



Treatment and survival outcomes of ceruminous carcinomas of the external auditory canal: a SEER database analysis and literature review

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Abstract

Ceruminous carcinomas of the external auditory canal (EAC), encompassing adenoid cystic carcinoma (ACC), ceruminous adenocarcinoma (CA), and mucoepidermoid carcinoma (MEC), are extremely rare with little known regarding the influence of demographics, tumor characteristics, and treatment on survival. This study aimed to summarize existent data and describe prognostic factors affecting survival in ceruminous carcinoma. Cases of ceruminous carcinoma of the EAC in the Surveillance, Epidemiology, and End Results (SEER) database were analyzed to provide demographic, cancer-related, and treatment data and assess their influence on disease-specific and overall survival. A literature review was also performed. No significant difference in overall survival (OS) existed for localized versus regional disease, tumor type, or use of radiation therapy. In those with ACC, distant disease had a lower OS compared to regional disease. On review of the literature, local recurrence was a common finding with a low risk for nodal metastasis in ACC and CA. In conclusion, local recurrence was common despite aggressive surgical intervention (\pm radiation therapy); overall survival was unaffected by radiation therapy, tumor type, or local versus regional disease; and more cases of MEC are needed for analysis.

Keywords Ceruminous carcinoma · Adenoid cystic carcinoma · Ceruminous adenocarcinoma · Mucoepidermoid carcinoma · Epidemiology · Survival

Introduction

A small proportion (~0.2%) of head and neck cancers occur in the external auditory canal (EAC) [25, 39, 46, 49]. The majority of these tumors are squamous cell carcinoma (~70%), with basal cell carcinoma, melanoma, Merkel cell carcinoma, lymphoma, angiosarcoma, and ceruminous neoplasms comprising the remainder [21].

Ceruminous neoplasms arise from distinct, modified apocrine glands known as ceruminous glands [14]. Each person has 1000–2000 ceruminous glands confined to the skin of the outer third of the EAC. Tumors of these glands are

exceedingly rare and account for <0.001–2.4% of neoplasms in this location [14, 21, 39, 46]. The World Health Organization (WHO) separates ceruminous tumors of the EAC into benign adenomas and malignant adenocarcinomas [49]. The adenocarcinomas are further distinguished, based on histologic features, into ceruminous adenocarcinoma (CA), adenoid cystic carcinoma (ACC), and mucoepidermoid carcinoma (MEC). Importantly, ACC and MEC originating in the EAC are histologically indistinguishable from a primary salivary gland ACC or MEC. As such, to make a definitive diagnosis of a primary ceruminous gland neoplasm, extension of these tumors to adjacent salivary glands (i.e., parotid gland) must be excluded via preoperative imaging or intraoperatively [3].

ACC is the most common ceruminous gland malignancy of the EAC. The second most common is CA, with MEC being the least frequently reported [14, 39, 49]. Despite limited data, the malignant behavior of ceruminous carcinomas is well-documented with a propensity for local recurrence and metastatic potential [14]. As such, aggressive surgical resection with or without adjuvant radiation is advocated to

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ensure tumor removal [49, 57]. However, even with aggressive therapy, recurrences are common, and death can occur from metastasis and/or progression of loco-regional disease [14, 21, 57]. The degree to which these treatments influence survival remains largely unexplored and the rarity of ACC, CA, and MEC limits the available clinical, treatment, and prognostic data. The purpose of this study is to utilize population-based cancer data to describe patient demographics, assess prognostic utility of staging data, and examine the influence of various treatment modalities on overall survival for ceruminous carcinomas of the EAC. In addition, a review of the literature was performed to contextualize results from this study with historical cases.

