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A Systematic Review and Meta-Analysis of Mapping Biopsy for Primary Extramammary Paget's Disease in Reducing Recurrence Following Surgical Excision

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Objective: To examine the association between the performance of mapping biopsies and surgical outcomes postexcision of extramammary Paget's disease (EMPD).

Background: Primary EMPD is a rare entity associated with poorly defined surgical margins and difficult-to-access sites of lesions. Surgical resection with clear margins remains the preferred management method. The use of mapping biopsies might be beneficial, particularly in lowering disease recurrence.

Methods: Available literature was reviewed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses methodology before a fixed-effect meta-analysis was performed to identify the presence of a correlation between performing mapping biopsies and positive margins on permanent sections as well as disease-free survival. Additional study results not included in the quantitative assessment were qualitatively assessed and reported.

Results: A total of 12 studies were shortlisted for final analysis. 294 patients who underwent mapping biopsies and 48 patients who did not undergo mapping biopsies were included in the assessment. Forest plot analysis revealed a pooled rate ratio of 0.50 (95% CI, 0.32–0.77) in the prevalence of positive margins in patients with mapping biopsies performed as compared to patients without. The pooled rate ratio of the prevalence of disease-free survival in patients with mapping biopsies performed as compared to patients without was 1.38 (95% CI, 1.03–1.84). Qualitative assessment of the remaining selected studies revealed equivocal results.

Conclusions: Mapping biopsies are able to improve EMPD surgical excision outcomes but given the rarity of the disease and heterogeneity of mapping biopsy procedures, further confirmation with randomized controlled trials or a larger patient pool is necessary.

Keywords: extra-mammary paget's disease, mapping biopsy, recurrence

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INTRODUCTION

Extramammary Paget's disease (EMPD) is a rare cutaneous malignancy affecting the apocrine cells of the skin. Commonly affected sites include the vulva, scrotum, groin, penile, perianal, and perineal regions, and less commonly, the axilla. Lesions typically present as erythematous plaques with either well-defined or ill-defined borders, which can become erosive, ulcerated, scaly, or eczematous, causing immense discomfort to the patient or may be mistaken for other pruritic skin lesions.[1] Possibly owing to the rarity of the disease and difficulties in characterizing it, there are no established guidelines or consensus statements regarding its management. Yet, this is not without its drawbacks, as EMPD has high rates of recurrence following surgical excision.[2] To better understand the disease course of EMPD, it is important to consider its' categorization. Primary EMPD is of cutaneous origin and can be further categorized as in situ, with invasion, or occurring as a feature of underlying skin adenocarcinoma arising in a skin appendage or the vulvar glans.[3] In the absence of metastasis or concurrent primary tumor, complete surgical excision with negative margins is the current standard of care.[4] Secondary EMPD, on the other hand, arises from underlying concomitant noncutaneous adenocarcinomas.[3] There is also a high association between invasive disease and delayed diagnosis. Perhaps it is because of the multifocal and asymmetrical spread of Paget cells beyond the grossly visible margins that surgical excision does not lead to the best outcomes in disease control.

It is thus proposed that to increase the chances of complete clearance, negative surgical margins should be aimed for, and this can be done by better assessing microscopic margins.[5] One way to achieve this is through mapping biopsies performed around the gross borders of the lesion. These are typically either punch or shave biopsies. It is believed that achieving negative margins around the entire excised lesion will reduce rates of recurrence and improve the patient's quality of life postsurgery. It may also be helpful in better delineating the required margins for a lesion in areas with limited access, such as the groin. Mapping biopsies may also be preferable to procedures such as Mohs micrographic surgery (MMS), which require trained personnel and are time-consuming to perform with a longer operating duration.[6] However, there are mixed conclusions regarding the efficacy of preoperative mapping biopsies in improving margin status and reducing the risk of recurrence. Hence, this study aims to collate the available evidence on mapping biopsies and assess the outcomes of their use to determine their viability in improving surgical treatment and clinical outcomes of primary EMPD.

