Original Investigation

Primary Cutaneous Mucinous Carcinoma
A Systematic Review and Meta-analysis of Outcomes After Surgery

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IMPORTANCE  Evidence-based treatment guidelines are not available for primary cutaneous mucinous carcinoma (PCMC).

OBJECTIVE  To assess outcomes associated with surgical treatment of PCMC.

DATA SOURCES  MEDLINE, Cumulative Index to Nursing and Allied Health, and Embase from 1952 to 2010. Search terms were “primary cutaneous mucinous carcinoma,” “primary mucinous adenocarcinoma of the skin,” “primary mucinous sweat-gland carcinoma,” and “endocrine mucin-producing sweat gland carcinoma.”

STUDY SELECTION  Articles describing primary data on treatment (ie, case reports, case series, and cohort studies) of any patients with PCMC. A total of 116 articles were identified, with 90 of these assessed for eligibility and 87 used for final analysis.

DATA EXTRACTION AND SYNTHESIS  Each case was verified to be of primary cutaneous origin by 2 observers. Histopathologic descriptions were confirmed to be consistent with PCMC. Extracted fields included age, sex, race, lesion duration, tumor diameter, method of treatment, follow-up, and whether the lesion recurred or metastasized.

MAIN OUTCOMES AND MEASURES  Outcomes were dichotomized into good and bad depending on the presence of recurrence or metastasis during follow-up. Multivariate logistic regression analysis was performed to determine significant factors for predicting bad outcomes.

RESULTS  One hundred fifty-nine cases of PCMC, of whom 54.7% were male and 77.2% were white, with mean (SD) age 63.5 (13.2) years, were analyzed. Most had been treated with traditional surgical excision (85.5%), with only 9.4% of cases treated with Mohs surgery. Older (odds ratio [OR], 0.93; \( P = .04 \)) and Asian (OR, 0.02; \( P = .01 \)) patients had relatively better postsurgical outcomes. Larger tumors (OR, 6.71; \( P = .14 \)), those persistent for longer prior to surgery (OR, 1.02; \( P = .11 \)), and those located on the trunk (OR, 103.24; \( P = .005 \)) also were associated with poorer outcomes. Limitations included reliance on case report data.

CONCLUSIONS AND RELEVANCE  Patient demographic characteristics and tumor-specific features may provide predictive information regarding the risk of postsurgical recurrence and metastasis after treatment of PCMC.
Primary cutaneous mucinous carcinoma (PCMC) is a rare low-grade malignant neoplasm originally believed to be of eccrine origin. These tumors are slow growing, arising on the face (particularly the eyelids), axilla, scalp, and trunk of middle-aged and older individuals. The lesions typically present as erythematous, asymptomatic nodules measuring 0.5 to 7 cm in diameter; however, larger variants have been reported. The contemporary, but still somewhat controversial, view is that these tumors actually demonstrate apocrine-type differentiation.

Morbidity related to PCMC is primarily associated with incomplete resection. While PCMC tends to grow slowly and have a good prognosis, late recurrences and rare metastases have been reported. Recurrence portends substantial morbidity, as recurrent tumors do not tend to respond to radiation treatment or chemotherapy.

As is the case with many rare nonmelanoma tumors, there is no standard of care for the surgical treatment of PCMC. Currently employed modes of treatment for PCMC vary from standard excision to wide local excision, including dissection of regional lymph nodes. Mohs surgery was first introduced as a means for PCMC treatment by Weber et al in 1988.

The purpose of this review was to compare the risk of poor postsurgical outcomes, specifically risk of recurrence and metastasis, by the type of surgery performed (ie, Mohs vs excision), as well as by demographic features of patients and tumor-specific characteristics in all patients reported to have been treated by surgery for PCMC in the recent English-language literature. Due to the rarity of PCMs, the studies included were observational, primarily case reports and case series.

Methods

We reviewed the MEDLINE, Cumulative Index to Nursing and Allied Health, and Embase databases for articles published from 1952 to 2010 in the English language that reported primary data on surgical treatment (ie, case reports, case series, and cohort studies) of PCMC. Expansive parameters regarding patient population and country of origin were selected to maximize data volume for this rare malignant neoplasm. Time restrictions were implemented for uniformity, since it was expected that nomenclature variation over time would prevent ascertainment of diagnosis in earlier cases and since surgical methods like Mohs were not available earlier. Search terms included “primary cutaneous mucinous carcinoma,” “primary mucinous adenocarcinoma of the skin,” “primary mucinous sweat-gland carcinoma,” and “endocrine mucin-producing sweat gland carcinoma.” Each case was reviewed to verify that it was of primary cutaneous origin and that if histopathologic analysis was provided, it was consistent with a diagnosis of PCMC. The date last searched was July 18, 2010.

Prior to the start of the screening process, the review team completed an informal training exercise to ensure consistent application of search parameters. Initial screening of potentially eligible records was performed by 1 investigator (R.T.B.). Subsequent full-text record screening was performed independently by 2 investigators (R.T.B., M.A.) who each classified each study on a yes/no/maybe scale. A consensus process (ie, forced agreement) was used to select data used in the analyses.