Materials and methods

Patient cohort

This retrospective cohort study utilized the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) program, which draws from 21 population-based cancer registries to provide information on approximately 34.6% of the United States population. Patients included were diagnosed with CA, ACC, or MEC (World Health Organization's International Classification of Disease for Oncology, 3rd edition: ICD-O-3 code 8420/3 [CA], 8200/3 [ACC], and 8430/3 [MEC]) of the external ear (C44.2) within the SEER database between 1975 and 2017. Ceruminous carcinomas occurring outside the external ear were excluded. Follow-up data were collected on available patients until 2017. All patient diagnoses were biopsy-proven and did not include patients who received clinical, radiographic, or posthumous diagnoses. Since SEER data are publicly available and de-identified, this study was exempt from institutional review board approval by The Ohio State University Human Research Protection Program.

Study variables and definitions

The following categorical variables were constructed: age (< 45, 45–55, 55–65, 65–75, 75–85, and > 85), race (White, African American, Native American/Native Alaskan, Asian, and other/unknown), ethnicity (Spanish–Hispanic–Latino or Non-Spanish–Hispanic–Latino), and treatment type (surgery only, radiation therapy only, chemotherapy only, or combinations thereof). Survivorship was categorized as either overall survival (OS) or disease-specific death (DSD). Follow-up time frames were collected as continuous variables in months. For missing data, the available case method was utilized.

The SEER Summary and Historic staging variables were used to classify tumors as localized, regional, and distant

stage. Due to discrepancies between Summary and Historic staging variables, SEER Summary staging was prioritized if both Summary and Historic variables were present. Local stage is defined as a malignancy limited to the organ of origin. Regional stage is defined as a malignancy that either (1) extends beyond the organ of origin directly into surrounding tissue, (2) involves a regional lymph node via the lymphatic system, or (3) demonstrates both direct extension and lymphatic spread beyond the site of origin. Distant stage is defined as tumors involving a distant organ or lymph node by noncontiguous metastases or by direct extension. For unstaged tumors, information is insufficient to assign staging.

Statistical analysis

Dichotomous and categorical variables were defined with proportions. Continuous variables were described with means, standard deviations, and ranges. Age-adjusted incidence rates, rate ratios, and trends were analyzed based on the year 2000 U.S. standard population. For incidence calculations, a 16-year study period (2000–2016) was chosen with data drawn from 18 available SEER registry groupings. Rates were calculated as new cases per year per 1,000,000 persons. Kaplan–Meier (KM) curves were used to describe time-to-event data with overall survival as the outcome variable. A log-rank test was used to complete pairwise-comparison of KM curves. The Cox proportional hazards model, adjusted for age, gender, race and ethnicity, SEER summary stage, and primary treatment, was used to model overall survival given the infrequency of disease-specific death. The proportional hazards assumption was evaluated with a Schoenfeld residuals test. A two-sided *p* value of less than 0.05 was considered statistically significant. Statistical analyses were performed on Stata 15.1 (College Station, TX), aside from incidence calculations performed on SEER*Stat 8.3.6.1 (Calverton, MD).

Literature review method

The PubMed database was searched using the following terms: (cerum* OR cylindroma OR adenoid cystic carcinoma OR ceruminous adenocarcinoma OR mucoepidermoid carcinoma) AND (ear OR external auditory canal). Cylindroma was included as a search term since previous sources used cylindroma as a synonym for ACC [54]. Eligible articles were published in English and contained human cases. Articles with parotid gland involvement were excluded since the primary site of origin cannot be distinguished. References of each article were searched for relevant cases. Case reports were included due to the low number of case series, cohort studies, and literature reviews. Recorded variables from each article included

the number of cases; treatment(s); the presence of local recurrence, nodal metastases, and/or distant metastasis; DSD; OS; and follow-up duration.

