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ORIGINAL ARTICLE

Behavior of Cutaneous Adnexal Malignancies: a Single Institution Experience

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Abstract

Cutaneous adnexal malignancies are biologically and pathologically diverse, and associated with a range of clinical outcomes. Given their rarity, the prognosis and optimal treatment of these neoplasms remains unclear. A single institution database from a tertiary care cancer center of patients treated for malignant cutaneous adnexal tumors was retrospectively analyzed. Clinicopathologic variables and outcome measures were analyzed in patients undergoing wide excision with or without sentinel node biopsy. 103 patients were analyzed; the majority of tumors were of eccrine sweat gland derivation ($n = 69$, 70%), and these exhibited a higher rate of nodal involvement and overall worse outcome. Sixteen patients (16%) demonstrated nodal metastasis, which included 10 (10%) with nodal disease at presentation and 6 who developed nodal metastasis during followup. 20 patients underwent sentinel node biopsy, and 2 (10%) had a positive sentinel node. 62% of nodal metastases occurred in patients with porocarcinoma. Seven patients died of disease (7%) with a median time from diagnosis to death of 48 months (range, 10–174). After a median follow up of 44.7 months, age > 70 years and larger tumor size were significantly associated with worse overall survival. Adnexal malignancies are rare tumors, and there is a paucity of information to guide the clinician in determining optimum surgical and medical treatment. Tumors of eccrine derivation, especially porocarcinomas, have a high risk of nodal involvement and may be considered for sentinel node biopsy.

Keywords Cutaneous adnexal neoplasms · Eccrine carcinoma · Sentinel lymph node biopsy

Introduction

Cutaneous adnexal malignancies (CAMs) represent a heterogeneous group of skin carcinomas that exhibit differentiation towards pilosebaceous or sweat gland (eccrine or apocrine) phenotypes. The American Joint Committee on Cancer staging system incorporates CAMs under the non-melanoma skin cancer umbrella, a group of lesions dominated by the far more common cutaneous squamous and basal cell carcinomas [1, 2]. The rarity of CAMs is reflected in United States Surveillance, Epidemiology, and End Results (SEER) data showing an age-standardized incidence rate of 5.1 cases per million persons per year [3] and an incidence of 0.05% [4]. Similarly, cancer-registry-based studies in Europe have shown age-standardized incidence rates ranging from 2.1–5.3 cases per million per year [5, 6]. An increase in incidence of up to 150% was noted in several studies, likely reflecting increased awareness and improved identification of CAMs [3, 4, 6].

The role of nodal evaluation in patients with CAM's is controversial; Martinez *et al.* showed worse disease-specific and overall survival in patients with positive lymph nodes and no distant metastases [4]. And while sentinel lymph node biopsy (SLNB) is routinely performed for melanoma, its role in other cutaneous malignancies is still being explored [7].

Jonathan S. Zager and Jane L. Messina are co-senior authors with equal contribution.

Synopsis
Cutaneous adnexal malignancies, which include eccrine and apocrine carcinomas, are rare skin neoplasms. Their clinical behavior as well as the role of sentinel lymph node biopsy in their staging and management remain poorly understood. This retrospective outcome addresses clinical behavior and prognosis in a large, retrospective well-curated single institution series.

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Studies evaluating SLNB in CAMs have shown utility in detecting occult lymph node metastases [8, 9], but the impact on survival is unclear. Since information regarding clinical behavior and management of CAMs is currently insufficient to establish treatment recommendations, we undertook a retrospective study of our institutional experience in the management of these tumors.

Methods

Clinicopathologic Features

After Institutional Review Board approval, pathology records were queried by diagnosis for patients with CAMs diagnosed and/or treated at our institution from 1999 to 2015. Clinicopathologic features abstracted included demographics, history of other cutaneous malignancies, tumor anatomical location, surgical procedure(s), disease status and last known date of follow-up. Patients were excluded if tumors were in sites where histologically identical malignancies occur (i.e. apocrine carcinoma of breast, adenoid cystic carcinoma adjacent to salivary gland).