MATERIALS AND METHODS

Systematic Search Strategy

This study was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) methodology (Supplemental Material, http://links.lww.com/AOSO/A254). PubMed, Cochrane Library of Systematic Reviews, EMBase, and CancerLit databases were searched for relevant studies assessing outcomes such as survival and recurrence of disease following surgical resection with mapping biopsies performed. Searches were limited to articles in English and published between January 1, 2000 and June 29, 2021. The search strategy employed in this study is detailed in Supplemental Table S1, http://links.lww.com/AOSO/A255 (PROSPERO registration number: CRD42021285535).

Duplicates were removed from articles selected for relevance before further screening was done based on the risk of bias assessment and inclusion and exclusion criteria. Studies were included if the patient population comprises adults with primary EMPD with pathological confirmation of disease. Studies were excluded if the patient population comprises adults with recurrent EMPD or had underlying noncutaneous adenocarcinoma, had prior radiation therapy and/or chemotherapy before surgical excision, and there was less than 24 months of follow-up after the therapeutic surgery. For risk of bias assessment, case series reports were assessed using the Joanna Briggs Institute Checklist for Qualitative Research whereas retrospective cohort studies were assessed using the ROBINS-I checklist (Supplemental Table S2, http://links.lww.com/AOSO/A255).

The screening of articles was performed by 2 researchers and in the presence of any discrepancy, a final decision was made by a third independent reviewer. The PRISMA flowchart is illustrated in Figure 1.

Main Outcome Measure

The main outcomes assessed were positive margins on permanent section and disease-free survival following surgical excision.

Data Extraction and Statistical Analyses

From the results published in the selected records and individual patient data (IPD), the recurrence rate and prevalence of positive margins on permanent sections taken intraoperatively were recorded. Other data extracted include gender, depth of lesion invasion, lymph node involvement, metastatic disease, site of lesion studied, minimum distance from gross margins of lesion that the mapping biopsies were performed, mean number of mapping biopsies performed per patient, final surgical procedure performed, type of postoperative therapy provided (if any), rate of positive surgical margins on frozen section (if performed), and number of patients that additional excisions were performed on after primary procedure. Authors of selected articles were contacted via email to provide IPD and details to populate any data not found within the published records.

Extracted data was synthesized using STATA version 16.0, and a two-sided P value less than 0.05 was considered statistically significant. A fixed-effects meta-analysis using the Mantel-Haenszel method was performed to pool the individual study results, and a forest plot of the rate ratios comparing the absence of recurrence in patients who underwent mapping biopsies and in those who did not was generated. Likewise, a forest plot comparing the likelihood of positive margins on permanent sections in patients who underwent mapping biopsies and in those who did not was constructed. Random-effects meta-analysis was initially used to assess the between-study heterogeneity and fixed-effect meta-analysis was utilized if the I^2 statistics was less than 50%. Publication bias was assessed using funnel plots.

For the study by Hatta et al.[8] reported qualitatively below, the correlation between the performance of mapping biopsies and the likelihood of disease recurrence was calculated using the χ^2 and Fisher exact tests.

RESULTS

Selection Process

In total, 245 papers were identified from the databases searched. After the removal of duplicates, 243 papers remained and were screened for relevance based on inclusion and exclusion criteria. Of the remaining 40 papers, further screening and risk of bias assessment were performed to shortlist 12 papers for detailed analysis.