Results

Cohort description

The SEER cohort comprised of 135 individuals diagnosed with ceruminous carcinoma. Table 1 provides a summary of

Table 1 Demographic, treatment, and outcomes of patients with ACC, CA, and MEC

Characteristics	Tumor type		
	ACC (<i>n</i> =98) <i>n</i> (%)	CA (<i>n</i> =33) <i>n</i> (%)	MEC (<i>n</i> =4) <i>n</i> (%)
Gender			
Male	37/98 (38%)	17/33 (52%)	3/4 (75%)
Female	61/98 (62%)	16/33 (48%)	1/4 (25%)
Age at diagnosis (years)			
< 45	19/98 (19%)	6/33 (18%)	0
45–55	18/98 (18%)	3/33 (9%)	1/4 (25%)
55–65	25/98 (26%)	7/33 (21%)	1/4 (25%)
65–75	19/98 (19%)	10/33 (30%)	1/4 (25%)
75–85	11/98 (11%)	4/33 (12%)	1/4 (25%)
> 85	6/98 (6%)	3/33 (9%)	0
Race			
White	80/98 (82%)	21/33 (64%)	1/4 (25%)
African American	8/98 (8%)	5/33 (15%)	1/4 (25%)
Native American/Native Alaskan	1/98 (1%)	0	1/4 (25%)
Asian	8/98 (8%)	6/33 (18%)	1/4 (25%)
Other/unknown	1/98 (1%)	1/33 (3%)	0
Ethnicity			
Non-Spanish–Hispanic–Latino	90/98 (92%)	32/33 (97%)	4/4 (100%)
Spanish–Hispanic–Latino	8/98 (8%)	1/33 (3%)	0
SEER summary stage			
Local	57/98 (58%)	19/33 (58%)	1/4 (25%)
Regional	30/98 (31%)	9/33 (27%)	0
Distant	6/98 (6%)	3/33 (9%)	1/4 (25%)
Unstaged	5/98 (5%)	2/33 (6%)	2/4 (50%)
Primary treatment			
Surgery only	27/76 (36%)	9/22 (41%)	2/4 (50%)
Radiation only	16/76 (21%)	2/22 (9%)	0
Chemotherapy only	1/76 (1%)	0	0
Surg + Rad	32/76 (42%)	10/22 (45%)	0
Surg + Rad + Chemo	0	1/22 (5%)	0
Rad + Chemo	0	0	2/4 (50%)
Survival characteristics			
Disease-specific death	12/98 (12%)	2/33 (6%)	1/4 (25%)
Follow-up, mean (mo) ± SD	77 ± 64	45 ± 33	37
Follow-up, range (mo)	7–229	22–68	37
Overall survival	56/98 (57%)	19/33 (58%)	1/4 (25%)
Follow-up, mean (mo) ± SD	111 ± 80	107 ± 122	48 ± 18
Follow-up, range (mo)	5–397	2–426	37–69

ACC adenoid cystic carcinoma, CA ceruminous adenocarcinoma, MEC mucoepidermoid carcinoma, SEER Surveillance, Epidemiology, and End Results, *mo* month, *SD* standard deviation

the demographic, therapeutic, and survival characteristics. Age-adjusted incidence rates were analyzed using rate ratios with white as the referent group for race and male as the referent group for gender. During the incidence study period (2000–2016), a total of 93 cases of ceruminous carcinomas occurred with an age-adjusted incidence of 0.064 (95% CI 0.051–0.078) cases per year per 1,000,000 persons. The incidence of ceruminous carcinoma decreased over the study period with an annual percent change of -3.8% (95% CI -7.705 – 0.196). In general, ceruminous carcinoma tended to affect female patients to a greater degree ($\sim 1.5:1$ ratio), but this was not statistically significant. Similarly, there were no significant differences in incidence between races both as a whole and between tumor subtypes.

A total of 98 cases of ACC were identified. The age-adjusted incidence was 0.047 (95% CI 0.037–0.060) cases per year per 1,000,000 persons, based on 69 cases during the incidence study period. A similar distribution occurred among the age groups studied with a small peak in incidence in the 5th decade of life. Regional disease was noted in 30 cases, and of these, 24 had further lymph node evaluation with only 1/24 demonstrating metastatic lymph node involvement. Surgical intervention ($n = 59$, 78%) and radiation therapy ($n = 48$, 63%) were most commonly included as part of the primary treatment modality. Twelve patients (12%) died as a result of their tumor and fifty-six patients (57%) were alive at the conclusion of the study period.

