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Abstract

Background

Sebaceous carcinoma (SC) is a rare, potentially recurrent and life-threatening cutaneous malignancy that can be associated with Muir-Torre syndrome (MTS), a DNA mismatch repair-driven genodermatosis. Prior studies examining factors associated with recurrence have focused on periocular tumors only.

Objective

Examine outcomes of SC and identify factors associated with recurrence

Methods & Materials

Retrospective study from two tertiary care centers

Results

Sixty-seven cases from 63 patients were identified, including 7 cases of MTS and 13 arising in the context of immunosuppression. Fifty-five cases (82.1%) were treated with complete circumferential peripheral and deep margin assessment (CCPDMA) methods. Five recurrences developed during the post-operative period. On univariate analysis, periocular location (Odds Ratio [OR] 7.6, p=0.0410) and lesion size ≥ 2 centimeters (OR 9.6, p=0.005) were associated with recurrence, while CCPDMA (OR 0.052, p=0.0006) was inversely associated with recurrence. On multivariate analysis, only lesion size ≥ 2 centimeters (OR 9.6, p=0.0233) and CCPDMA approaches (OR 0.052, p=0.007) were significant.

Conclusion

Non-CCPDMA methods and large lesion size were independent risk factors predicting recurrence, while anatomic subtype and MTS status were not. These findings can assist in identifying SC cases that may benefit from more aggressive treatment and closer surveillance.

INTRODUCTION

Sebaceous carcinoma (SC) is a rare, potentially recurrent adnexal skin cancer that arises on sebaceous skin. SC is typically classified as periocular or extraocular.[1] Treatment for local disease is primarily surgical resection, with a preference for techniques offering full margin evaluation. Factors associated with worse outcomes have been reported primarily in single-center studies and one multicenter study, all focused on periocular SC.[2–7] Several registry-based studies examined outcomes in both periocular and extraocular sebaceous carcinomas.[8–16] Collectively, these studies showed worse outcomes in periocular SC, male patients, immunosuppressed patients, larger tumors, or tumors with multifocal spread.

The purpose of this study is to report on our combined cohort of patients with periocular and extraocular SC treated at Stanford University and the University of Texas Southwestern (UTSW) medical centers and identify factors associated with disease recurrence.

METHODS

For the Stanford University School of Medicine cohort, a search of the pathology records was performed for the diagnosis of SC rendered during the time period between January 1st, 2010 and January 1st, 2021. The search terms utilized were: “sebaceous carcinoma”, “sebaceous atypia”, “atypical sebaceous”, “sebaceous neoplasm”, and “sebaceous adnexal”. A total of 252 matching cases were identified for review. Cases where a definitive diagnosis of SC was not rendered but SC was favored diagnosis were also included. Of these, 213 were excluded because they: were benign sebaceous neoplasms (145), were a second opinion of an outside specimen only (39), were biopsies of nodal or visceral spread of sebaceous neoplasms (14), did not have a follow-up

visit after the biopsy (10), underwent treatment elsewhere (4), declined definitive treatment (1), or were duplicate (2). Thirty-seven cases met the final inclusion criteria.

For the UTSW Medical Center cohort, a search was performed in the electronic medical record for all ICD-9 and ICD-10 codes entered between January 1st, 2010 and January 1st, 2021 and related specifically to sebaceous carcinoma, as well as all generic codes for malignant eyelid neoplasms and other specified and unspecified carcinomas of the skin. A total of 1948 matching cases were identified for review. Of these, 1919 were excluded because they did not meet SC diagnosis (1902) or were treated elsewhere (17). Twenty-nine cases met the final inclusion criteria.

The study was approved by the Stanford University Institutional Review Board (IRB) protocol # 60691and the UTSW IRB protocol # STU-2022-0866.

