CURRENT ONCOLOGY

ORIGINAL ARTICLE

Adenoid cystic carcinoma of head and neck: clinical predictors of outcome from a Canadian centre

J.J. Ko MD,* J.E. Siever MSc,† D. Hao MD,* R. Simpson MBChB,‡ and H.Y. Lau MD§

ABSTRACT

Objectives Adenoid cystic carcinoma (ACC) is often treated with surgery, with or without adjuvant radiation therapy (RT). We evaluated disease characteristics, treatments, and potentially prognostic variables in patients with ACC.

Methods Our retrospective analysis considered consecutive cases of ACC presenting at a tertiary care hospital between 2000 and 2014. Factors predictive of overall survival (OS) and disease-free survival (DFS) were identified by univariate analysis.

Results The 60 patients analyzed had a mean age of 58 years (range: 22–88 years), with a 2:1 female:male ratio. Tumour locations included the major salivary glands (40% parotid, 17% submandibular and sublingual), the oro-nasopharyngeal cavity (27%), and other locations (16%). Of the 60 patients, 35 (58%) received surgery with adjuvant RT; 12 (20%), RT only; 13 (22%), surgery only. Of 18 patients (30%) who experienced a recurrence within 5 years, 3 (5%) developed local recurrence only, and the remaining 15 (25%), distant metastasis. The 5-year OS and DFS were 64.5% [95% confidence interval (CI): 45.9% to 78.1%] and 46.2% (95% CI: 29.7% to 61.2%) respectively. In patients without recurrence, 5-year OS was 77% (95% CI: 52.8% to 89.9%), and in patients with recurrence, it was 42.7% (95% CI: 15.8% to 67.6%). Patients treated with RT only had a 5-year OS of 9.2%. Predictors of 5-year DFS were TNM stage, T stage, nodal status, treatment received, and margin status; age, nodal status, treatment received, and margin status predicted 5-year OS.

Conclusions Despite surgery and RT, one third of patients with ACC experience distant recurrence. Patients whose tumours are not amenable to surgery have a poor prognosis, indicating a need for alternative approaches to improve outcomes.

Key Words Adenoid cystic carcinoma, head-and-neck cancer, prognostic factors

Curr Oncol. 2016 Feb;23(1):26-33 www.current-oncology.com

INTRODUCTION

Adenoid cystic carcinoma (ACC) is a relatively uncommon cancer with an annual incidence of approximately 1200 cases in the United States[1]. Adenoid cystic carcinoma occurs primarily in the major and minor salivary glands, but can also be found at other sites[2]. The disease usually presents in a localized manner, but is known for its propensity for late metastasis (up to 15 years after initial diagnosis)[3]. Although ACC can be found at any age, it typically presents in the 5th decade (median age: 57.4 years), and it has a slight female preponderance (up to 60% of cases)[2]. Organs of presentation include the major salivary glands (50%) and the minor salivary glands of the oral cavity (35%)[2,4]. Rare occurrences in other sites have been reported, including the oropharyngeal and nasopharyngeal spaces, external ear, trachea, breast, lacrimal gland, skin, and lower female genital tract. Stage at initial presentation is variable. Approximately 50% of cases are limited to the primary sites; another 30% have regional lymph node involvement at diagnosis. A small proportion of patients present with distant metastatic disease, usually in the lungs.

Surgery, the traditional mainstay of treatment for localized ACC, results in improved survival[5–8]. Negative prognostic indicators in surgically resectable cases include positive margins, perineural invasion, and positive lymph

Correspondence to: Harold Y. Lau, Tom Baker Cancer Centre, 1331 29th Street NW, Calgary, Alberta T2N 4N2.
E-mail: hlau@ucalgary.ca ■ **DOI:** http://dx.doi.org/10.3747/co.23.2898

nodes[4,9–11]. In cases in which surgery is not possible, radiotherapy alone has been used, but with inferior results[8,12–18]. The role of adjuvant radiation therapy (RT) after surgery varies widely depending on the centre[19–23].

