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Prognostic factors and survival outcomes for head and neck cutaneous adnexal cancers☆

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ABSTRACT

Objectives: Malignant cutaneous adnexal tumors (MCAT) are rare and comprise a heterogeneous group of cancers. There have been several studies reviewing prognostic factors of these tumors, but no studies focusing on the head and neck. This study aimed to review a large population based database to evaluate prognostic factors that could impact survival.

Methods: The Surveillance, Epidemiology, and End Results (SEER) database was utilized to identify patients with MCAT of the head and neck. Both overall and disease specific survival were the main outcome measures for the study. Univariate and multivariate analyses were performed to evaluate the association of suspected prognostic factors with survival.

Results: The five-year OS and DSS were 72.6 and 95.5%, respectively. A favorable factor for OS was surgical resection ([HR] 0.324; $P = 0.001$), while unfavorable factors for OS include older age (1.051; $P < 0.001$), higher tumor grade (1.254; $P = 0.049$), larger tumor size (1.293; $P = 0.003$), and positive nodal involvement (3.323; $P = 0.002$). A favorable factor for DSS was surgical resection (0.026; $P < 0.001$). Unfavorable factors for DSS include older age (1.058; $P = 0.046$), larger tumor size (2.528; 1.565–4.085; $P < 0.001$), and positive nodal involvement (4.761; $P = 0.022$).

Conclusion: Review of the SEER database shows good 5-year OS and DSS rates, similar to those cited in other studies. We identified several prognostic factors associated with survival, while histologic sub-type does not seem to be associated with survival. Surgical resection is the mainstay of treatment.

1. Introduction

Skin cancers are generally divided into melanoma and non-melanoma types. Non-melanomatous skin cancers account for 93–96% of skin cancers, while melanoma skin cancers account for the remaining 4–7% [1]. The majority of non-melanomatous cancers are basal cell and squamous cell carcinomas, but there are at least 82 types of skin malignancies [2]. Benign and malignant adnexal cancers represent only 1–2% of non-melanomatous cancers [1]. Malignant adnexal tumors are rare and comprise a heterogeneous group of cancers. They derive from eccrine, apocrine, sebaceous, or ceruminous glands within the skin or follicular cells. The diagnosis relies on histological evaluation and they are classified according to the predominant morphological component [3]. The underlying etiology is unknown but Ultraviolet (UV) light and radiation have been implicated in the pathogenesis [4]. A study by Martinez et al. looking at malignant adnexal tumors showed a prevalence of 65.2% localizing to the head and neck [5]. They reported a 10 year overall survival of 54% and disease specific survival of 97%. However, this was not specific to the head and neck. These malignancies are more locally aggressive than other non-melanomatous cancers, have the potential for local and distal metastasis, and worse outcomes [1,4].

This is the first study to review a large population based database for adnexal carcinomas confined to the head and neck. Our aim was to assess a variety of factors (patient, tumor and treatment) that could impact overall survival (OS) and disease specific survival (DSS).

2. Methods

The Surveillance, Epidemiology, and End Results (SEER) database

☆ Level of evidence: Level 4.

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was utilized to identify patients for this study (SEER 18 registry, 1973–2013). This public-use registry of cancer incidence and survival represents 28% of the U.S. population, and contains detailed information on patient demographics, tumor histology and staging, and follow-up for vital status. Data are updated and validated annually by the National Cancer Institute, and use of the database does not require Institutional Review Board approval.

Patients diagnosed with a cutaneous adnexal malignancy of the head and neck were eligible for analysis (site codes C44.0-C44.4 from the *International Classification of Diseases*, *Tenth Revision*, *Clinical Modification*). Tumor histologies were identified using diagnostic codes from the *International Classification of Diseases for Oncology*, *Third Edition*. The histologies included in the cohort were: skin appendage carcinoma (8390), sweat gland adenocarcinoma (8400), apocrine adenocarcinoma (8401), nodular hidradenoma (8402), malignant eccrine spiradenoma (8403), sclerosing sweat duct carcinoma (8407), eccrine papillary adenocarcinoma (8408), eccrine poroma (8409), sebaceous adenocarcinoma (8410), eccrine adenocarcinoma (8413), ceruminous adenocarcinoma (8420), mucoepidermoid carcinoma (8430), mucinous adenocarcinoma (8480), and mucin-producing adenocarcinoma (8481). Patients whose malignancy was not histologically confirmed or was diagnosed at autopsy were excluded from the study.