Patient Characteristics

All patients analyzed had primary EMPD with no underlying malignancy. Lesions were either in situ, invasive, locally invasive, had regional spread, or had distant spread. Some patients had disease involving the lymph nodes or with distant metastasis. All patients had primary lesions in the external genitalia. The range

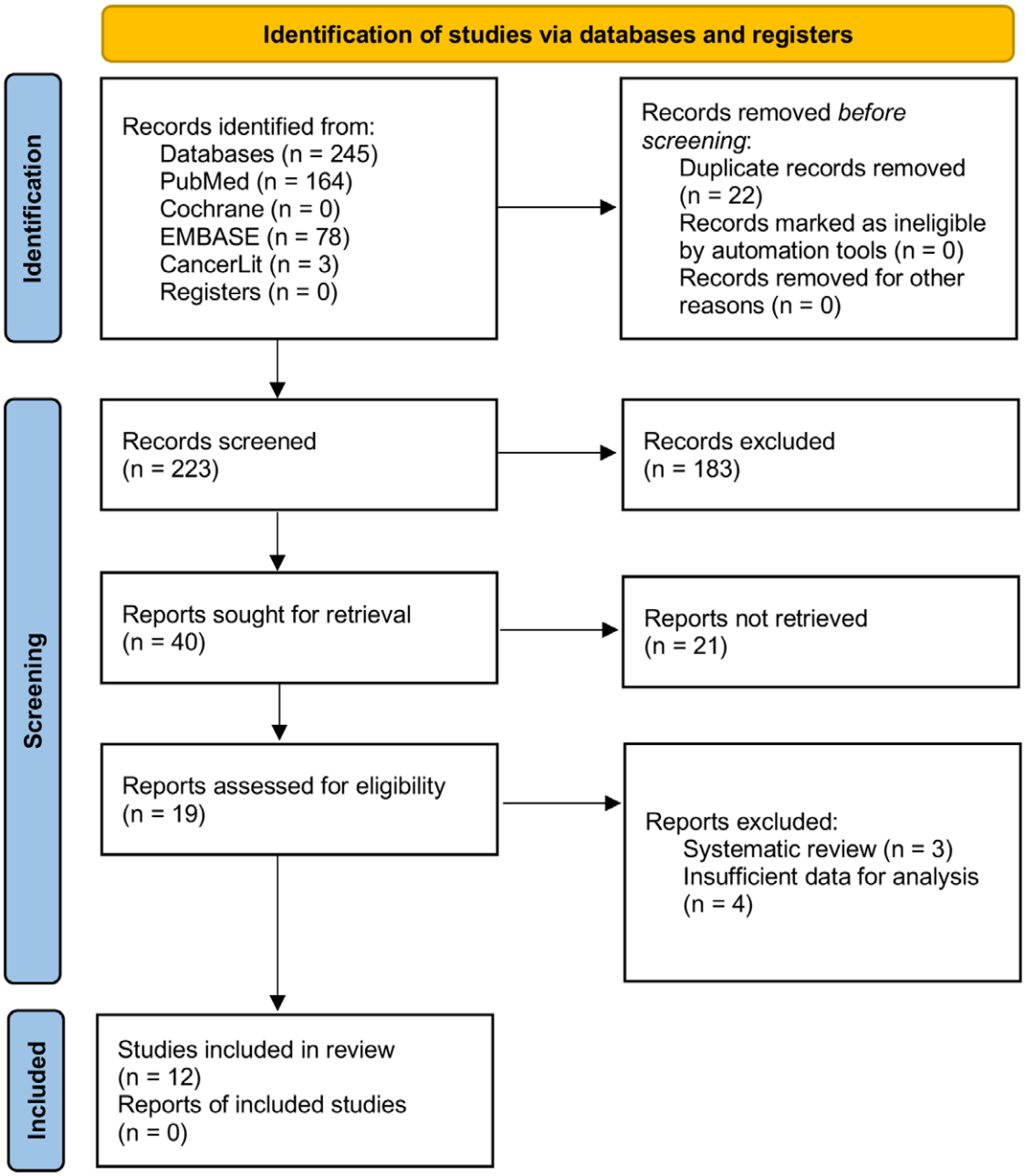

FIGURE 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram for study selection. Adapted from Page et al.[7]

