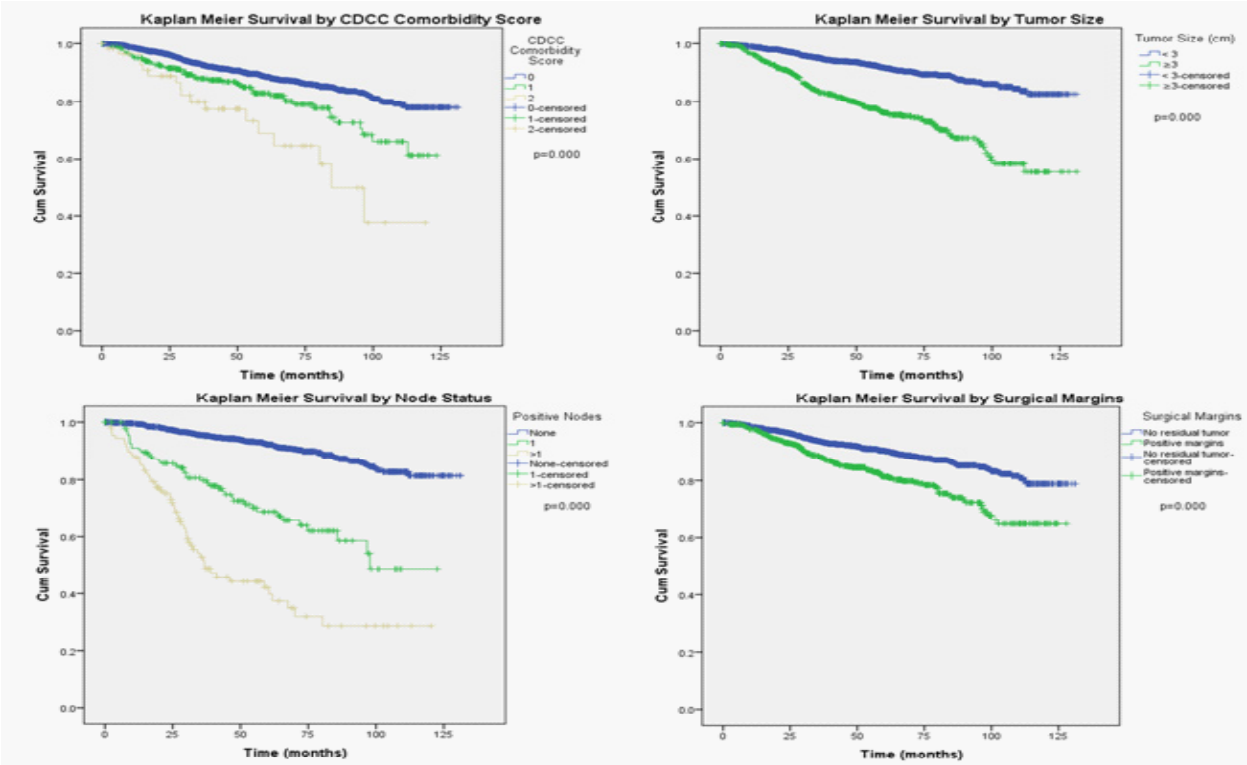

Figure 1. *Kaplan-Meier survival analysis (p<0.001)*

Table V. *Multivariate Cox Regression Analysis*

Variable	p-value	Hazard Ratio	95% CI
Age (continuous)	<0.001	1.050	1.037 – 1.063
Sex Male	0.011	1.485	1.095 – 2.013
Tumor size ≥3 cm	<0.001	2.057	1.541 – 2.747
Surgical Margins (positive)	0.010	1.508	1.102 – 2.064
1 positive lymph node	<0.001	3.063	2.046 – 4.586
>1 positive lymph node	<0.001	6.320	4.363 – 9.156