A total of 33 patients with CA were identified. The age-adjusted incidence was 0.015 (95% CI 0.010–0.023) cases per year per 1,000,000 persons, based on 22 cases during

the incidence study period. Males and females had similar age-adjusted incidence rates and the majority of patients were 55–75 years of age ($n = 17$, 51%). Treatment data were available for 67% of patients and surgical intervention was the most commonly reported ($n = 20/22$, 91%). Radiation therapy was frequently utilized with over half of the cohort ($n = 12$, 55%) receiving radiation with or without surgery. Survival characteristics showed 2 patients died from their disease (6%) and 19 (58%) were alive at the conclusion of the study period.

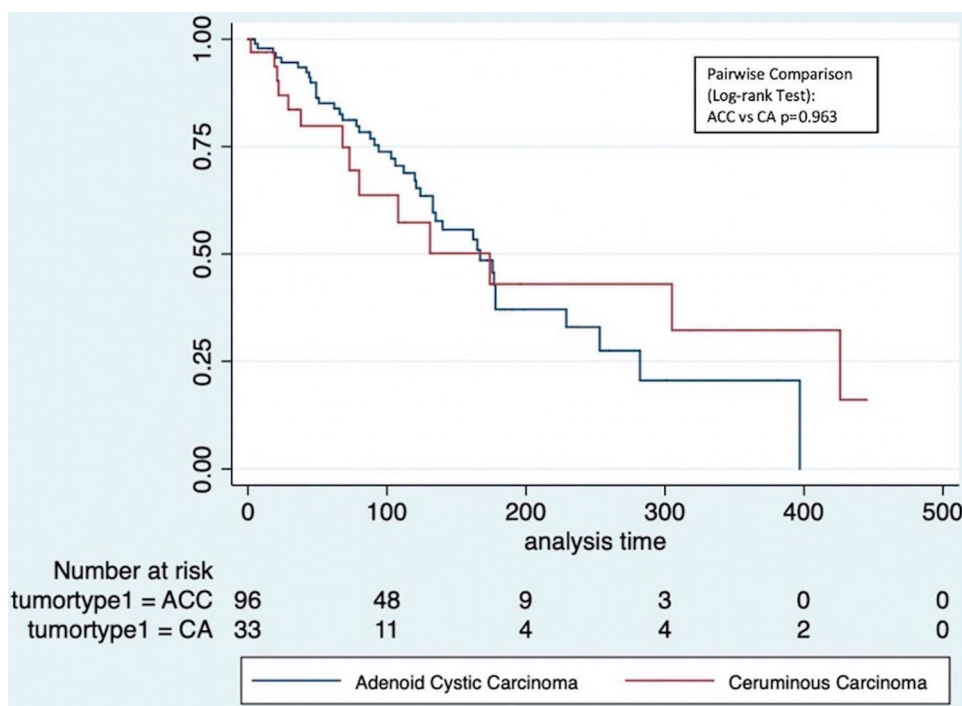
A total of four patients with MEC of the EAC were identified. One patient was found to have distant disease at diagnosis. One patient died as a result of their tumor and one (25%) was alive at the conclusion of the study.

Survival characteristics

A log-rank test of the KM curves for the ACC cohort found regional tumor stage had a higher OS compared to distant tumor stage ($p < 0.001$). However, when comparing localized versus regional stage for ACC, log-rank testing of the survival curves demonstrated no significant difference in survival ($p = 0.510$). For the CA cohort, there was no difference in OS between localized and regional tumor stage ($p = 0.589$). Due to an insufficient number of patients, distant tumor stage for the CA cohort was not included in the analyses.