Where possible, data extracted from each patient case included age, sex, race, lesion duration, tumor diameter, method of treatment, follow-up, and whether the lesion recurred or metastasized. Lesion duration was defined as the duration of time that the patient had reported noticing the lesion prior to seeing the treating physician. Follow-up was defined as the time in months between the patient’s initial treatment for their original PCMC lesion and the time they were last seen in clinic. Review of author names, dates of publications, and institutions, as well as comparison of patient-specific factors like age and sex, was used to censor duplicate records; when duplicate records were detected, the record with the more complete case information or more extractable fields was analyzed. Records with 0 months follow-up were excluded from analysis of outcomes but were included to provide baseline demographic information pertaining to PCMC.

To facilitate comparison, outcomes were dichotomized into good and bad outcomes. Good outcome was defined as a case having no recurrence or metastasis during follow-up, whereas bad outcome was defined as a case having either a recurrence or metastasis. We performed multivariate logistic regression analysis to determine significant factors in predicting bad outcomes. Explanatory variables considered included patient age, sex, race, method of treatment, lesion location, lesion size, follow-up time, and duration of patient symptoms prior to presentation. For the purpose of logistic modeling, lesion size was dichotomized into 2 categories: those less than 1.5 cm in diameter (the median diameter) and those greater than or equal to 1.5 cm in diameter. All statistical analysis was completed with SAS, version 9.2 (SAS).

Since studies were observational, including case reports, case series, and small retrospective cohort studies, there was a high risk of bias in individual studies. Application of the Cochrane risk of bias tool, developed primarily for randomized controlled trials, indicated that the observational studies we analyzed were at an intrinsically high risk of incomplete outcome data, especially longer-term outcome data (6-12 weeks after treatment), as well as a high risk of selective outcome reporting. Early stopping of ascertainment of postsurgical outcomes may have resulted in underdetection of bad outcomes. Publication bias may have led some investigators to preferentially report good outcomes rather than bad, and within the context of a given case series, selective reporting may have resulted in preferential reporting of successful surgical cases. Other potential sources of bias would be baseline imbalances, such as demographic selection, which are inherent in observational studies.

Results

Overall, 114 articles were identified through database search, and an additional 2 articles were found by review of endnotes. After duplicate records were removed, 105 records were screened by review of abstracts and summary information. An additional 15 articles were excluded due to duplicate records.
or the absence of patient-level data. A remaining 90 full-text articles were assessed for eligibility, with 3 more removed when it became apparent that their cases were subsumed within or duplicated in other articles. Eighty-seven articles reporting a total of 215 cases of PCMC were included in the qualitative review (see eTable and eReferences in Supplement).1,3,9-62 Cohort characteristics and outcomes are presented in Table 1. There was a slight male predominance (n = 87 [54.7%]), and the mean (SD) age was 63.5 (13.2) years. There was an increased prevalence of white patients (n = 122 [77.2%]) as compared to Asian (12.7%) and African American patients (10.1%). The most commonly reported tumor location was the eyelid or brow region (49.7%), followed by the nonperiorbital face or neck area (19.5%) and scalp (17.0%). Mean (SD) tumor diameter prior to excision was 1.8 (1.5) cm. The lesions were first noticed by the patient a mean (SD) 35.6 (53.9) months prior to presentation to the treating physician. The mean (SD) follow-up was 37.4 (38.8) months.

In terms of treatment, only 9.4% of cases were treated with Mohs micrographic surgery, with the majority being treated with traditional surgical excision (85.5%). Among the 15 cases treated with Mohs surgery, only 2 cases (13%) recurred, and there were no cases of metastasis. Among the 136 cases treated with excision, 46 cases (34%) recurred or metastasized. Mean (SD) follow-up time was 30.1 (39.4) months for cases treated with excision and 23.1 (17.5) months for cases treated with Mohs surgery.

As expected, bias was apparent at the individual study level, with empirical evidence of incomplete reporting, including variable follow-up and absence of any follow-up in selected reports.

After exclusion of cases with no follow-up, a total of 159 cases from 74 studies were included in the quantitative review. In multivariate logistic regression analysis (Table 2), after adjusting for demographic characteristics, lesion location, size (median diameter), duration, method of treatment, and follow-up, significant predictors for outcome were found to be age, race, lesion location, and follow-up.

Lesion location on the trunk (compared to head and neck) was predictive of a bad outcome (odds ratio [OR], 103.24; \( P = .005 \)), as was longer follow-up (OR, 1.07; \( P = .01 \)). Asians had better outcomes than whites (OR, 0.02; \( P = .01 \)), and older patients had better outcomes than their younger counterparts (OR, 0.93; \( P = .04 \)).