Discussion

To our knowledge, this study is the largest population-based analysis of ACC of the salivary glands to date. One of the more recently published population-based ACC studies used the SEER database created by the National Cancer Institute (NCI), which includes 17 regional registries and approximately 28% of the US population. This study utilized the American College of Surgeon's Commission on Cancer Program's NCDB, which is the largest cancer registry in the world, including 70% of all new cancer diagnoses nationwide. While SEER provides patient demographics comparable to that of the general population, it does not include key variables such as margin status and type of surgery, thus limiting the analysis of this primarily surgically-treated disease process [4,9,10]. The most recent study of this patient population also utilized the NCDB, examining this ACC patient cohort between 2004-2012[7]. While similar analyses were undertaken, the results of the review by Scherl et al highlighted the importance of histologic grade in the overall prognosis of patients with ACC. Not surprisingly, they too found that nodal status and tumor size were also primary drivers of outcome. It is important to note that the majority of cases reported within the NCDB had an "unknown" grade, while less than 6% of cases were classified as high grade. This limited sample size of complete histopathologic data, along with our focus on the clinical features of the disease, led us to omit this feature from our analysis. However, the importance of the conclusions reached by Scherl et al cannot be overstated histologic grade of tumor must also be taken into account when considering overall prognosis of this patient population.

Our goal with this analysis was to examine the prognostic factors that influence survival with the largest cohort of ACC to date, with an emphasis on clinical features of the disease. As one might reasonably expect, patients with increasing nodal involvement and larger primary tumor size had worse outcomes. However, the degree to which these clinical features impacted survival was surprising. Similar to the impact on prognosis that we observed at 3 cm, Schwarz et al found that a size >4 cm, in addition to extracapsular extension and high-grade mitotic activity, was a negative prognostic factor [6].

Due to the rarity of this disease, it is unlikely that conclusions from analyses of administrative databases such as the NCDB will ever be validated with prospective trials. Therefore, these analyses are particularly useful to help guide patient counseling and treatment decision-making. In particular, the algorithm presented in **Figure 2** may allow treating clinicians to more thoroughly discuss treatment options and prognosis with their patients. Since there are no treatment guidelines specific to ACC, we aimed to identify the most significant clinical variables that might help guide decision-making for the escalation of treatment intensity, particularly as it relates to the questions surrounding the utility of elective neck dissections and adjuvant radiation. Extent of surgery based on pre-operative exam and imaging, as well as consideration for post-operative radiotherapy may be more precisely determined with clinically-applicable algorithms such as this. Based on our multivariate analysis, tumor size and the number of lymph nodes involved are the primary clinical drivers of patient outcomes. As the algorithm in **Figure 2** demonstrates, there are significant and dramatic differences in the five-year survival rates based on these two variables alone. Despite ACC classically being described as a low-grade tumor, there is clearly a subset of patients with poor prognostic factors that have poor outcomes and may benefit from escalated treatment intensity.