All cases were reviewed by a board-certified dermatopathologist, classified according to their histologic differentiation–apocrine, eccrine, pilar or sebaceous–and then into specific histopathologic entities when possible. Tumor depth using Breslow's technique [10], diameter, perineural and lymphovascular invasion, and tumor grade (Broder's classification [11]) were assessed. Diameter was measured microscopically if possible, and grossly or clinically if not; the largest of these measurements was used as the final tumor size. Surgical treatment, margin status, and adjuvant therapy including radiation, chemotherapy and immunotherapy were recorded. Patients underwent SLNB at the time of primary wide excision, with patient selection for SLNB at the surgeon's discretion and after multidisciplinary tumor board review. SLNB was performed as previously described [12, 13]. Completion lymph node dissection (CLND) or therapeutic lymph node dissection (TLND) were performed in patients with a positive SLNB or clinically apparent lymph node metastases at presentation or after recurrence, respectively.

Statistical Analysis

All statistical analyses were performed using SAS (version 9.2, SAS Institute Inc., Cary, NC), with a two-sided p-value ≤ 0.05 considered significant. Categorical variables were compared with Fisher's exact tests; Kaplan-Meier plots were used for survival analyses with log-rank tests for comparison.

Results

Patient Demographics and Clinicopathologic Features

103 patients were identified, (Table 1). Males predominated ($n = 63$, 61%); the average age at diagnosis was 61 (range 23–91 years). Racial distribution was available in 100 patients; the majority were white ($n = 89$), followed by African-American ($n = 7$), Hispanic ($n = 3$) and Asian ($n = 1$). Thirty-six of 96 patients (37%) with available information had a prior history of cutaneous malignancy: 28 (78%) non-melanoma skin cancer, 3 (8%) melanoma, 4 (11%) with both melanoma and at least one non-melanoma skin cancer, and 1 (3%) with dermatofibrosarcoma protuberans. The anatomic distribution of the 103 CAM's was as follows: head and neck 55%, extremities 29%, and trunk 16% (Table 2). In the head and neck, the scalp was most frequently affected (37%). The 30 extremity tumors occurred in acral regions 60% of the time, in non-acral regions in 39%, and 1 in an unspecified site. Of the 17 truncal tumors, the most frequent location was the back (42%), followed by the axilla (29%).

The majority of adnexal malignancies showed eccrine differentiation ($n = 69$, 70%), followed by sebaceous ($n = 20$, 19%) and apocrine ($n = 11$, 18%) derivation (Tables 2 and 3). One case was classified as follicular/pilar (pilomatrical carcinoma), and 2 cases where unequivocal classification was not possible were recorded as adnexal carcinoma, not otherwise specified (NOS). Three extraocular sebaceous carcinoma patients fulfilled criteria for Muir-Torre syndrome [14]. There was a predilection of certain tumor subtypes for characteristic anatomical regions; for instance, most MACs ($n = 13$, 76%) were found on the face or scalp. Tumor grading was available in 62 lesions: 35 (56%) were well differentiated, 6 (10%) moderately differentiated, and 21 (34%) poorly differentiated. Measurement data was available in 69 tumors; the median tumor dimension was 1.0 cm, with 30% of tumors ≥2 cm. The median tumor depth was 8 mm (range 1–22 mm) (Table 1).

Therapeutic Interventions, Sentinel Lymph Node Biopsy and Regional Nodal Disease

All patients were treated with wide excision with margins of 1 to 2 cm, based on surgeon discretion taking into consideration cosmetic/anatomical/functional factors. Twenty patients (19%) underwent SLNB, and 2 (10%) had a positive sentinel node (Table 2). The two patients with a positive SLNB had MAC and apocrine carcinoma. One of these patients underwent CLND and had no further positive lymph nodes; CLND was not performed on the second patient because he died of a myocardial infarct in the immediate post-operative period. Eight patients (8%) presented with regional nodal disease at diagnosis and underwent TLND. Six of these 8 patients (75%) had porocarcinoma, and 2 (25%) had apocrine carcinoma;