of surgical procedures performed includes wide local excision, simple vulvectomy, and radical vulvectomy. Patient characteristics are detailed in Supplemental Tables S3 and S4, http://links.lww.com/AOSO/A255. A summary of the various mapping biopsy techniques utilized can be found in Supplemental Table S5, http://links.lww.com/AOSO/A255. A total of 294 patients who underwent mapping biopsies were included in the assessment. In total, 48 patients who did not undergo mapping biopsies before surgical excision were also included in the studies. Only 5 patients with mapping biopsies underwent additional excision procedures whereas 12 patients without mapping biopsies received additional excision procedures. On the aspect of treatment choice, 14 patients who underwent mapping biopsies and 7 patients who did not undergo mapping biopsies received postoperative systemic therapy such as radiotherapy, topical imiquimod, photodynamic therapy, and CO_2 laser. However, the number of patients who received such interventions was not large enough for a significant comparison of impact on surgical outcomes to be made.

Prevalence of Positive Margins

Meta-analysis was performed using a subset of studies with both arms of comparison. A total of 5 studies with mapping biopsies performed on 170 patients and no mapping biopsies performed on 48 patients were included to compare the prevalence of positive margins. The pooled rate ratio was 0.50 (95% CI, 0.32–0.77) (Fig. 2A). No publication bias was detected, and funnel plots of the selected studies are illustrated in Figure 2B.

Prevalence of Disease Recurrence

4 studies were included to compare the prevalence of no disease recurrence in patients with mapping biopsies and those without. A total of 53 patients with mapping biopsies and 32 patients without mapping biopsies were included. Forest plot analysis reflects a pooled rate ratio of 1.38 (95% CI, 1.03–1.84) (Fig. 2C). No publication bias was detected, and funnel plots of the selected studies are illustrated in Figure 2D.