The objectives of the present study were to evaluate patient and disease characteristics and treatment modalities in ACC, and to identify variables that are prognostic of treatment outcomes.

METHODS

The Tom Baker Cancer Centre is a tertiary cancer centre that serves a referral base for southern Alberta. Consecutive patients diagnosed with ACC and presenting to the Tom Baker Cancer Centre between January 2000 and September 2014 were identified by a pathology registry review of Calgary Laboratory Services and a review of the Alberta Cancer Registry, coded by histologic diagnoses. Electronic medical records for each patient were reviewed to ascertain patient demographics at diagnosis; clinical and pathology staging according to the American Joint Committee on Cancer staging manual[24]; tumour sites at diagnosis; details of surgery and RT; information about follow-up visits; outcomes, including locoregional control, disease-free survival (DFS), and overall survival (OS); and, if applicable, cause of death. The study was approved by the Health Research Ethics Board of Alberta.

Data were analyzed using the Stata S/E software application (version 13: StataCorp LP, College Station, TX, U.S.A.). Categorical variables are expressed as frequencies and percentages; patient age is expressed as mean and standard deviation. Overall survival was defined as the period from date of diagnosis to date of death or last follow-up visit, with patients censored at their last follow-up visit. Disease-free survival was defined as the period from date of diagnosis to date of relapse, progression, death, or last follow-up visit, and was similarly censored at the last follow-up visit. The Kaplan–Meier method was used to estimate both 3- and 5-year OS and DFS for the sample overall and for subgroups based on age, sex, TNM stage, T stage, N stage, treatment, margin status, and perineural invasion. Local and distant recurrences were also examined. For each estimate, 95% confidence intervals are also reported, and a log-rank test was used to analyze the equality of survivor functions by subgroup for the same variables. A p value less than 0.05 was considered statistically significant.

TABLE I Patient and disease characteristics

Characteristic	Value
Patients (*n*)	60
Mean age (years)	58±15
Sex [*n* (%)]	
Women	40 (67)
Men	20 (33)
Primary site [*n* (%)]	
Parotid	24 (40)
Oral cavity	9 (15)
Trachea	1 (2)
Submandibular or sublingual glands	10 (17)
Oropharynx	5 (8)
Nasal cavity or paranasal sinus or nasopharynx	7 (12)
Cutaneous	4 (6)
T stage [*n* (%)]	
T1–2	35 (58)
T3–4	25 (42)
Nodal status [*n* (%)]	
Negative	53 (88)
Positive	7 (12)
TNM stage [*n* (%)]	
I/II	36 (60)
III/IV	24 (40)
Treatment [*n* (%)]	
Radiotherapy	12 (20)
Surgery	13 (2)
Surgery and radiotherapy	35 (58)
Margins [*n* (%)]	
Negative	18 (38)
Positive	30 (62)
Perineural invasion [*n* (%)]	
Yes	32 (53)
No	15 (25)
Unknown	13 (22)

RESULTS

Table I summarizes patient and disease characteristics for the 60 eligible ACC patients who were identified. Mean age in the cohort was 58 years (range: 22–88 years), with a female preponderance (67% vs. 33%). The sites most commonly involved were the parotid glands (40%), the submandibular and sublingual glands (17%), the oral cavity (15%), and the nasal cavity, paranasal sinus, or nasopharynx (12%). More than half the patients presented with earlier-stage disease (T1/2: 58%); most had a negative nodal status (88%); and 60% presented with TNM stages I and II. Most patients were treated with surgery with or without RT, but 20% were treated with RT alone. Of patients who received surgical treatment, 62% had positive margins. The presence or absence of perineural invasion was documented in 46 patients (77%), 70% of whom had perineural invasion.

