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An international collaborative study

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Defining the surgical margins of adenoid cystic carcinoma and their impact on outcome: An international collaborative study

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Abstract

Background—The mainstay of treatment in adenoid cystic carcinoma (ACC) of the head and neck is surgical resection with negative margins. The purpose of this study was to define the margin status that associates with survival outcomes of ACC of the head and neck.

Methods—We conducted univariate and multivariate analyses of international data.

Results—Data of 507 patients with ACC of the head and neck were analyzed; negative margins defined as ≥5 mm were detected in 253 patients (50%). On multivariate analysis, the hazard ratios

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(HRs) of positive margin status were 2.68 (95% confidence interval [CI], 1.2–6.2; $p = .04$) and 2.63 (95% CI, 1.1–6.3; $p = .03$) for overall survival (OS) and disease-specific survival (DSS), respectively. Close margins had no significant impact on outcome, with HRs of 1.1 (95% CI, 0.4–3.0; $p = .12$) and 1.07 (95% CI, 0.3–3.4; $p = .23$) for OS and DSS, respectively, relative with negative margins.

Conclusion—In head and neck ACC, positive margins are associated with the worst outcome. Negative or close margins are associated with improved outcome, regardless of the distance from the tumor.

Keywords

adenoid cystic carcinoma; survival; margins; paranasal sinuses; oral cavity; salivary gland; head and neck cancer

INTRODUCTION

Adenoid cystic carcinoma (ACC) accounts for 3% to 5% of all head and neck malignancies. ACC is characterized by an intermediate growth rate, local invasiveness, low probability of lymphatic spread, and frequent lung metastases.[1,2]

Surgery is the primary treatment for ACC of the head and neck.[3,4] In the skull base, ACC is typically diagnosed late, and the proximity to vital structures (eg, dura, brain, orbit, and central nerves) makes adequate oncologic resection more complex.[5,6] In head and neck squamous cell carcinoma (HNSCC), margins that are <5 mm have been associated with worse outcome.[7,8] Similarly, positive surgical margin status in ACC is considered a poor prognostic factor.[9,10] Nevertheless, the impact of close margins, defined as a tumor-free margins of <5 mm, in ACC of the head and neck is unclear.[3,11,12] Most reports on head and neck ACC are based on small single institute cohorts, and tumors from different anatomic locations are grouped together, as are tumors subjected to different treatment regimens; information on predictors of outcomes in this specific population is sparse.[3,13]

In the present international multicenter study, our purpose was to characterize the impact of close margins in ACC of the head and neck.

PATIENTS AND METHODS

Patients

Our study cohort comprised all patients ($n = 507$) who were treated for ACC between 1985 and 2014 in 9 cancer centers worldwide, for whom data and archival slides for examination were available.[2] The study was approved by the local institutional review board committees of the participating centers. The age of the patients ranged from 16 to 91 years (median, 57 years). Their median follow-up was 73 months (range, 12–306 months). All patients underwent primary surgery, with or without adjuvant radiotherapy or chemoradiation. A standardized neck dissection involving levels I, I to III, or I to IV/V was performed in 265 patients (52%), as described by the American Head and Neck Society.[14] The type of neck dissection was preoperatively specified in all patients.

Histopathological analysis

Specimen dissections, as well as tissue sampling of the primary tumor, were carried out according to current guidelines for the histopathological assessment of head and neck cancer.[15] If any of the resection margins was involved by ACC, the case was classified as a positive margin, if the resection margins were not involved, yet <5 mm from the tumor, the case was classified as a close margin. The cases were examined for the presence or absence of perineural invasion, which was defined as the presence of viable tumor cells in the perineural space. The pathologic staging was classified according to the American Joint Committee on Cancer Staging Manual, seventh edition.[16]

Statistical analysis

Five-year overall survival (OS) and disease-specific survival (DSS) rates were calculated using the Kaplan–Meier method, and the differences in survival rates were assessed by the log-rank test.[17] OS was measured from the date of diagnosis to the date of death or last follow-up. DSS was calculated from the date of diagnosis to the date of death as a result of ACC or censored at the date of last follow-up. The variables that had prognostic potential, as indicated by univariate analyses, were subjected to multivariate analyses with the Cox proportional hazards regression model.[18] All analyses were performed on JMP software (SAS Institute, Cary, NC) and confirmed by an independent statistician on the IBM SPSS Statistics package (IBM, Armonk, NY). All p values were 2-sided, and a value of $< .05$ indicated statistical significance. Variables used to stratify survival included age, sex, T classification, N classification, M classification, margin status, perineural invasion, lymphovascular invasion, treatment group (ie, surgery alone vs surgery and radiation vs surgery and chemoradiation), and tumor grade (solid, tubular, and cribriform). Cases with involvement of ACC outside of the oral cavity, paranasal sinuses, skull base, or major salivary glands were excluded from the analysis because of a low number of cases ($n = 7$).