When comparing OS between the two most common tumor subtypes, ACC and CA, the KM curves demonstrated no statistical difference ($p = 0.963$) (Fig. 1). Additionally,

Fig. 1 Kaplan–Meier survival curves of adenoid cystic carcinoma (ACC) and ceruminous adenocarcinoma (CA)



when treatment groups were dichotomized into radiation versus no radiation, comparison between treatment groups demonstrated no difference in survival for either ACC ($p=0.614$) (Fig. 2) or CA ($p=0.255$) (Fig. 3). Quantitative survival analysis of MEC is limited by the small sample size.

On univariable and multivariable analysis, patients with distant disease in the ACC cohort were at increased risk

of death compared to those with localized disease (univariable: HR = 7.64; 95% CI 2.65–22.06; $p < 0.01$) (multivariable: HR = 16.63; 95% CI 2.80–98.92; $p = 0.002$). However, gender, race/ethnicity, regional disease, and primary treatment modality did not significantly affect survival (Table 2). Of note, Schoenfeld residual testing supported the proportional hazards assumption ($p = 0.964$). Due to an insufficient

Fig. 2 Kaplan–Meier survival curves of adenoid cystic carcinoma (ACC) with/without radiation

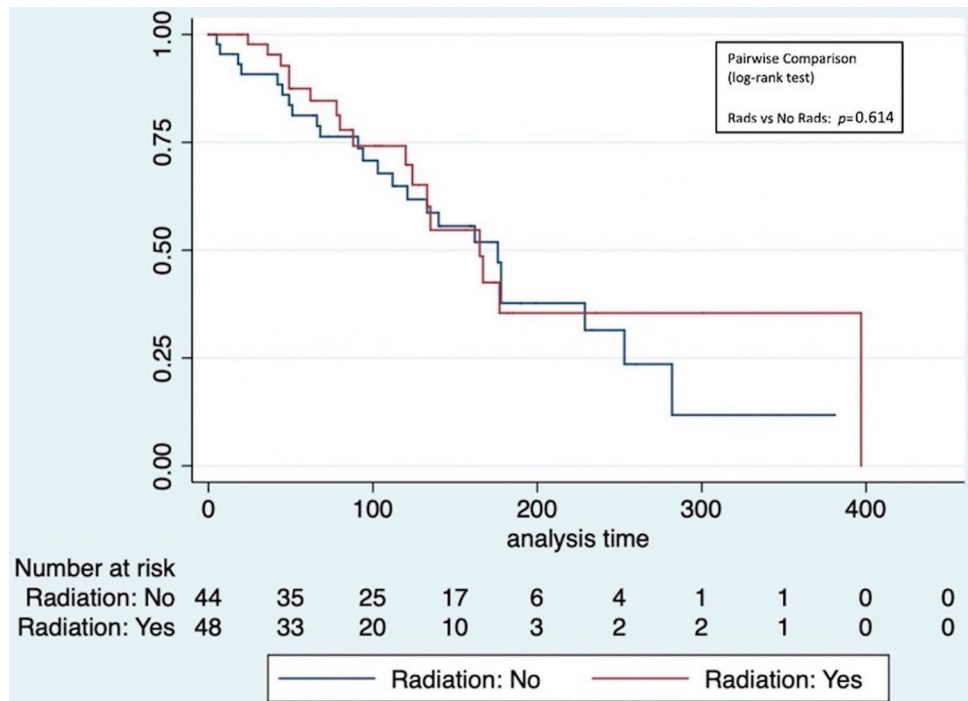


Fig. 3 Kaplan–Meier survival curves of ceruminous adenocarcinoma (CA) with/without radiation