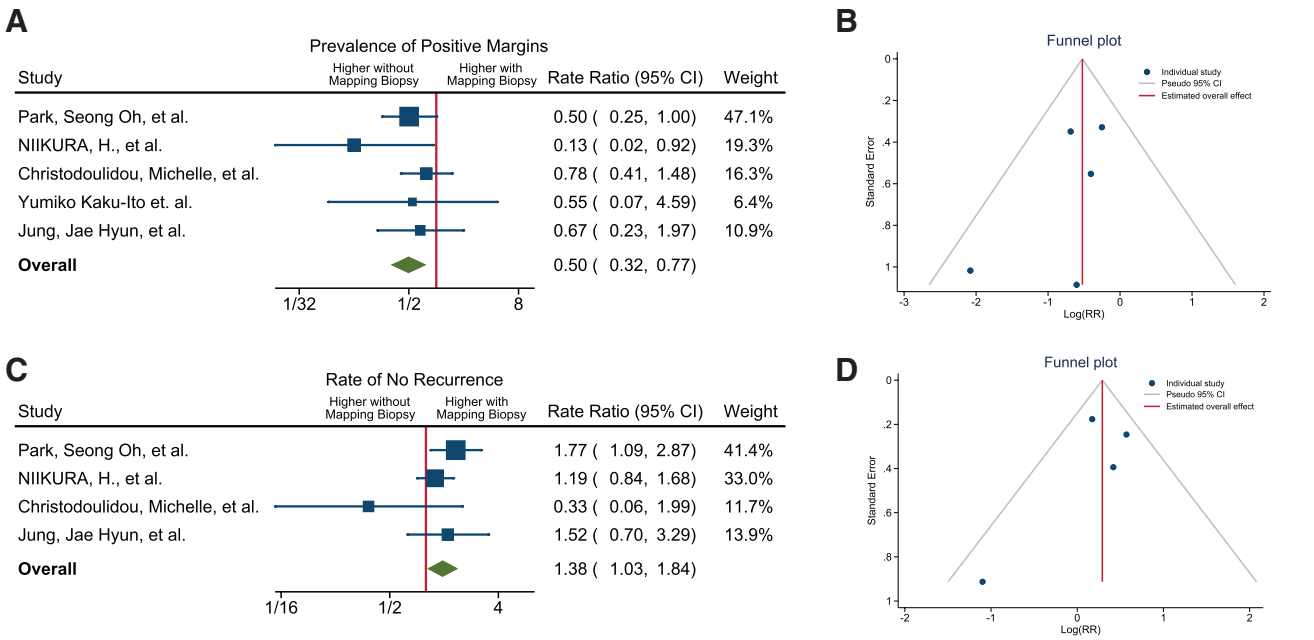

FIGURE 2. A, Forest plot analysis of studies comparing the rate ratios of prevalence of positive margins in patients who underwent mapping biopsies before surgical resection and those who did not. Pooled rate ratio of 0.50. B, Symmetrical funnel plots of selected studies comparing the prevalence of positive margins in patients who underwent mapping biopsies prior to surgical resection and those who did not indicate an absence of significant publication bias. C, Forest plot analysis of studies comparing the rate ratio of no disease recurrence in patients who underwent mapping biopsies before surgical resection and those who did not. Pooled rate ratio of 1.38. D, Symmetrical funnel plots of selected studies comparing no disease recurrence in patients who underwent mapping biopsies prior to surgical resection and those who did not indicate an absence of significant publication bias.

Qualitative Data Analysis

Single-armed studies that only evaluated the effects of mapping biopsies without comparing to patients who did not have mapping biopsies performed were analyzed qualitatively. Kim et al.[9] performed a retrospective review on 20 patients with vulvar, perianal, penoscrotal, and scrotal EMPD. Follow-up review revealed 2 of the 20 patients with positive margins on permanent sections whereas 1 patient had recurrence. Anchora et al.[10] performed a retrospective review on patients with vulvar EMPD and upon assessment of margins, determined 14 of 28 selected patients to have positive margins. In the assessment of the role of multiple scouting biopsies before MMS, Appert et al.[11] followed up on 3 male patients with scrotal EMPD and groin involvement. One of the 3 patients had positive margins, but none had recurrence. Kato et al.[12] performed a retrospective review on the use of punch biopsies to determine surgical margins on EMPD patients and determined that 8 of 17 selected patients had positive margins on permanent sections, but only 1 patient had disease recurrence. In summary, the median prevalence of positive margins on permanent sections is 0.40 ± 0.18, whereas the median prevalence of no disease recurrence is 0.94 ± 0.03.

Separately, the case study of an 82-year-old male patient with EMPD of the scrotum and groin was also identified.[13] He underwent contoured tissue removal from 1 cm beyond the margins of the lesion as identified under ultraviolet light for sampling to determine surgical margins. Central excision was carried out with the removal of subcutaneous tissue underlying the affected skin and the muscle fascia. Margins on the frozen section were negative, with no tumor identified at the level of the subcutaneous and adipose tissue. No recurrence was noted during the 25 months of follow-up.

Finally, a study of 76 EMPD patients with primary EMPD involving the genital, perianal, and axillary regions found that 45 patients underwent mapping biopsy due to the presence of clinically ill-defined margins or the presence of margins with widths that needed to be reduced.[8] A calculation of the correlation between performing mapping biopsies and the likelihood of recurrence gave rise to a P value of 1.00, leading to the conclusion that performing mapping biopsies did not have any significant impact on the likelihood of recurrence.

DISCUSSION

The rarity of EMPD leads to a paucity of primary data that makes an assessment of the effectiveness of various treatment options difficult. Hence, systematic reviews such as these that allow for the consolidation of available data are important in better understanding and guiding treatment options for primary EMPD. For the patients themselves, EMPD can be a debilitating condition with a significant impact on the quality of life, as seen in the study by Liu et al.[14] where patients with EMPD were found to have a worse health-related quality of life than patients with basal cell carcinoma. This discussion is further driven by the translational nature of the findings, as mapping biopsies play a key role in determining the spread of disease and delineating surgical borders in other malignancies where the likelihood of spread is high but larger margins are difficult to obtain due to the location of the lesion and poor cosmetic outcomes.[15] There is a strong need to review the current protocol in performing such mapping biopsies and evaluate the utility of the procedure both for improved clinical outcomes and better patient satisfaction.