RESULTS

Data of 507 patients with ACC of the head and neck were analyzed; 154 patients (30%) had ACC of a major salivary gland, 242 patients (48%) had ACC of the oral cavity, and 111 patients (22%) had ACC of the paranasal sinuses. Table 1 presents the clinicopathological variables of the patients. Negative margins were detected in 38% of patients with advanced local disease (T3 to T4 classification) and in 59% of patients with early disease ($p < .0001$). Adjuvant treatment was administered in 57% of the patients with negative margins, compared to 68% and 78% of those with close and positive margins, respectively. Negative margins were achieved in 57% of the patients with oral cavity ACC compared to 49% and 35% of those with major salivary glands and paranasal sinus ACC, respectively ($p = .001$). Neck dissection was performed on 265 patients (52%); of them, 74 patients (38%) had nodal metastases. Rates of nodal metastasis were 17%, 14%, and 14% for patients with positive, close, and negative margin status, respectively ($p = .6$).

The 5-year and 10-year postoperative OS rates for patients with ACC of the head and neck were 74% and 55%, respectively; the respective DSS rates were 78% and 60%. As shown in Figure 1, the 5-year OS rates for positive, close, and negative margins were 63%, 71%, and

79%, respectively ($p < .001$); the respective 5-year DSS rates were 69%, 75%, and 83% ($p = .003$). Disease-free survival rates were 86%, 74%, and 69% for negative, close, and positive margins, respectively ($p = .01$). We found significantly higher rates of local recurrence ($p = .01$) and distant metastases ($p = .009$), but not for regional recurrence-free survival ($p = .08$; Figure 2).

Next, we assessed the survival outcomes for each subsite according to margin status. For oral cavity ACC, the 5-year OS rate was 83%, 74%, and 73% for patients with negative, close, and positive surgical margins, respectively ($p = .012$); the respective 5-year DSS rates were 86%, 80%, and 75% ($p = .043$). For patients with major salivary gland ACC, the 5-year OS rate did not differ significantly by margin status (74%, 70%, and 67%, respectively; $p = .57$) and DSS (80%, 77%, and 75%, respectively; $p = .65$). For patients with ACC of the paranasal sinuses and skull base, the respective 5-year OS rates were 74%, 72%, and 41% ($p = .009$); and the respective 5-year DSS rates were 77%, 75%, and 40% ($p = .003$).

Factors that were associated with outcome on univariate analysis were: margin status, pT classification, overall TNM classification, tumor site, intraneural invasion, and bone invasion (Table 2). These factors were then evaluated in a multivariate model (Table 3). Hazard ratios (HRs) for positive margin status were 2.68 (95% confidence interval [CI], 1.2–6.2; $p = .04$) and 2.63 (95% CI, 1.1–6.3; $p = .03$) for OS and DSS, respectively. Compared with negative margins, close margins had similar impact on survival, with HRs of 1.1 (95% CI, 0.4–3.0; $p = .12$) and 1.07 (95% CI, 0.3–3.4; $p = .23$) for OS and DSS, respectively. Other variables that showed independent impact on outcome were: T classification, overall TNM classification, and intraneural invasion of the tumor.

DISCUSSION

Local recurrence and survival in head and neck malignant neoplasms are significantly associated with the involvement of margins.[19–21] Sound oncologic surgery requires an adequate margin of normal tissue around the tumor. For HNSCC, the American Joint Committee on Cancer and the Union for International Cancer Control guidelines have focused on involved margins, whereas the National Comprehensive Cancer Network and the American Society of Clinical Oncology guidelines define close margins as <5 mm, without any distinction for anatomic subsite.[22–25] However, there is currently no published data that defines the required width of this margin for ACC. Available literature does not refer to the prognostic value of margin status and its potential contribution to decision-making. Furthermore, assessment of the specific prognostic value of close margins is especially lacking, and some authors consider positive and close margins jointly in follow-up assessment.[26–28] Conversely, some studies of head and neck malignancies, particularly those involving paranasal sinuses, have grouped together outcomes according to margin status for different histologies (including ACC).[19] This is despite the knowledge that histological varieties differ regarding pattern of invasion, spread, and risk of recurrence.

The best results for treatment of salivary gland tumors are achieved by complete tumor resection.[3,7,29] Complete surgical resection, which is largely dependent on tumor size, site, and surgeon, is the single most important prognostic factor for patients with these tumors.

