Rare Tumors Through the Looking Glass

An Examination of Malignant Cutaneous Adnexal Tumors

Steve R. Martinez, MD, MAS; Keira L. Barr, MD; Robert J. Canter, MD

Objective: To identify prognostic factors related to malignant cutaneous adnexal tumors.

Design: Population-based study using the Surveillance, Epidemiology, and End Results database from January 1, 1988, through December 31, 2006.

Setting: Seventeen population-based cancer registries.

Participants: A total of 4032 patients with malignant cutaneous adnexal tumors.

Main Outcome Measures: overall survival (OS) and disease-specific survival (DSS).

Results: Ten-year OS and DSS rates were 54% and 97%, respectively. Unfavorable factors for OS were increasing age (hazard ratio [HR] 1.08; 95% confidence interval [CI], 1.07-1.09; P < .001), distant metastases (3.26; 2.34-4.53; P < .001), no surgical procedure (1.27; 1.01-1.59; P = .04), grade IV tumors (1.97; 1.18-3.28; P = .03), and T3 tumors (1.37; 1.00-1.87; P = .04). Favorable factors for OS were a wide surgical excision (HR, 0.78; 95% CI, 0.68-0.89; P < .001), female sex (0.73; 0.65-0.82; P < .001), malignant eccrine spiradenoma (0.72; 0.53-0.99; P = .04), and histologic findings of sweat duct carcinoma (0.63; 0.44-0.90; P = .01). Unfavorable factors for DSS included N1 status (HR, 6.77; 95% CI, 2.11-21.68; P < .001), distant metastases (12.24; 6.03-24.85; P < .001), histologic findings of malignant eccrine spiradenoma (5.62; 1.25-25.34; P = .02), and no surgical procedure (2.81; 1.09-7.23; P = .03). Favorable factors for DSS included female sex (HR, 0.52; 95% CI, 0.30-0.91; P = .02).

Conclusions: Five-year survival among patients with malignant cutaneous adnexal tumors is good in the absence of distant metastases. Wide resection may be preferable to less aggressive excision. The prognostic importance of lymph node metastases warrants consideration of lymph node basin staging.

Arch Dermatol. 2011;147(9):1058-1062

MALIGNANT CUTANEOUS adnexal tumors (MCATs) are a rare and heterogeneous group of malignant neoplasms. The differentiation of these tumors may be from eccrine, apocrine, sebaceous, or ceruminous glands within the skin or follicular cells. The incidence of these tumors is increasing, but information regarding prognostic factors and long-term outcome is limited and based predominantly on small case series and single-institution reports.

Our goal was to assess the importance of patient-, tumor-, and treatment-specific factors on rates of overall survival (OS) and disease-specific survival (DSS) using a large patient sample derived from a population-based database.

METHODS

The Surveillance, Epidemiology, and End Results (SEER) database of the National Cancer Institute was used to identify all patients with invasive cutaneous sweat gland or adnexal tumors diagnosed from January 1, 1988, through December 31, 2006. SEER collects cancer incidence and survival data from 17 population-based cancer registries representing 26% of the US population. The registries used and their attributes and limitations have been reported previously.2,3

All cases of cutaneous sweat gland tumors (codes 8390, 8400-8403, 8407-8410, 8413, 8420, 8430, and 8480-8481 from the International Classification of Diseases for Oncology, Third Edition) diagnosed from 1988 through 2006 were eligible for study inclusion. The original sample included 4049 patients with MCAT. Patients were excluded for lack of histologic confirmation of their diagnosis (n = 4) or if the diagnosis of cutaneous sweat gland tumor was made at autopsy (n = 13). The final sample included 4032 patients.

Survival was calculated as the number of completed months between the date of diagnosis and whichever of the following occurred first: date of death, date last known to be alive, or December 31, 2006. The survival end points for the present study were OS and DSS. Patients who were lost to follow-up or survived beyond December 31, 2006, were censored.
as censored observations. For the determination of DSS, patients who died of other nonneoplastic skin cancer, excluding melanoma, were considered to have died of cutaneous sweat gland or adnexal tumors; patients dying of other causes were censored.