The goals of preoperative mapping biopsies are twofold: first, to improve the delineation of surgical margins to increase the chances of complete clearance; and second, to demarcate borders that allow for better excisions in areas with limited access and space for maneuvering. These aims are at times at odds with each other as better clearance of the lesion might necessarily mean a larger excision and thus poorer tissue preservation with poorer cosmetic results and wound recovery. Mapping biopsies also show promise at being more effective at preventing recurrence than procedures such as MMS which are technically more demanding. Preoperative mapping biopsies may thus be able to assist in minimizing the likelihood of disease recurrence without compromising either goal.

Based on our quantitative results, the effect of performing mapping biopsies as opposed to not doing so significantly reduces the rate of disease recurrence and the likelihood of having positive margins on intraoperative permanent sections taken. To lower disease recurrence, a better assessment of tissue involvement is required. Based on our understanding of the histopathology of EMPD, Paget cells found in the epidermis occur either singly or in multifocal clusters with intervening nonpathological tissue.[16,17] Using the traditional wide excision method, taking gross margins of the lesion carries a higher likelihood of missing such malignant cell clusters. Scouting biopsies may thus minimize the chances of this occurring and lower the chances of positive margins. Additionally, though the one-armed studies do not prove or disprove the efficacy of scouting biopsies, they provide an assessment of the expected prevalence of positive margins and the likelihood of recurrence. Both qualitative and quantitative analyses performed are in support of mapping biopsies as a viable option to improve EMPD surgical excision outcomes.

Our current analysis, however, cannot prove a correlation between the prevalence of positive margins and the likelihood of recurrence. As observed in the study by Kato et al.,[12] although 47% of patients in the study had Paget's cells along the margins of the gross resected specimen, only 1 of the 17 patients had recorded disease recurrence. The significance of permanent margins of resected specimens or negative surgical margins on the likelihood of recurrence is itself contested.[18] Based on the study by Fishman et al.,[19] permanent margin status did not predict disease recurrence in EMPD. Even in studies utilizing mapping biopsies, the status of permanent margins may not be correlated with the likelihood of disease recurrence as seen by the conflicting reports by Kim et al. and Kato et al.[4,9,12] The question remains whether negative margins can be used as a proxy or an endpoint for good surgical outcomes. Our results on the likelihood of positive margins and rate of recurrence with mapping biopsies do concur. It may thus be valid to continue to look at both factors.

Even if both factors are not correlated, we can look to reports by Kaku-Ito et al.,[20] that show the chances of reconfiguration of surgical borders due to positive mapping biopsies might be low, particularly in the case of well-defined borders. This suggests that the final surgical margins selected may not be affected by whether mapping biopsies had been performed in a subset of cases. Instead, mapping biopsies may be of greater use in select subgroups of patients where the border of the lesion is ill-defined or when the surgery needs to be kept as minimal as possible.[21,22] As this study only looked at the aggregated effects of mapping biopsies on recurrence rate, this potential subset effect could not be elicited. In fact, the Clinical Practice Guidelines on EMPD highlight that while mapping biopsies are a possible alternative for margin assessment, their clinical utility is inconclusive.[23]

Finally, we consider the presence of sustained positive margins despite mapping biopsies. This observation could be due to pathological tissue present in areas between biopsy points or as skip lesions beyond the gross border. These would still fail to be sampled despite the mapping biopsies, and the subsequent surgical margins mapped would still fail to achieve complete clearance due to residual pathological tissue being left unresected. Wider horizontal invasion may be missed as a result, and a study by Wang et al.[24] revealed that such invasion is an independent risk factor for recurrence, potentially indicating subclinical tumor extension that is difficult to assess. While more recent studies dispute the prevalence of such irregular and discontinuous borders,[25] the inability of current mapping biopsy techniques to accurately assess residual disease may explain the lack of consensus in this matter. This is compounded by the absence of a standardized mapping biopsy technique making for difficult comparison across datasets. Updated literature has yet to find a correlation between free-margin status and recurrence-free survival following surgical excision.[26,27]