Data Collection

Data were extracted from the electronic medical record for analysis. The following demographic data were collected: age, sex, race, MTS or Lynch syndrome diagnosis, including any confirmatory genetic testing, immunosuppressed status (solid-organ transplant recipient, hematologic malignancy, HIV, immunosuppressant medication), and prior radiation at the tumor site. The following tumor factors were recorded: primary versus recurrent on presentation, pre-treatment lesion size (centimeter x centimeter), anatomic location, orbital involvement, if present, and disease status on presentation: local, nodal, or distant. The following histopathological features were recorded: depth of invasion, differentiation status, pagetoid

spread, perineural invasion, lymphovascular invasion, and immunohistochemistry for mismatch repair protein loss. Primary and adjuvant treatment approaches were collected. The type of surgery recorded were the following: wide local excision, Mohs micrographic surgery, frozen section margin control, and orbital exenteration. Both MMS and frozen section margin control were considered methods of complete circumferential peripheral and deep margin assessment (CCPDMA). Surgical margins, if applicable, margin status upon completion of surgery, and defect size were noted. Additional treatment approaches beyond original surgery were recorded: radiation regimen and/or topical or systemic chemotherapy regimens.

Disease status at initial follow-up and final follow-up were recorded. The type of recurrence (local, nodal, distant) and treatment of recurrence were recorded.

Statistical analysis:

Descriptive and inferential statistics were used for patient demographics, clinical characteristics of SC, histopathological features, and treatments. Student t-test and Mann-Whitney U test were used for parametric and non-parametric variables, respectively. Chi-squared analysis was used to significant differences in categorical variables. Univariate regression analyses to predict recurrence were completed for age, sex, periocular location, poor histopathological grade, lesion size, MTS by germline testing, and tumors treated with CCPDMA. A multivariate regression model with age, periocular location, mean, MTS by germline, and tumors treated with CCPDMA was also performed to determine significant predictors of recurrence. Odds ratios were calculated for variables in the univariate and multivariate regression analyses. Statistical significance was set at a p-value of 0.05 or less. All analyses were completed in Excel (version 16.74).

RESULTS

Demographics and clinical features: Sixty-seven cases of SC from 63 patients were included from both cohorts: 65 were primary and two were recurrent on presentation (**Table 1**). There were no significant demographic differences between the two cohorts. Across both cohorts, the mean age was 70.0 years (range 42-94), and 29 tumors (43.3%) arose in males. Seven cases (10.4%, 3 male, 4 female) were associated with MTS, confirmed by germline genetic testing. Thirteen cases (20.6%) arose in patients who were immunosuppressed, including from solid organ transplantation (7 cases). Thirty-seven cases (55.2%) were extraocular, with 28/37 (75.7%) located in the head and neck region. The remaining 44.8% were periocular (30/67 cases), confined predominantly to either the upper eyelid (12 cases) or lower eyelid (11 cases). Eighteen periocular SC tumors were category T2b or lower, by AJCC 8th edition. The median lesion diameter was 1.1 centimeters (range 0.2-6.2). No significant differences in gender, age, immunosuppression status, or lesion size were noted by anatomic subtype.

Histopathology: Most tumors (48/67, 71.6%) were confined to the epidermis or dermis, and only five had invaded into the muscle, bone, or orbit (**Table 1**). Pagetoid spread was reported in 10 cases, all periocular. Loss of mismatch repair proteins (MMR) by immunohistochemistry was performed in 27 cases: 12 with no loss of MMR, 12 with loss of 2 MMR (10/12 with loss of MSH-2 and MSH-6), and 1 case with loss of 4 MMR (MLH-1, MSH-2, MSH-6, PMS-2). Seven of these IHC-positive cases underwent genetic testing: 3 were positive (all with *MSH2* mutation), but 4 were negative. An additional 4 cases (that did not undergo tumor immunohistochemical testing) underwent germline testing and were found to have MTS (3 with *MSH2* mutation, 1 with *MLH1* mutation). All MTS-confirmed cases were of the extraocular SC subtype.