Table II and Figures 1 and 2 present survival outcomes stratified by disease and treatment variables. With a median follow-up duration of 32 months (range: 2–165 months), the OS and DFS rates at 5 years were 64.5% (95% CI: 45.9% to 78.1%) and 46.2% (95% CI: 29.7% to 61.2%) respectively. The OS for disease stages I/II and III/IV did not differ statistically, although we observed a trend toward improved OS for earlier TNM stages (3-year OS: 87.2% vs. 74.3%, log-rank $p = 0.227$; 5-year OS: 75.9% vs. 46.7%, log-rank $p = 0.198$). On the other hand, DFS was significantly different between

TABLE II Treatment outcomes according to clinical and pathologic variables

Variable	Overall survival						Disease-free survival					
	3-Year (%)	95% CI	Log-rank *p* value	5-Year (%)	95% CI	Log-rank *p* value	3-Year (%)	95% CI	Log-rank *p* value	5-Year (%)	95% CI	Log-rank *p* value
Age group												
<60 Years	91.2	70.6 to 97.9	0.049	79.0	52.1 to 91.8	0.021	58.3	35.8 to 75.4	0.905	47.7	25.9 to 66.7	0.981
≥60 Years	68.0	41.0 to 84.7		45.4	19.9 to 67.9		58.5	32.6 to 77.5		43.9	19.6 to 66.0	
Sex												
Women	81.0	62.2 to 91.1	0.779	64.4	43.2 to 79.4	0.799	65.7	46.0 to 79.6	0.274	48.9	29.2 to 66.0	0.504
Men	80.2	40.3 to 94.8		60.2	16.3 to 86.7		40.4	13.3 to 66.6		40.4	13.3 to 66.6	
TNM stage												
I/II	87.2	65.3 to 95.7	0.194	75.9	50.9 to 89.4	0.137	79.8	57.7 to 91.1	<0.001	62.1	37.2 to 79.5	0.001
III/IV	72.9	46.3 to 87.8		50.0	23.2 to 71.9		29.7	11.1 to 51.2		23.8	7.5 to 45.0	
T stage												
T1/T2	91.4	70.0 to 97.8	0.062	72.4	44.7 to 87.9	0.180	80.4	58.8 to 91.4	0.002	61.3	35.5 to 79.3	0.007
T3/T4	69.1	43.4 to 84.9)		54.4	28.0 to 74.8		33.2	13.8 to 54.1		27.7	10.2 to 48.5	
Nodal status												
Negative	89.7	74.7 to 96.1	<0.001	70.3	49.7 to 83.8	<0.001	64.5	45.6 to 76.8	0.011	49.1	31.0 to 64.9	0.032
Positive	20.0	8.4 to 58.2		20.0	8.4 to 58.2		20.8	8.7 to 59.5		20.8	8.7 to 59.5	
Treatment modality												
Radiotherapy alone	54.5	22.9 to 78.0	0.014	40.9	11.7 to 68.9	0.019	18.3	2.9 to 44.4	0.003	9.2	0.5 to 33.5	0.002
Surgery alone		100			100		90.9	50.8 to 98.7		75.8	30.5 to 93.7	
Surgery and radiotherapy	86.9	64.0 to 95.6		64.3	38.7 to 81.4		67.3	44.0 to 82.6		55.1	31.1 to 73.8	
Margin status												
Negative	Reference		0.187	Reference		0.040	Reference		0.009	Reference		0.014
Positive	85.6	61.3 to 95.2		59.4	31.9 to 78.8		58.4	34.4 to 76.3		45.4	22.3 to 66.1	
Perineural invasion												
Yes	86.4	63.0 to 95.5	0.851	69.3	43.3 to 85.2	0.439	61.1	37.8 to 78.0	0.280	44.5	22.5 to 64.4	0.145
No	88.9	43.3 to 98.4		88.9	43.3 to 98.4		77.9	35.4 to 94.2		77.9	35.4 to 94.2	