Table 1 Demographic and clinicopathologic features of 103 patients with CAMs

Gender ($n = 103$)	
Male	63 (61%)
Female	40 (39%)
Race ($n = 100$)	
White	89 (89%)
African-American	7 (7%)
Hispanic	3 (3%)
Asian	1 (1%)
Mean age at diagnosis (Range) ($n = 103$)	61 (23–91)
History of additional cutaneous malignancy ($n = 96$)	
Yes	36 (37%)
NMSC	*28 (78%)*
Melanoma	*3 (8%)*
Both	*4 (11%)*
Other	*1*[a] *(3%)*
No	60 (63%)
Median follow up (Range) ($n = 103$)	1.16 Years (0.01–14.48)
Histologic subtype ($n = 103$)	
Eccrine	69 (70%)
Apocrine	20 (19%)
Sebaceous	11 (8%)
Pilar	1 (1%)
Adnexal, NOS	2 (2%)
Anatomic location ($n = 103$)	
Head and Neck	56 (55%)
Scalp	*21 (37%)*
Periocular	*9 (16%)*
Cheeks	*8 (15%)*
Nasolabial	*4 (7%)*
Other	*14 (25%)*
Extremities	30 (29%)
Non-Acral	*18 (60%)*
Acral	*11 (39%)*
NOS	*1 (1%)*
Trunk	17 (16%)
Back	*7 (42%)*
Axilla	*5 (29%)*
Other	*5 (29%)*
Tumor Size	
Greatest measurement ($n = 69$)*	
Median tumor dimension (range) (in cm)	1.0 (0.1–12)
≥ 2 cm	*21 (30%)*
< 2 cm	*48 (70%)*
Microscopic Depth ($n = 49$)	
Median (range) (in mm)	8 (1–22)
≥ 6 mm	*29 (59%)*
< 6 mm	*20 (41%)*
Perineural invasion and lymphovascular invasion ($n = 102$)	
Perineural Invasion	
Identified	19 (19%)
Not Identified	83 (81%)
Lymphovascular Invasion	
Identified	5 (5%)
Not Identified	97 (95%)

The italicized percentages represent the proportion of overall patients within each category belonging to that subset

[a] Dermatofibrosarcoma protuberans. *Measurements include depth (26%) and width (74%) obtained microscopically in 52 cases (75%), grossly in 10 cases (15%) and clinically in 7 cases (10%)

dissections contained a median of 4 positive nodes (range 1–6). Six patients (6%) developed regional nodal disease during followup, with median time to disease development of 12 months (8–67 months).

A total of 18 patients received nonsurgical therapy. Fifteen received radiotherapy either locally due to positive margins on their wide local excision specimens ($n = 10$) or regionally due to lymph node positivity/recurrence ($n = 5$). Perineural invasion was identified in 3 of the 10 tumors that received local radiotherapy. In addition, 4 of 15 patients treated with radiotherapy also received cytotoxic chemotherapy and/or interferon either due to systemic involvement ($n = 2$, both died of disease [DOD]) or for treatment of persistent local disease ($n = 2$). Finally, 3 patients received only cytotoxic chemotherapy and/or interferon due to regional nodal disease ($n = 2$) or distant metastases ($n = 1$, DOD).

Clinicopathologic Parameters Associated with Recurrence and Survival

Followup information was available in 93 patients. At a median follow-up interval of 44.7 months (range, 0.1–174 months), in 10 patients (9%) had local recurrence and 6 patients (6%) had regional recurrence. The median time from initial surgery to recurrence was 11.5 months (range, 1–78 months). Four of the ten patients with local recurrence had positive margins on the initial excision; three of these were head and neck tumors. Porocarcinoma and MAC together accounted for 60% of the local recurrences (Table 3). Recurrent tumors were predominantly in the head and neck (80%). Measurements of the primary were available on 7 of the 10 recurrent cases, with an average tumor dimension of 2.3 cm (range, 0.2–5.0 cm). Neither tumor depth, diameter, perineural nor lymphovascular invasion were significantly predictive of recurrence. Regional recurrence occurred in patients with porocarcinoma (71%) and sebaceous carcinoma (29%); these patients had undergone wide excision but not SLNB at the time of initial diagnosis. There were no regional recurrences in patients with negative SLN.