Treatment: Forty-eight tumors (71.6%) were treated with Mohs micrographic surgery (MMS), 7 cases (10.4%) with other complete circumferential peripheral and deep margin assessment (CCPDMA) methods (other than MMS), 7 cases (10.4%) with wide local excision, and 5 cases (7.5%) with orbital exenteration (**Table 1**). Clear margins were achieved in 64 cases (95.5%). In all three remaining cases with positive margins, the patients underwent additional curative therapy and were deemed to be in remission. The first case (left ear canal) underwent wide local excision followed by additional radiation therapy and remained disease-free at follow-up. The second case (left lower conjunctiva SC) was treated initially with MMS and then with CCPDMA technique with positive margins each time, followed by adjuvant topical 5-fluorouracil. Following a year-long remission, the patient recurred with fatal pulmonary and cutaneous metastases. The third case (left nasolacrimal duct SC) was treated with orbital exenteration and found to have regional metastasis thus underwent maxillectomy, parotidectomy and neck dissection followed by radiation therapy to the primary bed and draining nodal basin. Initial radiographic remission was achieved but the patient developed recurrence and ultimately succumbed to his disease.

Follow-up and recurrences: The median follow-up was 19.9 months (range 0.2-110.1). Five recurrences (2 local, 2 nodal, 1 metastatic) were identified over a median period of nearly 19.8 months (range 11.6-41.4): 4 were periocular and 1 was extraocular (left neck) (**Table 2**). Recurrent cases were treated with systemic chemotherapy (Cases 1 and 3), neck dissection and adjuvant radiation therapy (Case 2), orbital exenteration (Case 4), and surveillance (Case 5).

On univariate analysis comparing recurrent cases to disease-free cases (**Table 3**), the following variables were noted to be significant: lesion size ≥ 2 centimeters (odds ratio, OR 9.6, p-value=0.005), tumors treated with CCPDMA (OR 0.052, p-value=0.0006), and periocular location (OR 7.6, p-value=0.041). Tumor histopathological grade, MTS status, and immunosuppressed state were not significant factors. On multivariate analysis incorporating age, MTS syndrome, anatomic subtype, lesion size, and primary treatment, the following variables were significant: lesion size ≥ 2 centimeters (OR 9.6, p=0.023), CCPDMA (OR 0.052, p=0.007), and age (OR 1.0, p=0.015). As the OR for age was 1.0, this was not considered a clinically meaningful result. No changes to this result were noted when MTS syndrome and age were excluded from the analysis.

DISCUSSION

Recently published clinical practice guidelines on SC reported the pooled analysis comparing various surgical modalities and found that Mohs surgery or other CCPDMA techniques resulted in superior cure rates.[1] The data collected was based on a systematic review of previously published cohort studies which have several limitations. The studies were either restricted to periocular SC cohorts only,[2–7] SC cohorts with only a minority of extraocular cases,[17] or included cases treated primarily with wide local excision.[18,19] This study presents a well-sized two-center cohort for a rare malignancy with a balanced representation of periocular (44.8% of cohort) vs extraocular (55.2% of cohort) subtypes and includes MTS-associated SC (10.4% of cohort), nearly all of which were treated primarily with CCPDMA techniques.

Our study reveals new findings regarding the risk of recurrence by treatment type and lesion size, that have not been previously shown in cohorts of extraocular and periocular SC.[17,19–

[21] First, CCPDMA was a significant predictor of disease-free survival on univariate and multivariate analysis, which is consistent with data from prior registry-based studies showing the importance of achieving clear margins[22] and the contribution of MMS to lowering recurrence rates.[23] Second, lesion size was an important predictor of recurrence, and this has been demonstrated by other cohort studies before, though these were confined to eyelid SC.[5] Lesion size has also been demonstrated to be a strong predictor of overall survival in registry-based studies of SC.[12,14] Importantly, our study showed this to be the case even after controlling for treatment type. Thus, for a SC tumor that is ≥ 2 centimeters, regardless of anatomic subtype, it may be worth not only considering CCPDMA techniques for disease control, but given the higher risk of recurrence, additional adjuvant therapy and close monitoring. In light of our findings, it would be reasonable to consider either adjuvant radiation therapy to the primary tumor bed or, in certain cases of periocular SC (such as those with pagetoid spread), adjuvant topical chemotherapy to the primary tumor bed. Unfortunately, our study was not powered to explore the impact of adjuvant therapy on recurrences, but future studies are needed. Close surveillance, such as with baseline imaging, can be considered in these large cases, and imaging can be repeated every 6 months for at least the first 2 years when nodal metastasis is most commonly encountered.[1] We could not study the role of additional treatment (such as adjuvant radiation) in our cohort due to the small sample size, but a population-based cohort failed to show that adjuvant radiation results in improved overall survival, though its impact on recurrence has not been studied.[20]