The outcome measure of this study was survival, which was calculated from the date of diagnosis of malignancy to whichever of the following occurred first: date of death, date of last follow-up, or end of the study period (December 31, 2013). Both OS and DSS were assessed for each patient; OS was defined as the time from diagnosis to death from any cause, while DSS was defined as the time from diagnosis to death directly attributable to the primary malignant tumor. Any patients lost to follow-up were coded as censored observations.

Statistical analyses were performed using the SPSS 22 software (IBM Corporation, Aramonk, NY). Univariate Kaplan-Meier analysis was performed to evaluate the association of suspected prognostic variables with survival. The variables tested in the univariate analysis include: race, gender, age, primary tumor site, tumor grade, tumor histology, tumor size (American Joint Committee on Cancer [AJCC] T stage), nodal involvement (AJCC N stage), presence of distant metastases (AJCC M stage), radiation administration, and surgical resection. Each association was analyzed using the log-rank test, and was deemed statistically significant at the $P < 0.05$ level. Any variables that were found to be significant predictors of OS or DSS were subsequently tested with a multivariable Cox proportional hazards regression analysis.

3. Results

3.1. Patient characteristics

A total of 5298 patients with cutaneous adnexal malignancies of the head and neck were included in the study cohort (Table 1). The mean age of patients was 69; males comprised 54.1% of the sample, and the cohort was predominantly white (83.9%). The most common specified cutaneous site for malignancies was the eyelid (24.9%), and the most common tumor histologies were those of sebaceous adenocarcinoma (46.6%) and skin appendage carcinoma (17.4%). The majority of tumors were not evaluated for grade, size, nodal involvement, or metastases; tumors that did undergo evaluation predominantly were well-differentiated (45.6%), were < 2 cm in size (19%), did not demonstrate lymph node involvement (47.1%), and had not metastasized (46.6%). With regards to treatment, the majority of patients did not receive radiation therapy (94.2%), but did undergo surgical resection (85.8%).

3.2. Univariate analysis

The five-year OS and DSS were 72.6% and 95.5%, respectively (Fig. 1). The results of the univariate Kaplan-Meier analysis are depicted in Table 1. Log-rank tests suggested that gender ($P < 0.001$), age ($P < 0.001$), race ($P < 0.001$), tumor site ($P < 0.001$), histology ($P < 0.001$), grade ($P < 0.001$), tumor size ($P = 0.001$), nodal involvement ($P < 0.001$), radiation administration ($P = 0.034$), and surgery ($P < 0.001$) were predictors of OS. Gender ($P = 0.06$), age ($P < 0.001$), race ($P = 0.001$), tumor site ($P < 0.001$), grade ($P = 0.009$), tumor size ($P < 0.001$), lymph node involvement ($P < 0.001$), distant metastases ($P = 0.001$), radiation administration ($P < 0.001$), and surgery ($P < 0.001$) were predictors of DSS.

Table 1
Patient demographics, tumor characteristics, and univariate analysis of overall survival and disease-specific survival.

