

## Surgical Experience With Genital and Perineal Extramammary Paget's Disease



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<b>OBJECTIVE</b>	To describe our surgical experience for the treatment and management of extramammary Paget's disease (EMPD).
<b>METHODS</b>	Our surgical approach involves excising a 2-cm margin of normal appearing skin around the EMPD-suspicious lesion. Prior to excision, the tissue is oriented and demarcated into predefined segments in coordination with a pathologist. Frozen sections are performed when necessary to guide additional excision. Xenograft or wet-to-dry dressings are applied depending on size and location of the wound while the specimen is expeditiously reviewed over the following 24-48 hours. If positive margins remain, further excision of the corresponding skin segment is performed. Delayed complex wound closure +/- split thickness skin grafting is performed once negative margins are confirmed.
<b>RESULTS</b>	Ten EMPD patients were referred to two academic centers between 2014 and 2018. Two patients had positive lymph nodes at diagnosis and underwent palliative surgery and died within 12 and 29 months. The remaining 8 patients underwent a median of 1 surgery (range 0-3) with referring providers before undergoing a median of 3 surgeries (range 2-5) at our institutions to achieve negative surgical margins and wound reconstruction (7 split thickness skin grafts, 1 secondary closure). At mean follow-up of 15 months, 1 patient recurred, required further excision, and remains disease free.
<b>CONCLUSION</b>	EMPD is a rare malignancy with poorly described treatment methodologies. Due to its multifocal distribution and asymmetric spread, obtaining negative margins can be challenging. Our systematic approach to obtaining wide margins and documenting excised skin has enabled us to achieve negative margins for this challenging malignancy. UROLOGY 128: 90–95, 2019. © 2019 Elsevier Inc.

Extramammary Paget's Disease (EMPD) is an uncommon yet lethal intraepithelial malignancy. Its true incidence has been reported to be as low as 0.12 per 100,000 people, with Asian men having a four-fold increased risk compared to their Caucasian counterparts.<sup>1</sup> According to United States registry-based studies, EMPD represents 21% of primary scrotal cancers and has an overall reported survival rate of 60% at 10 years after initial diagnosis.<sup>2,3</sup> Due to the sparsity of EMPD cases and lack of clinical studies, a clear consensus does not exist on diagnostic approaches, therapeutic interventions and follow-up management. EMPD has also been treated by an array of medical specialties who implement varying

treatment strategies which further impedes the ability to develop standardized treatments regimens.<sup>4</sup>

The most common treatment for EMPD is complete excision of the lesion with the goal of achieving microscopically clear margins.<sup>5,6</sup> Obtaining negative margins can be a challenging task since EMPD lesions are often multifocal and develop asymmetrically with skip lesions. Obtaining negative margins prior to definitive wound closure is important to minimize local recurrence and maximize durable cure. Unfortunately, few recommendations exist regarding management of positive margins. A recent study reported that of 16 patients who had a positive margin, 7 underwent further surgical excision to achieve negative margins, 4 underwent reoperation after initial monitoring, and 5 underwent surveillance alone.<sup>4</sup> This strategy is not optimal in our opinion. We describe our strategy for managing genital EMPD and approach to obtaining negative margins before definitive wound closure with the aim of reducing the number of necessary subsequent index operations in a multicentered cohort. Although our techniques to managing EMPD may not be

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novel, we believe this study will increase awareness, educate providers, decrease delay in care, and improve prognosis for this rare disease.

## MATERIALS AND METHODS

Institutional review board approval was received to perform a retrospective review of patients referred to our institutions with EMPD from 2014 to 2018. Patient demographics, history, lesion characteristics, treatment plans, and follow-up were evaluated.

### Workup

The initial work up for EMPD begins with a thorough history and physical examination (Table 1). Attention is paid to the suspected EMPD lesions to assess location, size, color, distribution, and morphology. A biopsy is obtained if not performed already. If available, outside pathology is reviewed to evaluate