Twenty patients died (10-year OS of 80%); 13 of unrelated causes and 7 due to disease. The median time from diagnosis to death was 48 months (range, 10–174 months), corresponding to a 10-year DSS of 93%. All patients who died of disease first experienced a local recurrence. Distant metastases to visceral organs and bone were present in 5 patients who died of disease, 4 with eccrine tumors (3 porocarcinomas and 1 malignant cylindroma) and 1 with apocrine carcinoma, whereas the remaining 2 patients (1 periocular sebaceous carcinoma and 1 porocarcinoma) succumbed to direct invasion of the tumor into the brain.

Age > 70 was significantly predictive of worse overall survival ($p = 0.0086$). Patients with a positive SLNB, as well as those with clinically positive nodes, were significantly more likely to exhibit recurrence than node-negative patients ($p = 0.0006$ and $p < 0.0001$, respectively). Tumor dimension >2 cm significantly predicted worse overall survival ($p = 0.044$) (Fig. 1), but not tumor depth or tumor grade. SLNB

Table 2 Lineage of differentiation related to lymph node positivity

Lineage of differentation and tumor subtypes ($n = 103$)		+SLN/pts. undergoing SLNB $n = 2/20$	Clinical + LN at presentation $n = 8$	Pts. with synchronous nodal disease $n = 10$	Pts. with metachronous nodal disease $n = 6$
Eccrine	69 (70%)	1/15	6	6	4
Porocarcinoma	28 (40%)	0/5	6	6	4
Microcystic adnexal carcinoma	17 (25%)	1/3	–	1	–
Eccrine carcinoma NOS	7 (10%)	0/2	–	–	–
Aggressive digital papillary adenoca.	6 (9%)	0/3	–	–	–
Others	11 (16%)	0/2	–	–	–
Sebaceous	20 (19%)	0/1	0	0	2
Extraocular sebaceous ca.	13 (65%)	–	–	–	2
Periocular sebaceous ca.	7 (35%)	0/1	–	–	–
Apocrine	11 (8%)	1/3	2	3	0
Apocrine carcinoma	10 (91%)	1/3	2	3	–
Apocrine cribriform carcinoma	1 (9%)	–	–	–	–
Pilar	1 (1%)	0	0	0	0
Pilomatrical carcinoma			–		
Adnexal NOS	2 (2%)	0/1	0	0	0

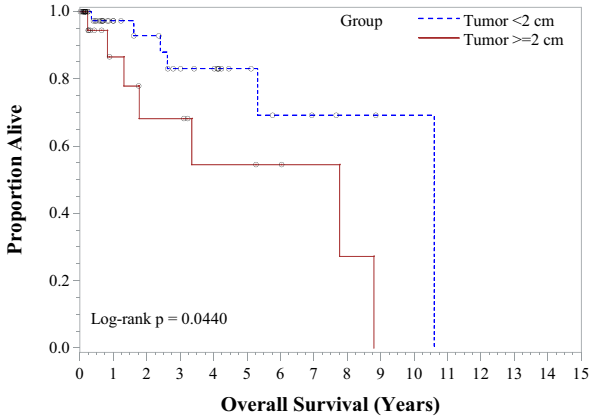
Abbreviations: *SLN* sentinel lymph node, *SLNB* sentinel lymph node biopsy, *LN* lymph node, *NOS* not otherwise specified, *adenoca* adenocarcinoma, *ca* carcinoma