	Value (percentage)	*P* value	
		OS	DSS
Gender		< 0.001	0.06
Male	2866 (54.1)		
Female	2432 (45.9)		
Total	5298		
Age		< 0.001	< 0.001
Mean	69		
Race		< 0.001	0.001
White	4444 (83.9)		
African-American	223 (4.2)		
Other	279 (5.3)		
Unknown	352 (6.6)		
Tumor site		< 0.001	0.009
Lip	175 (3.3)		
Eyelid	1322 (24.9)		
External ear	300 (5.7)		
Scalp or neck	1087 (20.5)		
Other unspecified face	2419 (45.6)		
Histology		< 0.001	0.30
Skin appendage carcinoma	920 (17.4)		
Sweat gland adenocarcinoma	295 (5.6)		
Apocrine adenocarcinoma	104 (2)		
Nodular hidradenoma	147 (2.8)		
Malignant eccrine spiradenoma	29 (0.5)		
Sclerosing sweat duct carcinoma	468 (8.8)		
Eccrine poroma	160 (3)		
Sebaceous adenocarcinoma	2470 (46.6)		
Eccrine adenocarcinoma	224 (4.2)		
Ceruminous adenocarcinoma	29 (0.5)		
Mucoepidermoid carcinoma	59 (1.1)		
Mucinous adenocarcinoma	393 (7.4)		
Grade		< 0.001	< 0.001
Well-differentiated	389 (45.6)		
Moderately-differentiated	353 (6.7)		
Poorly-differentiated	452 (8.5)		
Undifferentiated/anaplastic	60 (1.1)		
Unknown grade	4044 (76.3)		
Tumor size		0.001	< 0.001
T1	1004 (19)		
T2	195 (3.7)		
T3	70 (1.3)		
T4	173 (3.3)		
TX	3856 (72.8)		
Lymph node involvement		< 0.001	< 0.001
N0	2497 (47.1)		
N1	45 (0.8)		
NX	2756 (52)		
Distant metastases		0.41	0.001
M0	2467 (46.6)		
M1	173 (3.3)		
MX	2658 (50.2)		
Radiation		0.034	< 0.001
Radiation administered	306 (5.8)		
No radiation	4992 (94.2)		
Surgery		< 0.001	< 0.001
Surgery performed	4544 (85.8)		
No surgery	754 (14.2)		

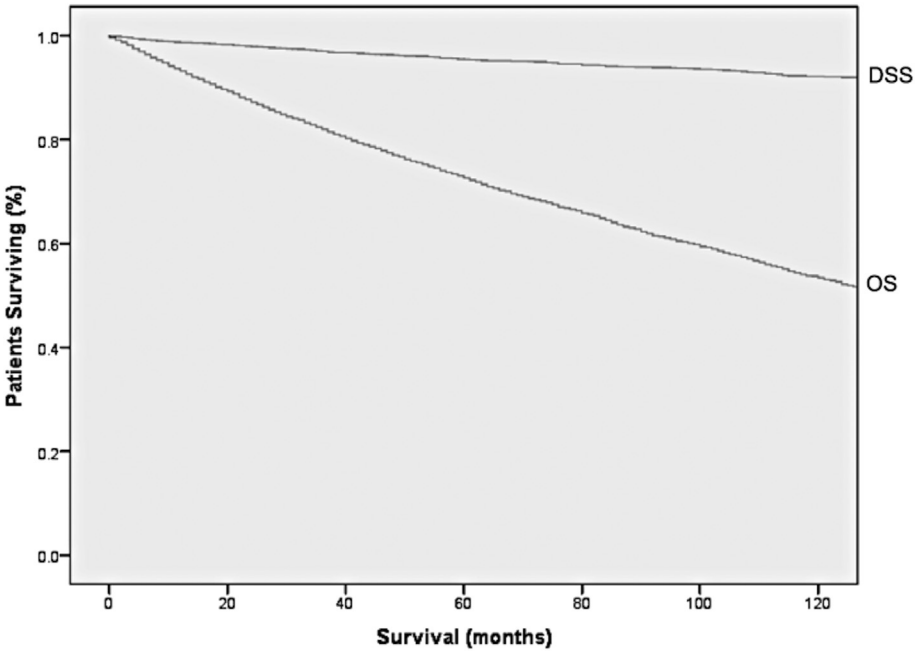

Fig. 1. Overall and disease-specific survival.