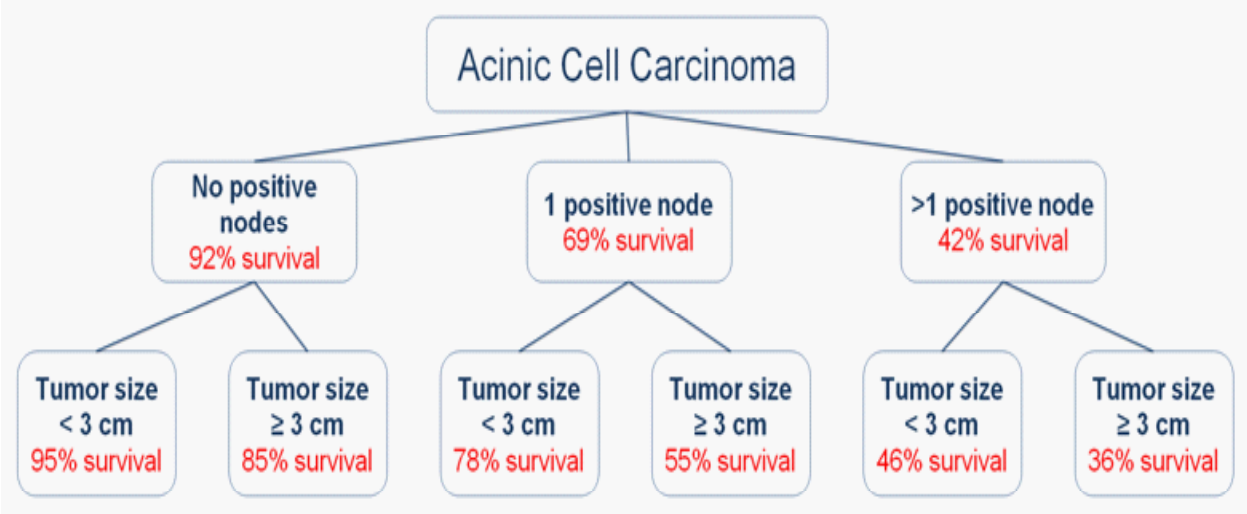

Figure 2. *Algorithm for predicting 5-year overall survival after surgery for patients with ACC based on lymph node and primary tumor size*

Elective nodal treatment for patients with low-grade salivary gland tumors is typically not recommended, although many often strongly consider prophylactic surgical treatment of the neck in T3 and T4 tumors, regardless of histologic grade. This data, showing the strong impact that tumor size and positive nodes have on survival, would support the strong consideration for elective treatment of the neck, especially for tumors greater than 3cm in size. The additional operative time, as well as the increased potential morbidity that would be present if elective neck dissection was undertaken, would certainly have to be taken into account while discussing these treatment options with patients. However, the accurate pathologic staging of the neck would allow for this important information to be taken into consideration when determining the need for adjuvant treatment. Adjuvant radiation therapy is recommended for incompletely excised T3/T4 salivary parotid tumors or those with adverse features after complete excision (intermediate/high grade, close/positive margins, lymph node metastases, lymphatic/vascular invasion) per NCCN[11]. The data within this cohort suggest that adjuvant radiation may be beneficial for patients with larger primary site tumors (>3cm) and lymph node involvement, the two worst prognostic features in this study. Due to the rarity of this tumor, there is little primary literature supporting this recommendation however, and one SEER study suggested no overall survival benefit from adjuvant RT for ACC [3]. However, they did not assess the quality of the RT (dose, timing after surgery, volume, primary site vs nodal) and did not assess local control, which would likely be the greatest benefit of local/regional adjuvant RT. Given these challenges, as well as the lack of tumor control data and missing RT data within the NCDB, we did not attempt to answer any questions about the role of adjuvant RT in this population and viewed it as out of scope for this project.

We acknowledge a number of limitations in this study. Our analysis only included patients that received surgery of the primary site as part of their treatment plan. While this is by far the most common treatment for salivary gland malignancies, this did limit our analysis of this disease process to this specific cohort of patients. As with previous retrospective population-based studies, inaccurate or incomplete data, and/or errors in coding, are possible while utilizing administrative data despite the high degree of quality control by the NCDB[10]. A specific example of this is represented in the surgical data that showed 270 patients within our cohort had positive nodes, while only 249 patients were listed as having N+ disease in the pathologic staging data. This could be explained by the 22 patients who were listed as "unknown" for the positive regional node surgical data (**Table III**). Pathologic staging data for nodal disease was also categorized as unknown in nearly 25% of our cohort. As previously mentioned, tumor grade has been found to be an important prognostic feature[7] but with more that 50% of patients in this cohort having an unknown grade and less than 6% being high grade, we decided not to include this pathologic feature as a prognostic factor in our analysis. When using a database such as

the NCDB, there are also clinical interpretations that must be made for adequate analysis to be undertaken. For example, when the primary surgery has been listed as "partial parotidectomy" for various entries, this includes both "superficial parotidectomy" and "less than total parotidectomy" categories. The extent of surgical excision of some of these primary tumors is therefore challenging to quantify to the degree that would be ideal.

Conclusion

While acinic cell carcinoma is typically considered a low-grade neoplasm with good overall prognosis, larger primary tumor size and lymph node involvement have strong negative impacts on patient outcomes. This in-depth population-based analysis of various prognostic factors clearly shows these clinical and pathologic factors to be the primary drivers of survival. These data may be used to help guide patient counseling, clinical decisions, and overall disease management.

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