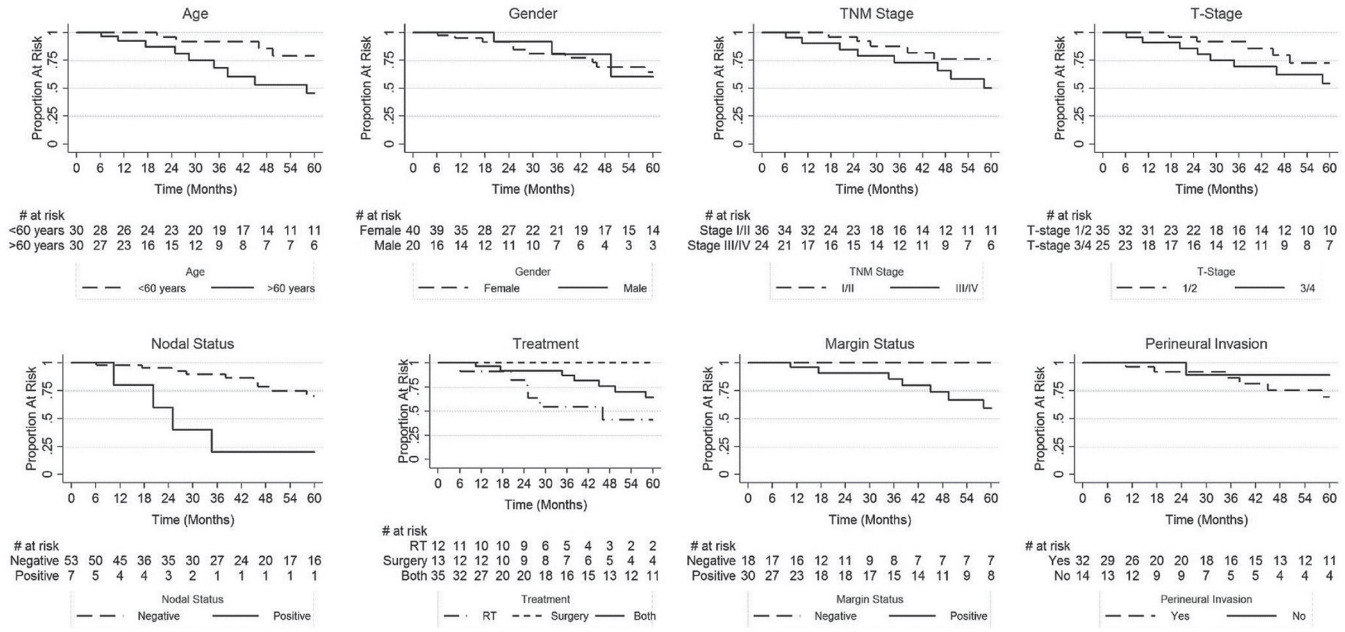

FIGURE 1 Overall survival by TNM stage, T stage, nodal status, treatment received, margin status, and perineural invasion. RT = radiotherapy.