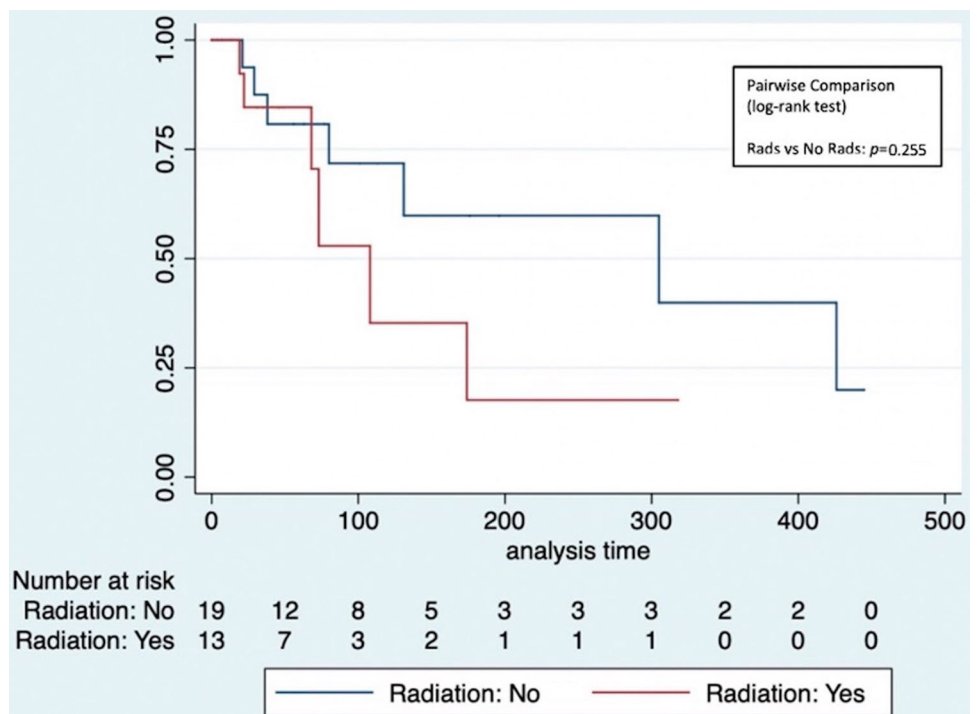


Table 2 Results of overall survival univariable and multivariable analysis for ACC

Patient features	Adenoid cystic carcinoma			
	Univariable analysis		Multivariable analysis	
	HR (95% CI)	Two-sided <i>P</i> value	HR (95% CI)	Two-sided <i>P</i> value
Age	1.06 (1.03, 1.08)	<0.01	1.08 (1.04, 1.12)	<0.01
Gender				
Male	Referent		Referent	
Female	1.42 (0.74, 2.71)	0.293	0.65 (0.22, 1.95)	0.439
Race/ethnicity				
White	Referent		Referent	
Non-white	1.29 (0.59, 2.81)	0.517	2.06 (0.71, 6.04)	0.186
SEER summary stage				
Local	Referent		Referent	
Regional	1.26 (0.63, 2.51)	0.516	1.04 (0.32, 3.40)	0.946
Distant	7.66 (2.67, 22.02)	<0.01	16.40 (2.82, 95.46)	0.002
Primary treatment				
Surgery only	Referent		Referent	
Radiation only	1.24 (0.50, 3.06)	0.641	1.48 (0.51, 4.27)	0.468
Surgery + RT	0.83 (0.32, 2.20)	0.713	0.69 (0.18, 2.65)	0.587

CI confidence interval, SEER Surveillance, Epidemiology, and End Results, S + RT surgery and radiation

number of patients, multivariable and univariable analysis of the CA and MEC cohorts were not included in the analyses.