There are a few limitations in this meta-analysis with regard to the pooled analysis, starting with the limited number of studies with both arms for comparison of the effectiveness of mapping biopsies. Of the 12 articles, 7 were single-arm reviews, and the statistical significance calculated should thus be evaluated with the caveat of a small study population. Hence, the results derived from this article would be best validated through subsequent pooled studies across multiple centers to increase the study size and strength of the conclusions drawn. This article does, however, prove the need for larger trials to minimize cross-study variability and bias introduced by small study populations.

The second limitation is the heterogeneity of mapping biopsy techniques as detailed in Supplemental Table S5, http://links.lww.com/AOSO/A255. As discussed previously, such heterogeneity can give rise to differences in outcomes, including whether negative margins can reliably be used as a proxy for disease clearance. All the included studies, except Christodoulidou et al.,[28] performed mapping biopsies preoperatively to determine resection borders. Christoudoulidou et al.,[28] on the other hand, performed mapping biopsies postoperatively; they also reported the highest rate ratio of positive margins when comparing both arms of the study and had the lowest rate ratio of no recurrence. Furthermore, the latest study by Rose et al.[26] attempted to create a standardized method for performing mapping biopsies but was unable to replicate any significant success in improving disease outcomes. It is thus suggestive that differences in outcome might be associated with the technique employed in performing mapping biopsies as well beyond simply employing the concept in primary EMPD surgical management. Identifying these various factors that can impact disease and treatment outcomes, lays the groundwork for subsequent trials to be run to improve the surgical management of EMPD.

A further confounder is that some studies included patients with regional spread of disease or disease that involved the lymph nodes and beyond, while others did not. However, as the subset of patients with such a distant spread beyond the primary site was small (Supplemental Tables S3 and S4, http://links.lww.com/AOSO/A255), subset analysis could not be carried out on these patients in this review. We do note that the prognosis for primary EMPD without spread is generally good regardless of what treatment modality is chosen, and hence the number of patients without recurrence might be inflated owing to the nature of the disease itself rather than the chosen treatment modality.[13] Prognosis of primary EMPD is directly linked to the extent of disease; hence, it is unclear whether preoperative mapping biopsies would improve outcomes for specific subsets of patients.

Finally, what fails to be discussed in several of these articles is the tedium and time-consuming nature of mapping biopsies. Patients would have to undergo an additional surgical procedure to obtain the mapping biopsies, which can prove to be logistically inconvenient. Furthermore, patients will have to undergo general anesthesia for both surgical procedures. Such factors may tilt the balance away from mapping biopsies becoming the modality of choice in EMPD management.

While this study looked at recurrence rates and the margin status postsurgical resection of patients who underwent mapping biopsies and those who did not, a comparison of the 5-year survival rate would be useful in comparing disease recurrence regardless of follow-up duration, which can only be achieved in a multi-center study in view of the rarity of the disease. Understanding the indolent nature of this disease, patients may opt for surveillance instead of a second operation when the disease recurs. The clarity on the definitive outcomes of EMPD, such as overall survival, visits to hospitals, and quality of life following disease recurrence or progression, is greatly lacking in the literature and needs to be further studied. Additionally,

a subset analysis of EMPD patients who underwent mapping biopsies, if more data can be obtained for meaningful assessment, should also be considered.

In conclusion, mapping biopsies may statistically improve EMPD surgical excision outcomes but are limited by the small number of cases and heterogeneity of mapping biopsy protocols. However, this remains the first attempt at aggregating disparate small population studies done thus far to assess the utility of mapping biopsies in the surgical management of primary EMPD. Further confirmation through randomized controlled trials or aggregating a larger patient pool would be necessary.

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