3.3. Multivariate analysis

The results of the Cox proportional hazards regression analysis are depicted in Table 2. Multivariate analysis suggested that increased OS was independently predicted by surgical resection of the tumor (hazard ratio [HR] 0.324; 95% confidence interval [CI] 0.165–0.636; $P = 0.001$) (Fig. 2), while decreased OS was predicted by older age (HR 1.051; 95% CI 1.032–1.071; $P < 0.001$), higher tumor grade (HR 1.254; 95% CI 1.001–1.572; $P = 0.049$), larger tumor size (HR 1.293; 95% CI 1.093–1.528; $P = 0.003$), and positive nodal involvement (HR 3.323; 95% CI 1.52–6.835; $P = 0.002$). Increased DSS was also independently predicted by surgical resection (HR 0.026; 95% CI 0.004–0.151; $P < 0.001$) (Fig. 2). Decreased DSS was predicted by older age (HR 1.058; 95% CI 1.001–1.118; $P = 0.046$), larger tumor size (HR 2.528; 95% CI 1.565–4.085; $P < 0.001$), and positive nodal involvement (HR 4.761; 95% CI 1.247–18.183; $P = 0.022$).

4. Discussion

This study reviewed and analyzed a large population based cancer database to determine which factors affect OS and DSS with respect to malignant cutaneous adnexal tumors (MCAT) of the head and neck. 5303 patients with MCAT of the head and neck were reviewed. The only significant patient specific factor portending a poor OS and DSS was age. Significant tumor specific factors included grade (poorer OS), tumor size (poorer OS and DSS), and nodal status (poorer OS and DSS). The only significant treatment specific factor included surgery, which portended an improved OS and DSS.

Fiver year OS and DSS rates for the entire cohort were 72.6% and 95.5%, respectively. Martinez et al. studied MCAT of the entire body with a cohort of 4032 patients. They found similar OS and DSS rates of 73% and 98%, respectively [5]. Avraham et al. looked specifically at eccrine differentiation of cutaneous adnexal cancers and they found an OS rate of 82% [6]. This suggests that certain subtypes of MCAT have a more favorable prognosis. When analyzing the data by specific histologic subtype, Avraham et al. found patients with microcystic adnexal carcinoma had an improved OS (90%) compared to patients with hidradenocarcinoma (74%) [6]. Martinez et al. also found certain histologic subtypes with improved OS, including apocrine adenocarcinoma, mucinous adenocarcinoma, and sweat duct carcinoma [5]. When breaking down our data by histologic subtype we did not find a statistical significant difference in OS and DSS. This may suggest that different MCAT sub-types do not behave differently in the head and neck.

When looking at tumor specific factors, grade, tumor size and nodal status all predicted poorer OS and DSS. The more poorly differentiated the tumor the worse the survival, which is corroborated by several studies [5,6]. Adnexal cancers spread via local invasion and through the lymphatic system. Nodal status specifically showed a 3-fold and 4-fold increased risk of all-cause and MCAT-related risk of death, respectively.

The role for sentinel lymph node biopsy is well studied in melanoma but not as well defined for other non-melanomatous lesions, including

Table 2
Multivariate Cox-regression analysis of predictors of overall survival and disease-specific survival.

Factor	Overall survival[a]	*P* value	Disease-specific survival[a]	*P* value
Race	N/A	0.664	N/A	0.435
Tumor site	N/A	0.356	N/A	0.404
Surgery	0.324 (0.165–0.636)	0.001	0.026 (0.004–0.151)	< 0.001
Radiation	0.692 (0.371–1.291)	0.247	1.198 (0.312–4.598)	0.792
Age	1.051 (1.032–1.071)	< 0.001	1.058 (1.001–1.118)	0.046
Grade	1.254 (1.001–1.572)	0.049	1.572 (0.701–3.526)	0.272
T	1.293 (1.093–1.528)	0.003	2.528 (1.565–4.085)	< 0.001
N	3.223 (1.52–6.835)	0.002	4.761 (1.247–18.183)	0.022

[a] Values are presented as hazard ratios (95% CI).