Literature review

A total of 52 articles were included for review and summarized in Table 3. ACC was reported most frequently ($n=199$) followed by CA ($n=45$) and then MEC ($n=8$). Most cases had surgical intervention either as the only treatment or in combination with radiation. Radiation monotherapy and adjuvant chemotherapy were not frequently reported. Additionally, local recurrence was common for each cohort (42% ACC, 49% CA, 38% MEC); however, nodal metastasis rates were low for CA (0%) and ACC (4%) despite higher distant metastasis rates (13% CA, 24% ACC). Of the 8 MEC cases, 2 (29%) had nodal metastasis and 1 (14%) had distant metastasis. Regarding survivorship, CA had the highest DSD rate (27%) and the lowest OS rate (56%) compared to ACC (DSD 18%, OS 74%) and MEC (DSD 14%, OS 86%).

Discussion

Comparable to previous studies, this analysis found ACC was the most frequently reported ceruminous neoplasm [1–57]. Published data regarding gender predilection for ceruminous carcinomas are mixed, with studies showing ACC more prevalent among females, equal gender distribution for CA, and MEC favoring males [34–38, 44, 46]. However, this study found there were no statistically significant

gender preferences in the subtypes of ceruminous carcinoma. Additionally, no racial predilection was observed for ceruminous carcinoma and its subtypes. Consistent with previous reports, this analysis shows ceruminous carcinoma primarily affects adults in their 5th–7th decade of life [14, 39, 46].

An important finding from this study is the lack of a statistical difference in OS between CA and ACC ($p=0.963$). This is in contrast to a previous report noting an improved OS for ACC compared to CA (mean survival of 100 months and 56 months, respectively) [14]. As shown in Fig. 1, the two cancers demonstrated comparable survival curves with similar mean follow-up times (111 months for ACC, 107 months for CA).

Given its risk of local recurrence and metastasis, adjuvant radiation therapy remains a common treatment modality for ceruminous carcinoma. However, objective evidence that radiation therapy improves outcomes is lacking. In a similar SEER investigation on CA, the authors noted that patients receiving adjuvant radiation therapy had shorter survival times [46]. Conversely, as demonstrated in Fig. 3 of this investigation, radiation therapy had no significant impact on survival time for CA (Fig. 2 also demonstrates no impact in ACC). There is a separation of the KM curves when the number at risk is low (the right-hand side of the curve); however, given the low numbers included in the risk set at this point, no conclusions can be made about survivorship. Of note, given the relative lack of specific staging and patient-level data available in SEER, patient and tumor characteristics that may confound this relationship remain.

Table 3 Reported cases of ceruminous carcinomas

Reference	Cases	Treatment	LR	NM	DM	DSD (%)	OS (%)	Follow-up (mean, mo)
Adenoid cystic carcinoma (ACC)								
Crain et al. [3]	4	4 S	2	0	2	2 (50%)	1 (25%)	119
Dalmaso [11]	4	1 S, 3 S+ART	3	0	2	2 (50%)	2 (50%)	66
Dong et al. [12]	22	4 S, 18 S+ART	4	3	6	6 (27%)	13 (59%)	116
Gu et al. [13]	43	14 S, 29 S+ART	NR	1	0	13 (30%)	30 (70%)	60
Liu et al. [14]	12	12 S	1	0	3	1 (8%)	11 (92%)	77
Zhang et al. [6]	77	48 S, 29 S+ART	40	0	25	3 (4%)	64 (83%)	39
Case reports [15–39]	37	21 S, 15 S+ART, 2 S+ART+C	14	3	10	7 (19%)	24 (65%)	64
Total	199	104/199 S (52%), 93/199 S+ART (47%), 2/199 S+ART+C (1%)	64/153 (42%)	7/196 (4%)	47/196 (24%)	34/191 (18%)	146/197 (74%)	68
Ceruminous adenocarcinoma								
Crain et al. [3]	12	9 S, 3 S+ART	3	0	0	3 (25%)	7 (58%)	109
Dehner [23]	5	1 S, 1 S+ART, 3 RT	4	0	4	4 (80%)	0	19
Pulec [35]	5	NR	4	NR	0	4 (80%)	0	48
Case reports [3, 8, 15, 26, 30–32, 40–53]	23	11 S, 12 S+ART	11	0	2	2 (9%)	18 (78%)	53
Total	45	21/40 S (53%), 16/40 S+ART (40%), 3/40 RT (8%)	22/45 (49%)	0	6/45 (13%)	12/45 (27%)	25/45 (56%)	54
Mucoepidermoid carcinoma								
8 Case Reports [3, 35, 54–57, 58, 59]	8	6/8 S (75%), 1 S+ART (13%), 1 S+ART+C (13%)	3/8 (38%)	2/7 (29%)	1/7 (14%)	1/7 (14%)	6/7 (86%)	28