Univariate estimates of survival were made for known and suspected prognostic variables using the Kaplan-Meier method. Survival curves were compared using the log-rank test. Variables subjected to univariate analysis included patient age (median split, ≤70 vs >70 years), sex, race or ethnicity (Asian, black, Hispanic, native American, unknown, or white), tumor size (American Joint Committee on Cancer [AJCC] T stage), lymph node status (AJCC N stage), presence of distant metastases (AJCC M stage), location of the primary tumor (head and neck, trunk, upper extremity, lower extremity, overlapping areas, or unknown), histologic confirmation of the tumor (apocrine adenoacanthoma, ceruminous adenoacanthoma, eccrine adenoacanthoma, malignant eccrine poroma, malignant eccrine spiradenoma, mucinous adenoacanthoma, mucoepidermoid carcinoma, malignant nodular hidradenoma, sebaceous adenoacanthoma, malignant skin appendage tumor not otherwise specified, sweat duct carcinoma, or sweat gland adenocarcinoma), histologic grade, type of surgical procedure, and use of radiotherapy (yes, no, or unknown). We included factors found to be significant predictors of OS, DSS, or both in our multivariate Cox proportional hazards regression models. Additional multivariate models were constructed that excluded patients with distant metastases to avoid any bias this may have had on rates of OS or DSS. In addition, because many clinicians would choose not to surgically treat patients with systemic disease, this subgroup analysis allowed us to more closely evaluate the role of treatment-related factors on survival. Multivariate models included age as a continuous variable. For categorical and ordinal variables, the most prevalent or clinically relevant variable served as the referent group. All analyses were conducted using commercially available statistical software (Stata, version 11; StataCorp, College Station, Texas).

A summary of the patient, tumor, and treatment characteristics of the 4032 patients meeting entry criteria is provided in Table 1. Briefly, the median age of the study patients was 70 years, and 53.5% were male. Most of the patients were white (78.0%). Although patients of every AJCC T stage were represented, 56.6% had no reported T stage. Similarly, most of the patients did not have a histopathologic nodal evaluation (71.3%). Of those undergoing histopathologic nodal evaluations, only 7.4% demonstrated lymph node metastases. Distant metastases were rare, with 87.8% of patients demonstrating no evidence of metastatic disease at initial diagnosis. Tumor grade was unknown for 76.4% of patients. The cutaneous sweat gland and adnexal tumors in this study showed a predilection for the skin on the head and neck (65.2%). This was followed, in order of decreasing prevalence, by tumors on the trunk (16.8%), upper extremity (9.6%), and lower extremity (7.2%). Although we considered a wide range of histologic tumor findings under the rubric of MCAT, most of the tumors (57.3%) were classified as sebaceous adenocarcinoma (36.1%) or skin appendage tumors (21.4%). Only 8.3% of patients did not receive surgical treatment. Local excisions and wide excisions accounted for the procedures received by 87.4% of patients. Few patients (5.8%) received adjuvant radiotherapy.

UNIVARIATE ANALYSIS OF OS AND DSS

The median OS for the entire cohort was 145 months (12.1 years); however, the median DSS (the point at which half the patients are dead owing to their disease) was not yet reached. Five- and 10-year OS rates were 73% and 54%, respectively. Five- and 10-year DSS rates were similar, at 98% and 97%, respectively. Univariate analysis of factors predictive of OS and DSS are detailed in Table 1. Univariate OS differences were noted for age, T stage, N stage, M stage, histologic tumor confirmation, histologic grade, type of surgical procedure, and use of radiotherapy (all P < .001); sex (P = .04); and race/ethnicity (P = .008). Univariate DSS differences were noted for T stage, N stage, M stage, tumor site, histologic grade, type of surgical procedure, and use of radiotherapy (all P < .001); sex (P = .02); and histologic tumor confirmation (P = .01).

MULTIVARIATE ANALYSIS FOR ALL PATIENTS

On multivariate analysis, increased risk of death due to all causes (Table 2) was predicted by increasing age (hazard ratio [HR], 1.08; 95% confidence interval [CI], 1.07-1.09; P < .001), distant metastases (3.26; 2.34-4.53; P < .001), no surgical procedure (1.27; 1.01-1.59; P = .04), grade IV tumors (1.97; 1.18-3.28; P = .009), lymph node metastases (2.19; 1.40-3.43; P = .001), and T3 tumors (1.37; 1.00-1.87; P = .04). Decreased risk of death from all causes was predicted by a wide surgical excision (HR, 0.78; 95% CI, 0.68-0.89; P < .001), female sex (0.73; 0.65-0.82; P < .001), and histologic confirmation of mucinous adenoacanthoma (0.72; 0.53-0.99; P = .04) and sweat duct carcinoma (0.63; 0.44-0.90; P = .01).