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Overall, No. (%) (N = 159)</th>
<th>Good Outcome (n = 109)</th>
<th>Poor Outcome (n = 50)</th>
<th>( P ) Valuea</th>
<th>Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD), y</td>
<td>63.5 (13.2)</td>
<td>64.9 (12.8)</td>
<td>60.4 (13.7)</td>
<td>.04</td>
<td>0.93</td>
</tr>
<tr>
<td>Male, No. (%)</td>
<td>87 (54.7)</td>
<td>55 (50)</td>
<td>32 (64)</td>
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<td>...</td>
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<tr>
<td>Race, No. (%)</td>
<td></td>
<td></td>
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<tr>
<td>White</td>
<td>122 (77.2)</td>
<td>82 (75)</td>
<td>40 (82)</td>
<td>1 [Reference]</td>
<td></td>
</tr>
<tr>
<td>East Asian or Indian</td>
<td>20 (12.7)</td>
<td>16 (15)</td>
<td>4 (8)</td>
<td>.01c</td>
<td>0.02</td>
</tr>
<tr>
<td>African American</td>
<td>16 (10.1)</td>
<td>11 (10)</td>
<td>5 (10)</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Lesion duration, mean (SD), mo</td>
<td>35.6 (53.9)</td>
<td>38.1 (59.3)</td>
<td>29.9 (39.0)</td>
<td>.11</td>
<td>1.02</td>
</tr>
<tr>
<td>Tumor diameter, mean (SD), cm</td>
<td>1.8 (1.5)</td>
<td>1.8 (1.5)</td>
<td>2.0 (1.4)</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Mean (SD), cm ( \geq 1.5 ) cm, % (n = 96)c</td>
<td>...</td>
<td>45</td>
<td>60</td>
<td>.14</td>
<td>6.71</td>
</tr>
<tr>
<td>Follow-up, mean (SD), mo</td>
<td>37.4 (38.8)</td>
<td>32.7 (31.5)</td>
<td>47.9 (50.3)</td>
<td>.14</td>
<td>1.07</td>
</tr>
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<td>Method of treatment, No. (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mohs surgery</td>
<td>15 (9.4)</td>
<td>13 (12)</td>
<td>2 (4)</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Traditional surgical excision</td>
<td>136 (85.5)</td>
<td>90 (83)</td>
<td>46 (92)</td>
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<td>...</td>
</tr>
<tr>
<td>Lesion location, No. (%)</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Head and neck</td>
<td>137 (86.2)</td>
<td>97 (89)</td>
<td>40 (80)</td>
<td>.005</td>
<td>1 [Reference]</td>
</tr>
<tr>
<td>Trunk</td>
<td>22 (13.8)</td>
<td>12 (11)</td>
<td>10 (20)</td>
<td>...</td>
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</tr>
</tbody>
</table>

a \( P \) value as determined by logistic regression analysis.

b There was one patient of race “other” (data not shown).

c Only significant race comparison.

d Overall value and number of patients not reported because tumor size was reported in only 96 cases.
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Discussion

We reviewed the literature on PCMC in an effort to determine factors that could affect outcomes for this rare tumor. Our findings suggest various demographic and tumor-specific factors are associated with poor outcomes, namely, recurrence and metastasis.

It is unclear what factors may lead to higher recurrence and metastasis rates among younger patients, but considerations would include the potential for delayed diagnosis, lack of awareness regarding cutaneous malignant tumors among young people, the possibility of more aggressive tumors in this group, or effects of socioeconomic status and access to care.

Patients with PCMC tumors located on the trunk were less likely to have good outcomes as compared to those with the more common head and neck tumors. This stands in contrast to basal cell and squamous cell carcinomas, which tend to have higher recurrence rates when located on the head and neck.

The worse outcomes seen with longer follow-up were likely due to patients returning to their physicians once recurrence or metastasis occurred, thus leading to longer follow-up with the treating physician. Also, in patients followed over a longer period, we would generally expect to see an increased number of recurrences as compared to those patients who were followed only briefly. Unsurprisingly, those patients with larger initial tumors (>1.5 cm) had increased rates of recurrence and metastasis. It is unclear why Asians with PCMC had better outcomes compared to whites, and this finding deserves further study to see if it is replicated.

Our study has the limitations imposed on any retrospective uncontrolled analysis, including potential patient selection bias, as well as incomplete follow-up data, leading to possible ascertainment bias in assessment of recurrence. Missing data points also limited study power. For example, follow-up was not noted in several of our studies, forcing these cases to be dropped when outcomes were examined. On the other hand, there was no apparent bias associated with funding sources for this study, as there were no external or commercial funding sources, with all support deriving from unrestricted research funds of the Northwestern University Department of Dermatology. Development of a central registry for rare tumors or collaborative prospective data would help to confirm or negate some of the data presented in this article.

Conclusions

In that the source data for this study were case-level reports and not randomized controlled trials, inferences about cure rates must be viewed in the context of the limitations of the data and the many likely biases. However, given the rarity of PCMC, it would be difficult to get a sufficient number of cases with a prospective study, and we believe that our analysis does provide new insight into this rare tumor, helping to further characterize factors that may influence recurrence and metastasis rates.

REFERENCES

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