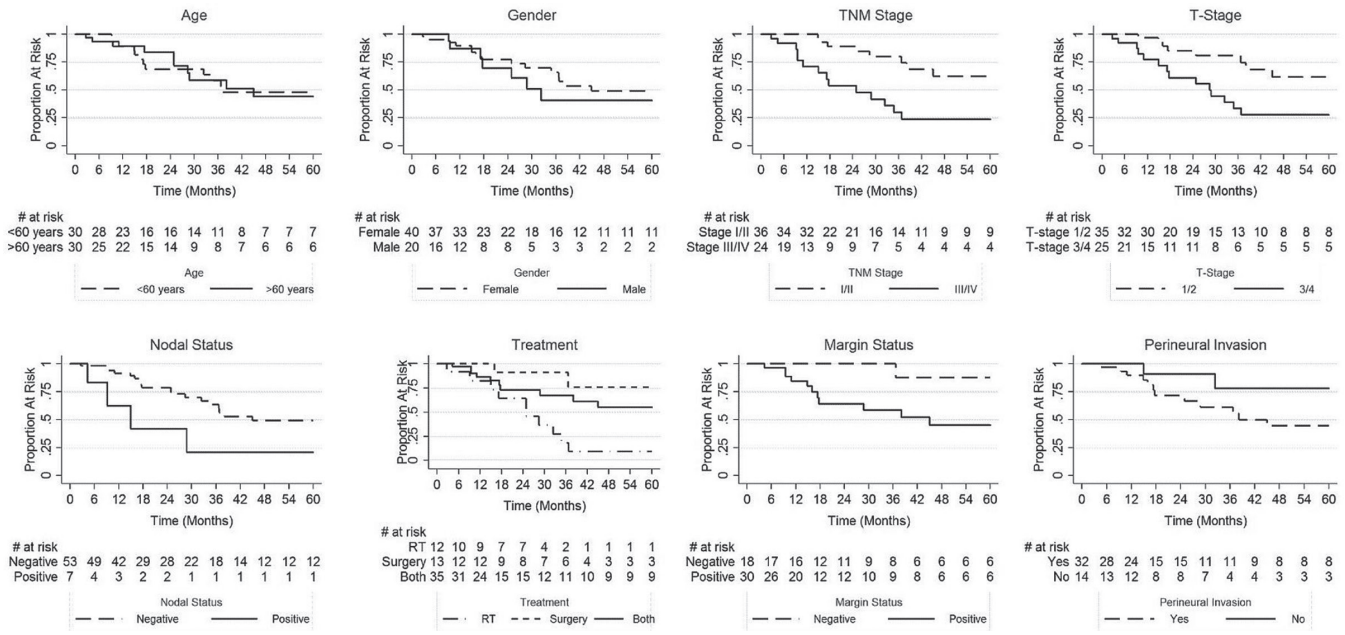

FIGURE 2 Disease-free survival by TNM stage, T stage, nodal status, treatment received, margin status, and perineural invasion. RT = radiotherapy.

the stage groups (3-year DFS: 79.8% vs. 33.2%, log-rank $p = 0.001$; 5-year DFS: 62.1% vs. 22.1%, $p = 0.002$). Earlier T stage predicted improved DFS but not OS, and negative nodal status predicted both improved DFS and OS.

Surgery was the only treatment in 13 patients (22%); all had stage I/II disease, none had positive lymph nodes, and 3 (23%) had a positive margin after surgery. An additional 35 patients (58%) had surgery followed by RT, and the most of them ($n = 27$, 77%) had a positive margin after surgery. Patients treated with RT only ($n = 12$, 20%) had been deemed unresectable after surgical evaluation, having presented mostly with stage III/IV disease ($n = 11$, 91%), and 3 (25%) had positive lymph nodes. The OS and DFS were most favourable in patients treated with surgery only and worst in patients treated with RT only (Table II). Patients with a positive surgical margin after resection had

far worse 5-year OS and DFS rates than did patients with negative margins (5-year OS: 100% vs. 59.4%, log-rank p = 0.040; 5-year DFS: 100% vs. 45.4%, log-rank p = 0.014). In contrast, the presence of perineural invasion did not affect OS or DFS (Table II).

Within 60 months, 17 patients had experienced a recurrence. Another 3 patients experienced a recurrence after 60 months. Local recurrence was experienced by 3 patients (5%); distant recurrence, by 8 patients (13%); and both local and distant recurrence, by 9 patients (15%). Factors associated with the rate of freedom from distant recurrence were similar to those associated with DFS (data not shown). Among patients who were recurrence-free at 5 years, OS at 5 years was 77% (95% CI: 52.8% to 89.9%); patients with any recurrence at 5 years had an OS of 42.7% (95% CI: 15.8% to 67.6%; data not shown).

DISCUSSION

Consistent with the literature, our study of patients with ACC found a median age of approximately 60 years and a female preponderance, although the female:male ratio in our study is much higher than has been reported in other studies[2,25–27]. Female sex did not affect survival in our cohort. The data related to female sex as a prognostic factor are conflicting: A study based on the U.S. National Cancer Institute's Surveillance, Epidemiology, and End Results database suggested improved OS; another study showed a worse DFS, even after matching for stage[2,28]. Although hormones or other sex-dependent biologic factors might explain a greater female:male ratio, whether the same factors affect disease behaviour or outcomes is unknown. Likewise, some—but not all—studies showed an association between advanced age and more advanced disease stage or DFS[9,25]. In the present study, advanced age (that is >60 years) did not affect DFS, implying that age alone does not modify the natural history of ACC. The parotid and other salivary glands, followed by the oro-nasopharyngeal spaces, were the most common sites of origin, consistent with the literature[11,28,29].