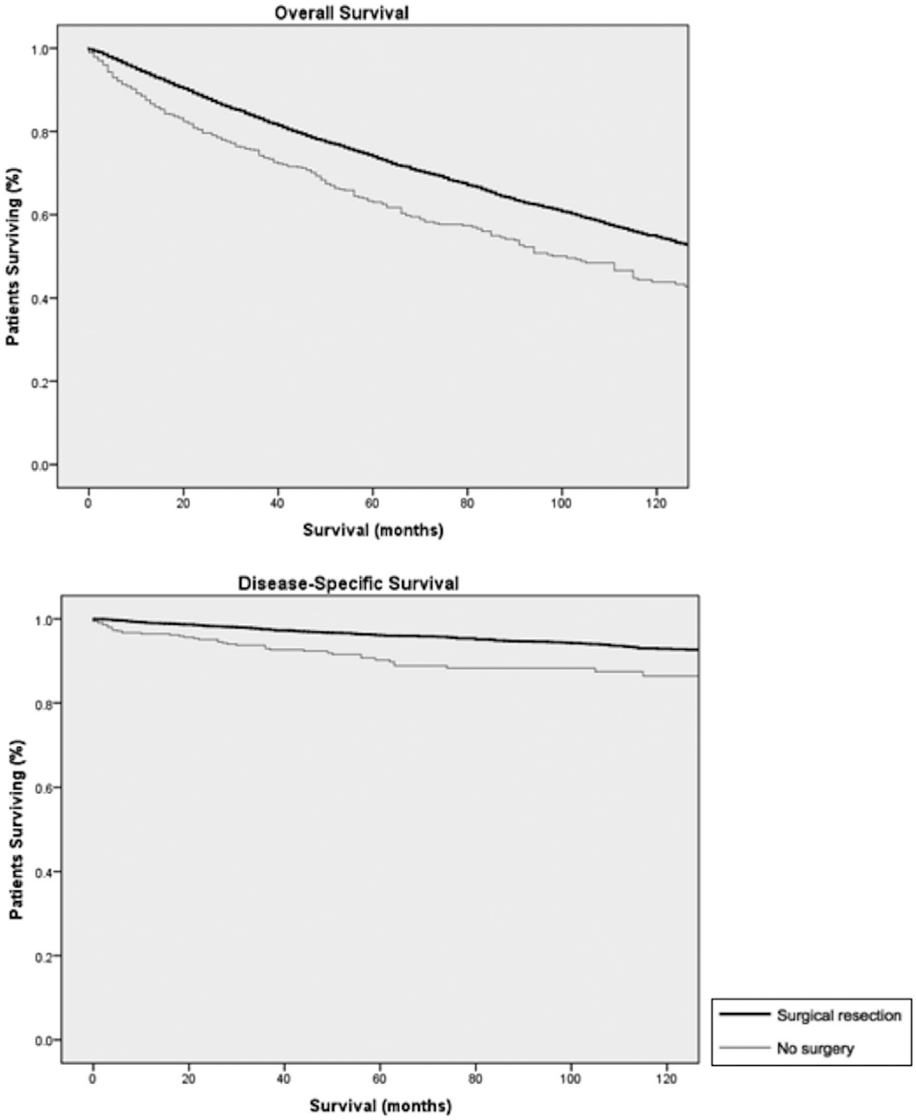

Fig. 2. Overall and disease-specific survival by surgery.

adnexal carcinomas. Knacktedt and Samie report a rate of regional nodal involvement in ocular sebaceous carcinoma (a subtype of adnexal carcinoma) between 10 and 28% [7]. This risk is less well defined in extraocular sebaceous carcinoma. Sawyer et al. recommend sentinel lymph node biopsy in extraocular sebaceous carcinoma due to risk of occult nodal metastasis [8]. Several other case series have recommended sentinel lymph node biopsy in specific subtypes of adnexal carcinoma to provide useful staging information [9,10].