Table 3 Lineage of differentiation related to clinical outcome

Lineage of differentiation and tumor subtypes ($n = 103$)		Patients w/local recurrence ($n = 10$)	Patients w/regional recurrence ($n = 6$)	DOD ($n = 7$)
Eccrine	69 (70%)	9	0	5
Porocarcinoma	28 (40%)	3	4	4
Microcystic adnexal carcinoma	17 (25%)	3	0	0
Eccrine carcinoma NOS	7 (10%)	1	0	0
Aggressive papillary digital adenoca	6 (9%)	1	0	0
Others	11 (16%)	1	0	1[a]
Sebaceous	20 (19%)	1	2	1
Extraocular sebaceous carcinoma	13 (65%)	0	2	0
Periocular sebaceous carcinoma	7 (35%)	1	0	1
Apocrine	11 (8%)	0	0	1
Apocrine carcinoma	10 (91%)	0	0	1
Apocrine cribriform carcinoma	1 (9%)	–	–	–
Pilar	1 (1%)	–	–	–
Pilomatrical carcinoma				
Adnexal NOS	2 (2%)	–	–	–

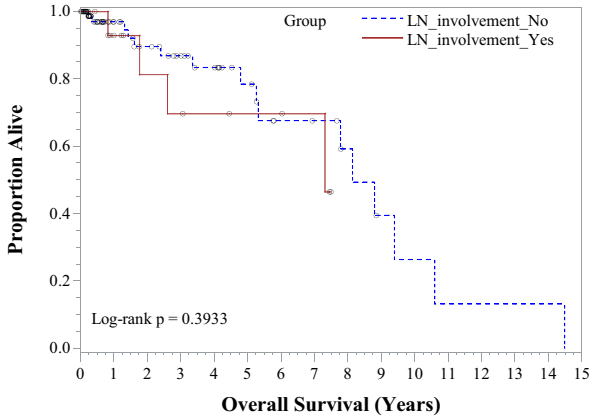
Abbreviations: *Adenoca* Adenocarcinoma, *NOS* No otherwise specified, *w/* with, *DOD* dead of disease

[a] malignant cylindroma



Group	N	Event	Censored	Median OS_time (95% CI)
Tumor <2 cm	48	6 (13%)	42 (88%)	10.6 (5.3, 10.6)
Tumor >=2 cm	21	7 (33%)	14 (67%)	7.8 (1.3, 8.8)

Fig. 1 Tumor size is related to overall survival



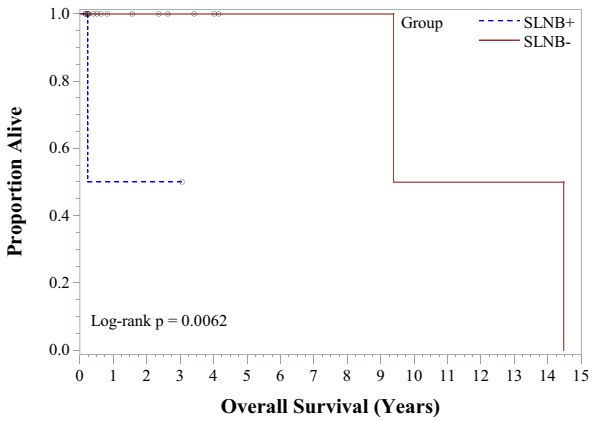
Group	N	Event	Censored	Median OS_time (95% CI)
LN_involvement_No	87	16 (18%)	71 (82%)	8.1 (5.3, 10.6)
LN_involvement_Yes	16	4 (25%)	12 (75%)	7.3 (1.8, NA)

Fig. 3 Relationship of any nodal involvement to overall survival

positivity ($p = 0.0062$) (Fig. 2) but not overall lymph node positivity ($p = 0.393$) (Fig. 3) was predictive of overall survival. The two deaths in patients not undergoing SLNB were not related to the CAM.

Discussion

CAMs are histologically diverse and extremely rare. Disagreement in histologic classification systems, heterogeneous diagnostic terminology, and frequent histologic and immunohistochemical overlap hamper uniform data analysis and clear delineation of clinicopathologic entities. Although an exhaustive review of diagnostic controversies is beyond the scope of this work, to achieve consistency in diagnosis, any study addressing the clinicopathologic behavior of CAMs should ideally include a centralized pathology review of the cases, which is lacking in most large series. In the current study, the lesions were classified by one of the two board-certified dermatopathologists at our institution, either alone or in consensus diagnosis. All treatment was carried out after multidisciplinary tumor board presentation and consensus.