Our study confirms that ACC is often a locoregional disease at diagnosis, but that it relapses with distant, and often late, recurrences. Almost one third of our patients developed distant metastasis; only 15% of the recurrences were locoregional. Those findings contrast with results published by other authors who have reported locoregional recurrences in 30%–50% of all patients with recurrence[11,17,26,30]. Without recurrence, the 5-year OS in our cohort was 77%; with recurrence, it was 43%, indicating that, although recurrence is associated with mortality, the disease is not rapidly fatal. The reported tumour doubling time in ACC ranges from 86 days to 1064 days, with an average of 393 days, explaining why subclinical metastatic deposits can manifest as disease 10–15 years after initial treatment[31]. In addition, 10% of the recurrences presented after 5 years of follow-up, suggesting the importance of long-term clinical follow-up given the indolent nature of ACC and its potential for late recurrences.

Despite advances in surgical and adjuvant RT techniques, ACC remains a challenging disease to cure. We report a 5-year OS of 64.5%, comparable to other published results that have reported OS to be in the 60%–90% range at 5 years (Table III). The differences in published survival rates could be reflective of a higher rate of distant metastasis, relative underutilization of adjuvant RT, or a higher proportion of initially unresectable tumours in our cohort, perhaps because of late clinical presentation. For example, Fordice *et al.*[10] reported that 88% of their patients received both surgery and RT; only 2% received RT alone. In our cohort, 58% received both therapies and 20% received RT alone at initial diagnosis. One third of the patients studied by Fordice *et al*. experienced a recurrence, but at least one third of the recurrences were locoregional; of our patients, more than 85% experienced their recurrence as distant metastasis. In contrast, Monteiro *et al.*[30] reported that 60% of their patients received both surgery and RT, and 11% received RT alone; 5-year OS in their cohort was 68%, similar to that in our cohort.

Our findings suggest a need for novel systemic therapies to lower the rate of distant relapse and to improve survival. The current standard of therapy for localized ACC is surgery with or without adjuvant RT. Based on similar small retrospective studies, the U.S. National Comprehensive Cancer Network guideline[34] suggests that adjuvant RT should be offered to patients with risk factors for recurrence such as high grade, positive margins, perineural invasion, lymph node metastasis, and lymphovascular invasion (evidence category 2B). However, adjuvant RT is associated with improved locoregional control or DFS, but not with OS when patients are matched for stage[30,32,33]. In addition, patients treated with RT alone in our study had a poor 5-year OS of 9.2%. This particular group is marked by advanced (and therefore unresectable) tumour stage and continued local and distant progression despite RT. The use of chemoradiation therapy in patients with unresectable ACC, with platinum-based chemotherapy as a radiosensitizer, has been reported in a small study that achieved limited success, but that approach is not considered a standard of care because of the unclear evidence for benefit with the addition of chemotherapy[35,36]. A better understanding of the disease's genomic pathogenesis could potentially lead to new therapeutic targets; one example is the recent discovery of a tumour-specific translocation—t(6:9)(q22–23;p23–24)—that results in the fusion of the *MYB* oncogene to the transcription factor *NFIB*[37].

In our cohort, predictors of DFS included T and N stages, TNM stage, and margin status; N stage and margin status were also associated with 5-year OS. Perineural invasion did not predict either DFS or OS. Prognostic factors for ACC are quite variable and often inconsistent across studies (Table III). The prognostic factors most consistently reported for OS include T and N stages, age, and histology. TNM stage shows no consistent association with OS, suggesting the possibility that an assessment and revision of the TNM staging is needed to reflect survival outcomes. In the literature, margin status (microscopic and macroscopic) and perineural invasion (most importantly, the major nerves) both variably predicted DFS or OS. It is likely that, although a positive resection margin and perineural invasion both adversely affect locoregional outcomes, the addition of adjuvant RT could, to some degree, be able to overcome their impact[35,38,39].