Importantly, our analysis did not find that periocular tumors were at increased risk of recurrence compared with extraocular tumors, in contrast with past reports.[20] This may reflect evolved practices using CCPDMA techniques to extirpate SC tumors on the head and neck that

have significantly reduced recurrence rates.[23] It may also reflect referral patterns of only the more complex extraocular SC cases to our centers, as evidenced by the development of 1 extraocular SC recurrence among the 5 recurrent cases in our cohort. Yet, our overall recurrence rate (7.4%) was low and may reflect the availability of multidisciplinary care at our institutions.

Our study also confirmed prior findings that MTS-associated SC is not more aggressive than sporadic SC,[24] which has also been demonstrated in other mismatch repair deficient syndrome cancers such as colorectal carcinoma when compared with sporadic cases.[25,26] Although this has not been studied in SC, microsatellite unstable tumors present with greater tumor mutational burden than sporadic cases which may account for increased immunogenicity and predict superior cure rates.[27]

In further examining our cases for microsatellite instability, we found that 13 cases tested for at least 2 MMR protein loss by immunohistochemistry, but among the 7 of those that underwent germline analysis, only 3 were confirmed by genetic testing to have MTS. Unlike in colorectal carcinoma where loss of MMR by immunohistochemistry is highly sensitive and specific for Lynch syndrome (92-94% and 88-100%, respectively), immunohistochemistry for SC is only 85% sensitive and 48% specific.[28,29] Our results continue to support that immunohistochemistry has limitations as a screening tool for MTS, and instead newer assays that detect microsatellite instability or more sensitive and specific clinical risk criteria are preferred.[1]

This two-center study is limited by its retrospective design and lack of systematic follow up. Our median follow-up time of was shy of 2 years, but most recurrences in SC occur within this time frame.[1] Other limitations include differing search strategies between the two institutions, and missing information on histopathological grade which precluded its inclusion in multivariate analysis. Interestingly, however, 4/5 recurrences were classified as poorly

differentiated tumors. A histopathological grading system in SC has not yet been defined, and future studies are needed to define a system and study its impact on disease outcomes.

In summary, this two-center cohort study examined factors associated with recurrence in SC. CCPDMA methods that ensure complete margin control were found to reduce the risk of recurrence. Lesion size was also found to be a significant independent risk factor, and regardless of tumor subtype, lesions ≥ 2 centimeters may benefit from CCPDMA methods and possibly adjuvant therapy and close surveillance. Lastly, while our MTS subgroup was small, we did not find that cases arising from MTS fared worse. These findings can further stratify SC cases into high- and low-risk, clarifying which patients may benefit from more aggressive treatment approaches.

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Table 1: Patient demographics, histopathological features, and primary treatment modalities.
MMR: mismatch repair. CCPDMA: complete circumferential peripheral and deep margin assessment.