LR local recurrence, NM nodal metastasis, DM distant metastasis, DSD disease-specific death, OS overall survival, mo month, S surgery, RT radiation, S+RT surgery and radiation, S+RT+C surgery and radiation and chemotherapy, NR not reported

Previously reported DSD rates trended higher for ACC (18%; 95% CI 13–23) and CA (27%; 95% CI 14–40) (Table 3) when compared to the present findings (12% ACC [95% CI 5–19], 6% CA [95% CI –2–14]) (Table 1), though in each case confidence intervals do cross. Considerable variation in DSD for MEC is to be expected given its rarity. In contrast, overall survival rates for ACC and MEC were lower in the present study relative to previously published values (Table 3). This may be partially explained by the longer mean follow-up periods for patients in SEER leading to higher observed death rates. Interestingly, previously reported treatment strategies also differ from SEER data. In most subtypes in SEER, surgical monotherapy was employed for a minority of patients and radiation, as either monotherapy or in combination, was frequently utilized. This may reflect an emerging trend in treatment strategies given ceruminous carcinoma's propensity for locally aggressive and metastatic behavior.

Despite increasingly aggressive treatment measures, high local recurrence rates remains a persistent issue (42% ACC,

49% CA, 38% MEC) (Table 3). The malignant potential of ceruminous carcinoma is well known. However, recent studies have demonstrated that metastatic involvement tends to be distant with rare reports of lymph node involvement (Table 3) [14, 23, 32]. These assertions are supported by the SEER data demonstrating only 1 ACC patient with regional lymph node involvement (of 24 with lymph node evaluation). This finding provides interesting insight into the unique malignant behavior of ACC (\pm other ceruminous carcinomas) and may provide an explanation for the non-impact of adjuvant radiation therapy on overall survival.

Limitations

Certain variables (e.g., clinical presentation, local recurrence, restaging) are not recorded within SEER and, therefore, preclude observing disease progression and monitoring treatment response. Low sample sizes limit the power of this study. Additionally, SEER uses a primary skin site of the external ear which is not specific for the EAC. Finally,

some cases of ceruminous carcinoma may have been primary parotid gland tumors with extension to the EAC and misclassified as a primary external ear neoplasm.

Conclusion

Ceruminous carcinomas of the EAC are exceedingly rare tumors with high local recurrence rates and metastatic potential. Outcomes-based data on optimal treatment strategies are limited by tumor infrequency, and surgical intervention, with or without radiation therapy, remains the mainstay of treatment. In the present study, radiation therapy did not improve overall survival for ACC and CA. Survival appears unaffected by many variables except distant tumor stage. Future studies are needed to further elucidate the malignant behavior of ceruminous carcinomas and evaluate the utility of lymph node evaluation.

Author contributions All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by KR and DRC. The first draft of the manuscript was written by BW and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Availability of data and material Data for this study are openly available in the Surveillance, Epidemiology, and End Results (SEER) database or by inquiry to the corresponding author.

Code availability Not applicable.

Declarations

Conflict of interest The authors declare they have no conflict of interest. SEER contains publicly available, de-identified data making informed consent and institutional review board approval unnecessary.

Ethics approval This study was performed in line with the principles of the Declaration of Helsinki. The study was exempt from institutional review board approval by The Ohio State University Human Research Protection Program.

Consent to participate Not applicable.

Consent for publication Not applicable.

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