On multivariate analysis, increased risk of disease-related death (Table 2) was predicted by N1 status (HR, 6.77; 95% CI, 2.11-21.68; P < .001), distant metastases (12.24; 6.03-24.85; P < .001), histologic confirmation of malignant eccrine spiradenoma (5.62; 1.25-25.34; P = .02), patients not undergoing surgical procedures (2.81; 1.09-7.23; P = .03), and patients whose radiation treatment status was unknown (5.58; 1.63-19.06; P = .006). Decreased risk of MCAT-related death was predicted only by female sex (HR, 0.52; 95% CI, 0.30-0.91; P = .02).

MULTIVARIATE ANALYSIS EXCLUDING PATIENTS WITH DISTANT METASTASES

We repeated these multivariate analyses after excluding patients with distant metastases. Increased risk of death from all causes was predicted by increasing age (HR, 1.08; 95% CI, 1.08-1.09; P < .001), grade III tumors (1.43; 1.02-2.01; P = .04), and positive lymph node status (2.28; 1.36-3.82; P = .002). Decreased risk of death from all causes was predicted by a wide surgical excision (HR, 0.80; 95% CI, 0.70-0.91; P = .001), female sex (0.74; 0.65-0.84; P < .001), and histologic confirmation of apocrine adenocarcinoma (0.61; 0.41-0.89; P = .01), mucinous adenocarcinoma (0.71; 0.51-0.97; P = .03), and sweat duct carcinoma (0.65; 0.45-0.92; P = .02).
Increased risk of MCAT-related death was predicted by increasing age (HR, 1.03; 95% CI, 1.00-1.05; \( P = .02 \)), unevaluable or unknown distant metastasis stage (3.11; 1.33-7.27; \( P = .009 \)), unknown use of radiotherapy (5.11; 1.38-18.92; \( P = .02 \)), positive lymph node status (21.10; 3.91-113.96; \( P < .001 \)), and histologic confirmation of malignant nodular hidradenoma (3.45; 1.20-9.94; \( P = .02 \)) and sweat gland adenocarcinoma (2.69; 1.14-6.32; \( P = .02 \)). Decreased risk of disease-related death was predicted only by female sex (HR, 0.49; 95% CI, 0.26-0.92; \( P = .03 \)).

**COMMENT**

We have analyzed a national, population-based database to assess the importance of patient-, tumor-, and treatment-specific factors on rates of OS and DSS. Five-year OS and DSS rates for our study population with MCAT were 73% and 98%, respectively. Among the entire cohort, significant patient factors in our analysis included increasing age (poorer OS) and female sex (improved OS and DSS). Predictive tumor-specific factors noted in our study included distant metastases (poorer OS and DSS), nodal metastases (poorer DSS), and histologic confirmation of apocrine adenocarcinoma (improved OS), mucinous adenocarcinoma (improved OS), sweat duct carcinoma (improved OS), and malignant eccrine spiradenoma (poorer DSS). Patients with distant metastases had a greater than 2-fold increased risk of death from all causes and a greater than 12-fold increased risk of MCAT-related death. Significant treatment-related factors included a wide surgical excision (improved OS), no surgical procedure (poorer DSS), and unknown use of radiotherapy (poorer DSS).
Five-year rates of OS and DSS for our study population with MCAT were 73% and 98%, respectively. Blake et al.1 examined a similar population of 1801 patients with cutaneous appendageal carcinoma identified in SEER to assess incidence rates and OD rates over time. They reported a relative 5-year OS rate of 96.5% for patients with cutaneous appendageal carcinoma, which differs significantly from our 5-year OS rate of 73%. We attribute this difference to the fact that Blake et al.1 used relative survival rates, which is defined as the ratio of the proportion of observed survivors in a cohort of patients to the proportion of expected survivors in a comparable cohort of the general population, whereas we used raw unadjusted OS rates. In addition, Blake et al. included only black and white patients in their analysis, whereas our study was open to all races and ethnicities.