TABLE III Prognostic factors for locoregional control, distant disease-free survival, disease-free survival, and overall survival, as reported in the literature

Reference	Country	Pts (*n*)	Median follow-up (months)	Cohort characteristics (%)		Factors that significantly[a,b] predict ...	
				Stage I/II vs. stage III/IV	5-Year overall survival	Disease-free survival	Overall survival
Fordice *et al.,* 1991 [10]	U.S.A.	160	78	Unreported	Unreported	—	N stage Symptoms Histology Perineural invasion
Bhayani *et al.,* 2001[27]	U.S.A.	60	198	Unreported	Unreported	—	—
Marcinow *et al.,* 2010[13]	U.S.A.	87	98	53 vs. 47	Unreported	Perineural invasion Positive margin	TNM stage Site of origin Lymphovascular invasion
Balamucki *et al.,* 2012[32]	U.S.A.	120	103.2	41 vs. 59	68	—	T stage Perineural invasion
Shen *et al.,* 2012 [30]	China	101	78.1	Unreported	91.7	T stage Treatment received	—
Choi *et al.,* 2013[33]	South Korea	88	57.1	53 vs. 47	89.7	Tumour grade N stage Adjuvant RT Diabetes mellitus	Age Diabetes mellitus
Monteiro *et al.,* 2013[29]	Portugal	114	90	53 vs. 47	60.5	Sex Perineural invasion	Age TNM stage Histology Perineural invasion
Van Weert *et al.,* 2013[4]	Netherlands	105	78.1	54 vs. 46	68	Histology T stage N stage Margin status	Histology T stage N stage Margin status
Zhang *et al.,* 2013[11]	China	218	63.6	59 vs. 41	Unreported	T-stage N-stage	—
Present work	Canada	60	32	60 vs. 40	64.5	TNM stage T stage N stage Treatment received Margin status	Age N stage Treatment received Margin status

[a] One-sided *p* values less than 0.05 were deemed significant in all studies. Univariate and multivariate analyses were both considered.
[b] Histology = solid vs. non-solid (cribriform, tubular).

Our study was limited by a small number of patients, its retrospective methodology, and a relatively short follow-up in a disease with a long natural history. To the best of our knowledge, this cohort is the largest Canadian series reported. The small number of patients in each subgroup means that we were not able to meaningfully match outcomes for stage or other risk features, nor to assess whether significant factors in the early-stage group were also present within the advanced-stage group. A larger nationwide database would represent a useful resource for better analyzing and understanding the clinicopathologic factors that influence outcome in ACC. Such a database could also form the basis for a tumour bank to study the underlying biology of ACC. Lastly, ACC can be a complex histologic diagnosis, whose differential included entities such as pleomorphic adenoma, acinic cell carcinoma, and polymorphous low grade adenoma; expert pathology review is therefore recommended.

CONCLUSIONS

Adenoid cystic carcinoma is a relatively rare tumour of head and neck. Despite aggressive therapy with surgery and RT, one third of patients experience distant recurrence. Patients whose tumours are not amenable to surgical resection at presentation have a poor prognosis, indicating a need for alternative approaches to improve outcomes. Larger prospective studies are needed to better characterize the disease and to define optimal treatments, because smaller, previously published retrospective studies have reported variable prognostic factors and survival outcomes.

ACKNOWLEDGMENT

The authors thank the Alberta Cancer Foundation via Daniel Topolinksy for providing research funds in support of the adenoid cystic carcinoma projects at the Tom Baker Cancer Centre.

CONFLICT OF INTEREST DISCLOSURES

We have read and understood *Current Oncology*'s policy on disclosing conflicts of interest, and we declare that we have none.

AUTHOR AFFILIATIONS

*Department of Medical Oncology, Tom Baker Cancer Centre, University of Calgary, Calgary, AB; †Department of Biostatistics, Public Health Innovation and Decision Support Population and Public Health, Alberta Health Services, AB; ‡Department of Pathology, Foothills Medical Centre, University of Calgary, Calgary, AB; §Department of Oncology, University of Calgary, Calgary, AB.

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