[21,29] Unlike HNSCC, for ACC, there is lack of standardization of margins status and no range of distance is currently considered for the definition of “close” in published studies.[3,29,30] Hence, even the definition used by various authors for positive margin status is obscure and may affect survival, despite the application of the same type of surgery. Efforts to identify reliable prognostic factors in ACC have dominated the literature for the last decade.[2,3,30–32] Consensus has not been reached regarding the key prognostic factors. Margins status was found significant for survival by some,[3] whereas others did not find positive margins to significantly influence survival.[31] In the current analysis, close margin status of <5 mm was analyzed as a separate risk group. Our data suggest that although positive margins in ACC are independently associated with worse outcome, patients with close margin status have similar OS and DSS as those with negative margins.

The ability to achieve wide free margins accounts for a variety of parameters, including tumor site, T classification, pattern of invasion, and prior treatment. In many cases, surgery is limited by proximity to vital structures. Patients with ACC arising from sites in proximity to the skull base (nasopharynx, nasal cavity, and paranasal sinuses) have been shown to have a significantly increased risk of local recurrence.[3] This is related to the difficulty of securing clear resection margins because of dense involvement of the skull base, dura, cranial nerves, or carotid artery, restricting the limits of resection. Achieving safe oncologic resection in these cases might entail significant morbidity for the patient, such as cranial nerve palsy or cerebrospinal fluid rhinorrhea.

Our subsite analysis showed similar outcomes for negative and close margin status for patients with ACC of the paranasal sinuses; whereas for patients with oral cavity ACC, close margin status represented a separate risk group with worse outcome than negative margins, although the difference did not reach statistical significance. In such an instance, a surgeon should balance between the advantage of achieving margins wider than 5 mm and potential resultant morbidity.

Achieving negative margins in ACC is also challenging because of its propensity for local invasion and neural invasion in particular.[32] In many cases, the presence of perineural invasion in specimens with “negative” margins is considered an independent factor that would have benefited from the addition of radiotherapy.[3,24] Perineural invasion is likely associated with clinical parameters, such as tumor cells at the surgical margin, major salivary gland tumors, and advanced stage.[33] We previously showed that intraneural invasion and not perineural invasion is associated with poor outcome.[32]

The routine use of radiotherapy in ACC is not clearly defined because of lack of level-1 evidence. Physicians frequently advocate adjuvant radiotherapy for patients with locally advanced tumors, or for those with histologically positive or close margins.[24] In HNSCC, adjuvant treatment in the form of chemoradiation is recommended for close or positive margins.[34,35] As current recommendations do not directly address close margin status for ACC, treatment decisions are frequently based on recommendations for HNSCC. Although the role of chemoradiation in ACC is not clear, this treatment carries significant morbidity and its use in a relatively radioresistant tumor, such as ACC, is controversial. Our data revealed that positive margin status harbors worse survival outcome on multivariate analysis;

however, close margin status did not affect outcomes significantly. Further study is needed to assess the utility of radiotherapy in patients with ACC in general, and in those with different margin status, specifically.

Our study had several limitations. First, possible inconsistencies in the surgical technique, adjuvant treatment, and processing of the pathological specimens may introduce errors. This prospective analysis of margins by each institutional head and neck pathologist did not enable analysis of the concordance rate for margin status between pathologists. Second, data, such as the occurrence of ACC among other cancer types, in each institute are lacking. The strength of this study stems from the use of individual data from 9 comprehensive cancer centers worldwide, which should increase the robustness and generalizability of the findings.

In conclusion, our study demonstrated that in head and neck ACC, positive margins are associated with the worst outcome, whereas negative and close margins are associated with improved outcome, regardless of the distance from the tumor. The presence of close margin status resulted in similar outcome as negative margins for ACC of all sites examined except the oral cavity. Negative margins should be achieved whenever possible in this disease. However, when wide resection requires removing a vital structure, achievement of close margins offers lesser morbidity without jeopardizing outcome.