	Cohort 1 (Stanford)	Cohort 2 (UTSW)	Combined cohorts
Total # cases	38	29	67
Recurrent at time of presentation	2	0	2
Total patients	36	27	63
Mean age, years (range)	70.0 (42-94)	70.0 (38-92)	70.0 (38-94)
Male	16 (44.4%)	13 (48.1%)	29 (46.0%)
Muir Torre syndrome (MTS)	6 (16.7%)	1 (3.7)	7 (10.4%)
Immunosuppressed	8 (22.2%)	5 (18.5%)	13 (20.6%)
Solid organ transplant recipient	6 (16.7%)	1 (3.7%)	7 (11.1%)
Anatomic location			
Periocular	17 (44.7%)	13 (44.8%)	30 (44.8%)
Extraocular	21 (55.3%)	16 (55.2%)	37 (55.2%)
Head + neck (excluding periocular)	15	13	28
Trunk + extremities	6	3	9
Median lesion diameter, cm (mean, range)	1.2 (1.4, 0.3-6.2)	1.1 (1.4, 0.2-5.3)	1.1 (1.3, 0.2-6.2)
Depth of invasion			
Epidermis	4	2	6
Dermis	21	21	42
Subcutis	5	1	6
Conjunctiva	2	4	6
Orbit/Muscle	4	0	4
Bone	0	1	1
Unknown	2	0	2
Pagetoid spread, present	4	6	10
Differentiation status			
Well-differentiated	2	6	8
Moderately differentiated	3	0	3
Poorly differentiated	7	4	11
Unknown	26	19	45
Perineural invasion, present	2	3	5
Loss of MMR by immunohistochemistry			
0	11	1	12
1	0	0	0
2	9	3	12
4	0	1	1
Not performed	18	22	40
Primary treatment modality			
Mohs micrographic surgery	26 (68.4%)	22 (75.9%)	48 (71.6%)
CCPDMA	3 (7.9%)	4 (13.8%)	7 (10.4%)
Wide local excision	7 (18.4%)	0 (0%)	7 (10.4%)
Orbital exenteration	2 (5.3%)	3 (10.3%)	5 (7.5%)
Median time from biopsy to surgery, months (range)	1.6 (0-15.6)	1.2 (0-10.1)	1.3 (0-15.6)
Cases with clear margins achieved	37 (97.4%)	27 (93.1%)	64 (95.5%)

Average number of Mohs stages, +/- SD Average surgical margin (range), cm (if applicable)	1.8 +/- 0.9 0.4 (0.1-1.0)	1.7 +/- 1.2 0.6 (0.4-1.0)	1.8 +/- 1.1 0.5 (0.1-1.0)
Median defect size following surgery, cm (mean, range)	1.4 (2.2, 0.7-10.5)	2.6 (2.8, 0.9-8.0)	1.8 (2.5, 0.7-10.5)
Adjuvant therapy Radiation Topical 5-FU	 2 2	 2 0	 4 2
Median follow-up, months (mean, range)	15.5 (23.5, 0.2-110.1)	26.0 (29.2, 0.2-99.4)	19.9 (25.7, 0.2-110.1)

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348 **Table 2:** Recurrences.

Case #	Patient age (years), sex, primary tumor location and size (cm)	Primary surgical modality	Time from surgery to recurrence (months)	Type of recurrence	Treatment of recurrence	Final status
1	83, M, left nasolacrimal duct, 3.1 x 2.9 cm	Wide local excision	11.6	Regional node	Cetuximab	PD, death due to disease
2	59, M, left neck, 2.5 x 2.5 cm	Wide local excision	12.5	Regional node	Left neck dissection with extracapsular extension in 1/29 nodes, adjuvant radiation to left neck (66 Gy, 33 fractions)	DF
3	42, F, left medial canthus, 1.0 x 0.5 cm	CCPDMA (MMS)	27.1 to first, 41.6 to second	-Local in the first recurrence -metastatic to pulmonary and integumentary systems in the second recurrence	-CCPDMA +adjuvant 5-FU injections for first recurrence -orbital exenteration, systemic capecitabine, cetuximab, 5-FU for second recurrence	PD, death due to disease
4	74, M, left upper eyelid, 2.0 x 0.5 cm	CCPDMA	41.4	Local with extension to the orbit	Orbital exenteration	DF
5	79, M, right upper and lower eyelids and orbit, 5.3 cm	Orbital exenteration	Unknown	Local	Ongoing surveillance	PD

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Table 3: Univariate and multivariate analysis comparing recurrent cases with disease-free cases. CCPDMA: complete circumferential peripheral and deep margin assessment.

Risk factor	Univariate OR (p-value)	Multivariate OR (p-value)
Age, years	1.37 (p=0.268)	1.0 (p=0.015*)
Sex, male	2.3 (p=0.355)	
Periocular location	7.6 (p=0.041*)	7.6 (p=0.234)
Poor histopathological grade	5.14 (p=0.182)	
Immunosuppression	1.9 (p=0.484)	
Mean lesion size >= 20 mm	9.6 (p=0.005*)	9.6 (p=0.0233*)
MTS by germline testing	0.14 (p=0.375)	0 (p=0.330)
Tumors treated with CCPDMA	0.052 (p=0.0006*)	0.052 (p=0.007*)