Our results did not yield a significant finding when looking at metastasis. An early case series of 6 patients with apocrine carcinoma by Paties et al. revealed excellent survival even in patients with local recurrence and regional metastasis. No patient died within two years of followup [11]. Breiting et al. showed no distant metastasis in 15 cases of mucinous adenocarcinoma and no death attributable to the disease [12]. On the other hand, Martinez et al. found a 2-fold and 12-fold increased risk of all cause and MCAT related death in patients with distant metastasis, respectively [5]. The difference can be potentially explained by several factors. First, the patients presented at an average age of 69 years. The majority of patients may have passed away before reaching metastasis. Second, there is a difference in location. This study focused on head and neck adnexal cancers, where lesions are more noticeable and easily detected. This makes it easier to treat the lesions prior to metastasizing. Lesions on the trunk and extremities, on the other hand, may be more difficult to detect and thus are more prone to grow and metastasize prior to treatment.

Optimal treatment for MCAT is poorly defined in the literature, but most of the studies recommend at least primary surgical resection. Yu et al. evaluated 223 patients with sclerosing sweat duct carcinoma identified from the SEER database and they found significantly improved survival rates with surgical resection [13]. In this study surgery was the main treatment related factor to influence survival. Undergoing surgery showed a decrease in both OS and DSS. Martinez et al. showed that patients who did not undergo surgical resection had lower rates of OS and DSS [5]. Several studies have advocated for the use of primary surgery, specifically Mohs micrographic surgery. Tolkachov looked at several cases of primary adnexal cancers and found a recurrence and metastatic rate of < 10% after MOHS [14]. Chiller et al. conducted a retrospective study comparing patients with microcystic adnexal carcinoma who underwent simple excision versus Mohs. The main difference they found was in the number of procedures required to obtain clear margins. While all patients who underwent Mohs excision obtained clear margins in one stage, 30% of patients required two stages in the surgical excision group [15]. Surgical resection is generally accepted as the preferred initial method of treatment, whether by Mohs micrographic surgery or wide local excision.

The role of radiation therapy is less defined. In this study

undergoing primary radiation therapy showed no effect on survival. Martinez et al. similarly showed no effect on survival with the use of radiation [4]. In the case series by Waqas et al. looking at 11 cases with adnexal carcinomas they offered adjuvant radiation therapy only to those with close margins (< 5 mm), positive margins, and high grade histology [1]. Wang et al. performed a retrospective study looking at all cases of head and neck cutaneous adnexal cancers who received primary surgery and adjuvant radiation. They found locoregional control to be 100% and progression free survival to be 89% [16]. While there are no formal recommendations for the addition of adjuvant radiation, there seems to be a role for its addition in cases with high-grade lesions, close margins, and regional lymph node metastasis. The addition of chemotherapy is not well established in the literature.

Populations based databases are appealing because of the centralized storage of information regarding rare cancers. While one can garner significant information from these databases, they are not without limitations. The SEER database does not provide information with respect to patient comorbidities, socioeconomic status, surgical margins, presence of neck dissection, and use of neo-adjuvant and adjuvant therapies to name a few. Furthermore, limited data is captured in these databases. A major limitation was that the majority of cases did not have information on grade or TNM status. Additionally, the final pathology is not standardized and is reported by various pathologists across the country. This is not ideal when discussing specific rare histologic entities and attempting to make broad assumptions about stage with respect to survival. Future prospective studies could help elucidate whether adjuvant therapy, specifically radiation, is beneficial in improving survival rates. Furthermore, the role of sentinel lymph node biopsy in the clinically N0 neck could be reviewed to attempt to clarify its role.

5. Conclusion

This is the first study to review a large population based database for adnexal cancers confined to the head and neck. Review of the SEER database shows good 5 year over survival and disease specific survival of the rare malignant cutaneous adnexal tumors of the head and neck. Certain patient (age) and tumor specific (grade and TNM stage) factors influence survival as described in previous studies. However, the histological sub-type does not seem to affect survival in the head and neck as described in other studies focusing on the whole body. Lastly, the data shows surgery leads to improved survival while radiation has no effect.

Conflict of interest

DJ: No conflict of interest. No financial disclosures.
AG: No conflict of interest. No financial disclosures.
SAK: No conflict of interest. No financial disclosures.
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