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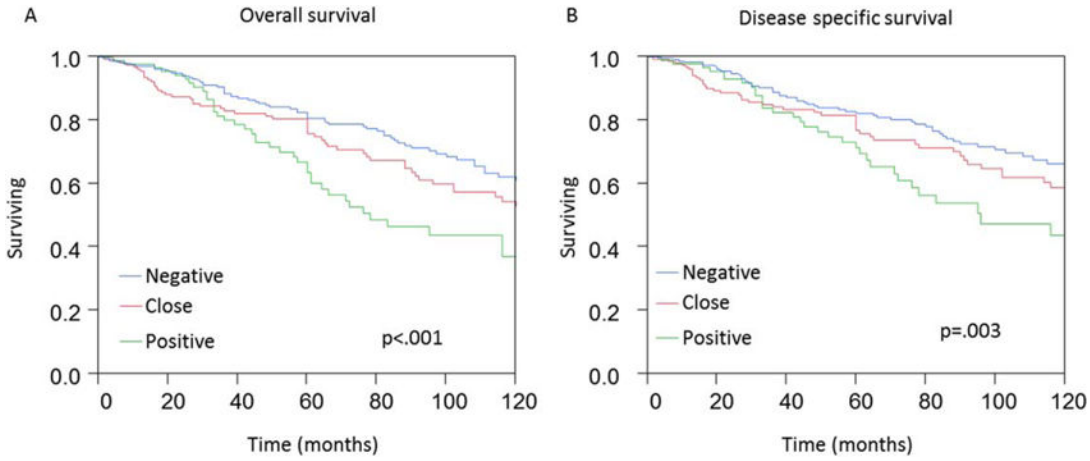

FIGURE 1.

(A) Overall survival and (B) disease-specific survival rates for patients with adenoid cystic carcinoma of the head and neck ($N = 507$) with positive (green), close (red), and negative (blue) margin status, calculated by the Kaplan–Meier method. [Color figure can be viewed at wileyonlinelibrary.com]

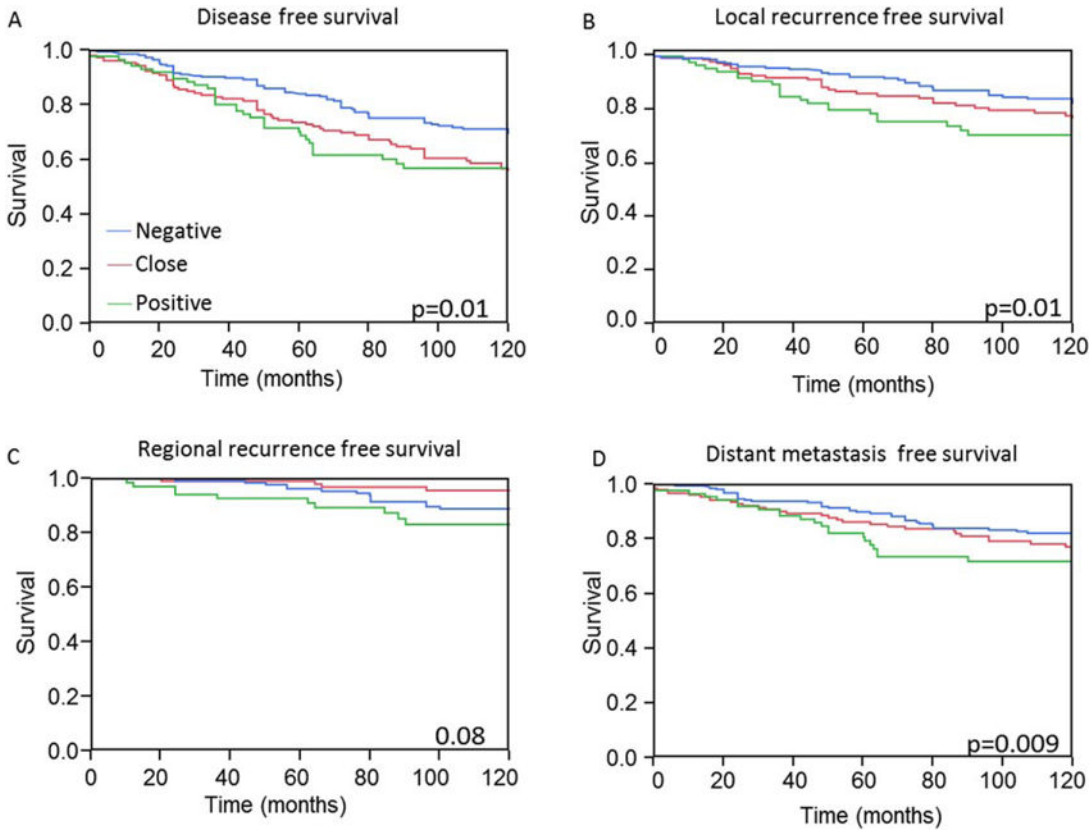

FIGURE 2.

(A) Disease-free survival, (B) local recurrence–free survival, (C) regional recurrence–free survival, and (D) distant metastasis–free survival rates for patients with adenoid cystic carcinoma of the head and neck ($N = 507$) with positive (green), close (red), and negative (blue) margin status, calculated by the Kaplan–Meier method. [Color figure can be viewed at wileyonlinelibrary.com]

TABLE 1

Patient demographic and clinical characteristics.