**Table 1.** Management and treatment of extramammary Paget's Disease (EMPD)

<b>Workup</b>
<ul style="list-style-type: none"><li>• History and physical examination</li><li>• Biopsy if not performed already</li><li>• Laboratory tests and carcinoembryonic antigen (CEA) levels</li><li>• Cross sectional imaging studies of abdomen and pelvis +/- chest</li><li>• Screening for secondary malignancies if clinically indicated<ul style="list-style-type: none"><li>◦ Prostate specific antigen (PSA)</li><li>◦ Cystoscopy</li><li>◦ Colonoscopy</li><li>◦ Pap smear</li></ul></li></ul>
<b>Treatment</b>
<ul style="list-style-type: none"><li>• Wide local excision<ul style="list-style-type: none"><li>◦ Excision is performed with a 2-cm margin from the clinically apparent lesion</li><li>◦ Tissue border is demarcated into predefined segments using sutures of varying color and numbered to assist with communication with the pathologist</li><li>◦ Photographs are taken at each step to guide further excision if positive margins are present</li><li>◦ Surgical wounds not amendable to primary closure are covered with xenografts or wet-to-dry dressings</li><li>◦ Patients are admitted for wound care if primary closure cannot be performed</li></ul></li><li>• Pathology review is performed expeditiously over 1-2 days<ul style="list-style-type: none"><li>◦ If positive margins are present, further excision of the corresponding segment is performed</li><li>◦ Once negative margins are confirmed, delayed complex wound closure is performed</li></ul></li></ul>
<b>Follow-up</b>
<ul style="list-style-type: none"><li>• Every 3 months in the first year</li><li>• Every 6 months in the second year</li><li>• Once a year from the third year onwards</li><li>• Recurrent evaluations may include:<ul style="list-style-type: none"><li>◦ Physical examination</li><li>◦ Laboratory tests and CEA levels</li><li>◦ Cross sectional imaging studies of abdomen and pelvis</li><li>◦ Mapping biopsies</li></ul></li></ul>

for dermal invasion which portends a greater risk for adverse prognosis and increased risk for local recurrence, nodal metastasis, distant metastasis, and mortality.<sup>4,7,8</sup>

A comprehensive laboratory workup, including serum carcinoembryonic antigen (CEA) is also obtained. Elevated serum CEA has been associated with systemic metastasis with 70% sensitivity and 94% specificity in EMPD.<sup>7</sup> Cross-sectional imaging of the abdomen and pelvis is also obtained to evaluate for nodal or metastatic disease. Chest imaging should be performed at the discretion of the provider, as one of our patients was noted to have subclinical inguinal lymph nodes in the setting of a palpable supraclavicular lymph node. Screening for malignancies, such as bladder, prostate, rectal, colon, and cervical, is also performed since EMPD has been associated with secondary malignancies in 20%-30% of patients.<sup>8,9</sup> If the patient has lapsed the recommended screening intervals, a referral to the respective specialty is obtained.

### Treatment

The preferred treatment method is wide local excision with a 2-cm margin and a depth below the dermis into the fatty tissue. Prior to excision, the tissue is oriented and demarcated into predefined segments. Sutures of varying color and number are utilized to demarcate the segments to assist with communication with the pathologist. Photographs are taken at each step to guide orientation if further excision is required for positive margins (Fig. 1). Intraoperative frozen sections are performed when needed, especially when lesions are close to sensitive areas (eg anus) where wide margins cannot be obtained.

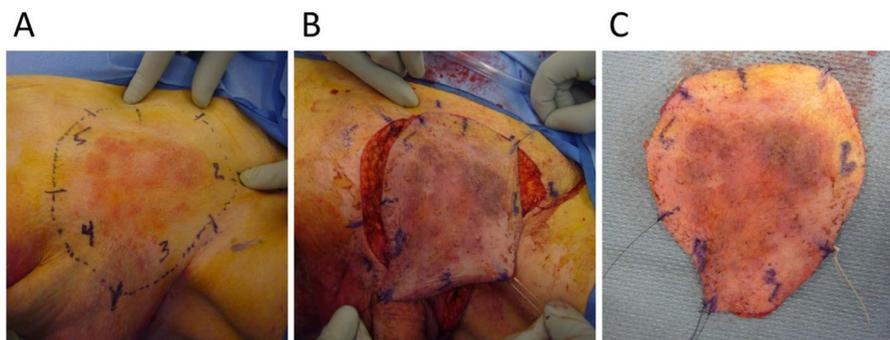
Xenografts or wet-to-dry dressings are applied to the surgical wounds when simple closure cannot be performed. Patients who require complex closure are admitted for wound care, dressing changes, and pain management while the specimen is expeditiously reviewed over the next 24-48 hours. If positive margins are present, patients are taken to the operating room for further excision utilizing the prior photographic documentation to assist with specimen orientation and coordination with the pathology report. This process is repeated until negative margins are confirmed. Delayed, complex wound closure with or without split thickness skin grafting or local flaps is performed, typically during the same admission, as soon as negative margins have been confirmed.

### Follow-Up

Patients are followed with a clinical exam every 3 months in the first year, 6 months in the second and annually thereafter. We have adopted a plan of cross-sectional imaging of the abdominal and pelvis and CEA level every 3-6 months during the first 2 years based on EMPD volume at the discretion of the surgeon. Mapping punch biopsies are performed according to clinical suspicion for disease recurrence. We do not administer adjuvant topical therapies such as imiquimod cream until further data supports its clinical usage and benefits.