Group	N	Event	Censored	Median OS_time (95% CI)
SLNB+	2	1 (50%)	1 (50%)	NA (0.2, NA)
SLNB-	18	2 (11%)	16 (89%)	11.9 (9.4, 14.5)

Fig. 2 Relationship of SLN involvement to overall survival

Indeed, the four largest series of CAMs are from SEER-related [3, 4] and European studies [5, 6], and all lacked centralized pathology review. These studies reported overall favorable survival similar to our patients. A large SEER-based study of 1801 patients reported a five-year relative survival rate (RSR) of 96.4% [3]. Relative survival, 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, may be the most accurate reflection of survival for this disease, which typically affects older individuals who have a significant portion of deaths from other causes. This was the case in our study, where 65% of deaths were due to causes other than adnexal carcinoma.

Another SEER analysis of over 4000 CAM patients demonstrated unadjusted 5-year OS and DSS rates of 73 and 98% respectively [4]. Disease-specific survival after exclusion of cases with distant metastases was associated with increased age, positive lymph nodes and histological subtypes of nodular hidradenocarcinoma and "sweat gland adenocarcinoma"[4]. Although this study did not specify whether lymph node metastases were found on SLNB or TLND, the authors concluded that some form of evaluation of lymph nodes could provide prognostic information in clinically localized disease. Two large European studies showed similar data, with a 5-year RSR of 87.7% [5] and 1, 5 and 10-year RSR of 95, 84 and 77% [6]. In the latter series of 2220 patients, 3.3% of patients demonstrated regional lymph node metastasis and 1.2% showed distant metastasis at diagnosis [6].

While the above and two small *ad hoc* studies [8, 9] show the impact of nodal involvement on outcome in CAMs, the role of SLNB and CLND in its management is largely undefined. A recent retrospective study of 48 patients with CAMs from Emory University showed a low rate of nodal involvement. Only 2/48 patients underwent SLNB, and both were negative. In this study, lymph node metastasis was seen in 8% of cases (4/48), and these all developed after local recurrence [7]. That study describes a local recurrence rate of 19% that was not influenced by margin status, and 5-year OS and DSS rates of 63 and 97%. Low rates of nodal involvement hampered analysis of the utility or prognostic impact of nodal evaluation.

The present series describes the clinicopathologic features and clinical outcome of a cohort of 103 patients with a diagnosis of CAM with pathologic confirmation and uniform, multidisciplinary treatment at a single institution and a median follow up of 44 months. These tumors occur in an older (median 61 years) and predominantly Caucasian (89%) population and affect males (61%) more often than females. Head and neck is the most frequent site of disease (56%). Similar to previous studies, tumors with eccrine differentiation dominated the landscape, comprising 70% of cases, with porocarcinoma being the most prevalent subtype. Tumors tended to be fairly large, with a median greatest tumor dimension of 1.0 cm. Almost one-quarter of patients underwent SLNB, with a 10% positivity rate. Porocarcinoma was the most frequent cause of nodal involvement, found in ten of the sixteen (62%) patients with this tumor. Local recurrence (9%) and regional recurrence (6%) were fairly rare, and the majority (69%) of these were of eccrine origin.

Our study population had 10-year OS and DSS of 80 and 93% with 7 patients dying of disease. Three of the deaths occurred in patients with lymph node involvement either at presentation (2) or as recurrence (1), suggesting the prognostic value of lymph node positivity. Unfortunately, the numbers are too small to allow for statistical analysis of nodal involvement or survival related to histologic subtype or tumor grade. Overall largest tumor size >2 cm, as well as the presence of metastatic disease in the lymph node basin demonstrated by SLNB, had a significant negative impact on overall survival.

Thus, despite the fairly small number of cases in our study that underwent lymph node sampling, there was a clear demonstration of the impact of nodal status on recurrence and survival. However, the numbers are too small to draw firm conclusions on the prognostic impact of SLNB. More studies and perhaps meta-analyses are necessary to amass sufficient evidence to definitively dictate the necessity for this procedure in patients with these unusual tumors.

Compliance with Ethical Standards

Conflict of Interest The authors declare no relevant conflict of interest.

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