Variables	No. of patients (%) *N* = 507 100%
Age, y, mean ± SD	56 ± 15
Sex	
Male	218 (43)
Female	289 (57)
T classification	
1	125 (25)
2	159 (31)
3	75 (14)
4	149 (30)
N classification	
N0	428 (82)
N1	42 (8)
N2	31 (7)
N3	1 (<1)
M classification	
0	478 (95)
1	24 (5)
Site	
Oral cavity	154 (30)
Paranasal sinuses	242 (48)
Major salivary glands	111 (22)
Margin status	
Positive	162 (32)
Close, <5 mm	92 (18)
Negative	253 (50)
Perineural invasion	
Present	237 (47)
Absent	270 (53)
Lymphovascular invasion	
Present	35 (7)
Absent	134 (26)
Bone invasion	
Present	187 (37)
Absent	318 (63)
Treatment modality	
Surgery	175 (35)
Surgery and RT	239 (47)
Surgery and CRT	81 (16)
Surgery and chemotherapy	12 (2)

Variables	No. of patients (%) *N* = 507 100%
Neck management	
Neck dissection	265 (52)
No neck dissection	242 (48)
Follow-up	
Months	73 ± 29

Abbreviations: RT, radiotherapy; CRT, chemoradiotherapy.

TABLE 2

Univariate analysis of prognostic factors.

	OS		DSS	
Variables	***p* value**	**5-y survival, %**	***p* value**	**5-y survival, %**
Sex				
Male	.9	74	.7	76
Female		77		79
Age, y	<.001	2/per y	.001	1.9/per y
T classification				
T1	.03	86	.02	89
T2		77		82
T3		67		73
T4		65		68
N classification				
N0	.1	78	.2	81
N1		57		69
N2		46		53
M classification				
M0	.7	74	.5	78
M1		55		61
Overall TNM classification				
I	.006	96	.01	97
II		82		85
III		59		61
IV		58		61
Site				
Oral cavity	.03	71	.02	76
Paranasal sinuses		69		72
Major salivary glands		78		83
Margins				
Negative	<.001	83	.003	86
Close, <5 mm		74		80
Positive		73		75
Intraneural invasion				
No	.006	78	.003	80
Yes		54	.003	55
Lymphovascular invasion				
No	.1	66	.3	67
Yes		47		52
Bone invasion				
No	.03	78	.04	81
Yes		69		69

	OS		DSS	
Variables	***p* value**	**5-y survival, %**	***p* value**	**5-y survival, %**
Treatment				
Surgery	.4	77	.4	79
Surgery and RT		75		78
Surgery and CRT		64		67
Surgery and chemotherapy		68		68
Neck management				
Neck dissection	.02	69	.1	74
No neck dissection		80		83
Differentiation				
Tubular	.6	82	.8	85
Cribriform		79		80
Solid		74		79

Abbreviations: OS, overall survival; DSS, disease-specific survival; RT, radiotherapy; CRT, chemoradiotherapy.

TABLE 3

Multivariate analysis of prognostic factors.

	OS			DSS		
Variables	***p* value**	**HR**	**95% CI**	***p* value**	**HR**	**95% CI**
Age, y per decade	.02	1.46	1.05–1.79	.01	10.09	1.6–62.8
Pathologic T classification						
T1	.03	1		.01	1	
T2		2.03	0.39–9.8		2.4	0.4–13.9
T3		8.4	1.2–63.7		6.6	1.1–15.8
T4		14.02	2.35–72.03		16.2	1.6–33.8
Overall TNM classification						
I	.008	1		.005	1	
II		1.66	0.18–15.6		1.2	0.1–16.1
III		6.05	1.1–39.7		5.2	1.5–33.4
IV		18.9	3.6–79.4		24.6	4.6–111.9
Margins						
Negative	.04	1		.05	1	
Close, <5 mm		1.1	0.4–3.02		1.07	0.3–3.4
Positive		2.68	1.2–6.2		2.63	1.14–6.3
Site						
Major salivary glands	.37	1		.26	1	
Oral cavity		1.7	0.7–3.9		2.05	0.82–5.2
Paranasal sinuses		2.1	0.6–6.4		2.1	0.63–7.4
Intraneural invasion						
No	.002	1		.006	1	
Yes		3.2	1.52–6.6		3.9	1.81–8.76
Bone invasion						
No	.23	1		.46	1	
Yes		1.95	0.65–6.01		1.54	0.4–4.9

Abbreviations: OS, overall survival; DSS, disease-specific survival; HR, hazard ratio; 95% CI, 95% confidence interval.