Distant metastases predicted poorer OS and DSS. Patients with distant metastases had a greater than 2-fold and 12-fold increased risk of all-cause and MCAT-related death, respectively. Nodal metastases were an important determinant of DSS but did not influence OS unless patients with distant metastases were excluded from the model. The histologic tumor findings were an important factor influencing survival in the current analysis. Histologic confirmation of apocrine adenocarcinoma, mucinous adenocarcinoma, and sweat duct carcinoma demonstrated decreased risks of death from any cause, but no histologic finding decreased death from MCAT. Eccrine spiradenoma was associated with poorer DSS. Paties et al.4 reported on a series of 6 patients with apocrine carcinoma of the skin and concluded that, even among patients with local recurrences and regional metastases, survival was excellent, with no patient dying of cancer despite a minimum of 2 years' follow-up. Breiting et al.5 identified 15 cases of mucinous carcinoma in their population-based study, with all but 1 occurring in the head or neck. Although a single incidence of local recurrence was documented, no distant metastases were seen, and no death was attributed to mucinous adenocarcinoma. In a previously reported meta-analysis, Martinez and Young6 reported a low mortality rate for mucinous adenocarcinoma. Similarly, Yu et al.7 evaluated sclerosing sweat duct carcinoma in 223 patients identified in SEER and found only 1 case with distant metastases, a 1% rate of regional metastases, and a 10-year OS of 86%. These are consistent with our current findings. Malignant ec-
crine spiradenoma has been reported only in limited case reports.8-15 Tanese et al16 presented a case of malignant eccrine spiradenoma and reviewed the 84 cases previously published and found an 18% mortality rate, presumably due to a relatively high metastasis rate of 33%. Although our sample size of malignant eccrine spiradenoma cases was small (n = 47), our mortality rate of 21% is consistent with these previous studies.

Several treatment-related factors were found to influence survival in our study. Patients undergoing a wide surgical excision had superior rates of OS relative to those undergoing more local excisions, but no difference in DSS was noted. Conversely, patients who did not undergo surgical resection had poorer DSS but not OS. These findings indicate that surgical excision is a necessary aspect of treatment, which optimally includes a wide resection. Only 32 patients in our series had unknown radiotherapy status, but this was found to predict poorer DSS. The reasons for this are unknown. It is possible that these patients had worse disease than their counterparts and therefore did not recover from the procedure in time to receive planned radiotherapy.

The rarity of these tumors precludes analysis via clinical trials, which makes the use of population-based data appealing. Such data have limitations, however. Briefly, SEER does not provide information regarding patient comorbidities, adequacy of surgical intervention (including margin status), use of systemic adjuvant or neoadjuvant therapy, socioeconomic status, or insurance status. Even among data fields included within SEER, data may be missing or incomplete. In our study, missing or incomplete data were analyzed as a separate category so that we could estimate the effects of this missing data on survival outcomes. Most important, cases entered into SEER do not undergo centralized pathologic review. The pathologic categories reported in our study represent those included in SEER as determined by the examining pathologist.

Clinically, our data emphasize that 5-year survival among patients with MCAT is good, particularly in the absence of distant metastases. Although patient-specific factors (such as age and sex) and tumor-specific factors (such as histologic findings) may influence mortality, these factors are static and not controlled by the treating physician. Our data indicate that, in the absence of distant metastases, surgical treatment of disease is warranted, and wide resection may be preferable to less aggressive forms of surgical intervention. In the absence of distant metastasis, lymph node metastasis was a significant predictor of survival. Therefore, lymph node staging should be considered for patients with MCATs.

Accepted for Publication: March 7, 2011.

Correspondence: Steve R. Martinez, MD, MAS, Division of Surgical Oncology, Department of Surgery, UC Davis Cancer Center, 4501 X St, Ste 3010, Sacramento, CA 95817 (steve.martinez@ucdmc.ucdavis.edu).

Author Contributions: Dr Martinez had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Martinez and Canter. Acquisition of data: Martinez and Canter. Analysis and interpretation of data: Martinez, Barr, and Canter. Drafting of the manuscript: Martinez. Critical revision of the manuscript for important intellectual content: Martinez, Barr, and Canter. Statistical analysis: Martinez and Canter. Obtained funding: Martinez. Administrative, technical, or material support: Barr and Canter. Study supervision: Martinez.

Financial Disclosure: None reported.

Funding/Support: This study was supported in part by grant UL1 RR024146 from the National Center for Research Resources, a component of the National Institutes of Health (NIH), and the NIH Roadmap for Medical Research.

Role of the Sponsors: The sponsors had no role in the design or conduct of the study; in the collection, analysis, or interpretation of data; or in the preparation, review, or approval of the manuscript.

Previous Presentation: This study was presented in part at the Sixth Annual Academic Surgical Congress; February 1, 2011; Huntington Beach, California.