## RESULTS

Ten patients (9 male, 1 female) were referred to 2 academic centers between 2014 and 2018 with a known diagnosis of EMPD (Table 2). Mean age at diagnosis was 70 years (range 55-88). Mean time from onset of symptoms to initial EMPD diagnosis was 20 months (range 3-60). Of the 10 patients, 8 experienced rash, 1 experienced itching, and 1 complained of erythema as



**Figure 1.** (A) A 2-cm margin is demarcated around the clinically suspicious lesion as shown by the dotted line. The tissue is demarcated into pre-defined segments as noted by the numbers separated by perpendicular lines. Wide local excision is performed (B). Sutures of varying color and number are utilized to further demarcate the predefined segments to assist with communication with the pathologist (C). Photographs are taken at each step to guide further excision if positive margins are present. (Color version available online.)

the presenting symptoms which were localized to the suprapubic, scrotal, groin, and perianal regions. All patients had a prior biopsy by a dermatologist and 6 among the 10 underwent a total of 10 surgeries prior to referral to our center for EMPD management. Among the 10 surgeries, 4 were Mohs micrographic surgery (MMS) performed by dermatologists, while the remaining 6 were wide local excisions performed by surgical oncologists (50%), a colorectal surgeon (33%), and a reconstructive urologist (17%).

At presentation, 2 patients (ID 3,5) were positive for lymph node metastasis and required palliative surgeries for pain and swelling. These patients died within 12 and 29 months, respectively. Serum CEA levels were available for 7 patients, all of which were normal except for the 2 patients with metastatic disease, both of whom had elevated serum CEA levels. No patient was diagnosed with a de novo secondary malignancy during our evaluation.

The remaining 8 patients without metastatic disease underwent a median of 1 surgery (range 0-3) prior to being referred to our institutions. These patients subsequently underwent a median of 2 additional surgeries (range 1-4) at our institutions to achieve negative surgical margins with an additional 1 surgery for complex wound closure. Mean lesion diameter was 18 cm (range 10-30). No patients experienced graft failure, donor site issues, or other postoperative wound complications. At a mean follow-up time of 15 months (range 7-30), 1 patient (ID 1) experienced a recurrence and required further excision and reconstruction. Of note, this was the lone patient with deep invasion beyond the dermis and no associated lymphadenopathy. During the initial resection, there was invasion to the left testicle necessitating a simple orchiectomy. The advanced local disease may have precluded him to a higher risk for EMPD recurrence. Fortunately, he has not had repeat recurrence of his EMPD.

## DISCUSSION

EMPD is distinct from Paget's disease of the breast. EMPD predominantly affects the apocrine gland-bearing skin such as the perianal, genital and axillary regions and most commonly presents as either a well-demarcated or poorly defined erythematous, pruritic, eczematoid rash that may subsequently undergo ulceration, erosion, or

even pigmentation (Fig. 2).<sup>10</sup> Topical emollients, powders, antifungal creams, and oral therapy are often initially prescribed but are ineffective. Due to the rarity of this disease and its similar clinical presentation to benign conditions, the diagnosis of EMPD is often delayed for months to years, with only 17% of patients being correctly diagnosed at first presentation.<sup>4,11,12</sup> To avoid a delay in diagnosis, providers should biopsy lesions that fail to respond to expectant treatments. Additionally, a referral to a specialist may be warranted to further decrease the risk of a delayed diagnosis when lesions demonstrate atypical findings on presentation.

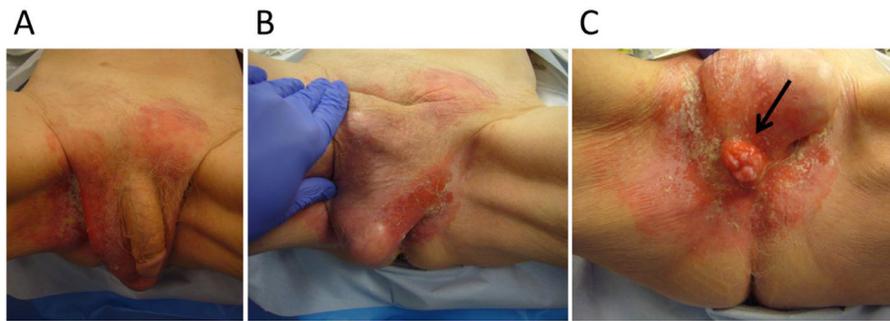
Current treatment recommendations are based on small case reports and single institutional series.<sup>13-15</sup> A recent study evaluating patients' experiences with EMPD found that various types of treatment modalities were being offered to patients with wide local excision (57%) being the most common, followed by MMS (26%) and topical imiquimod (26%), with radiation, laser, and photodynamic therapy representing a smaller minority.<sup>4</sup> The choice of surgical approach remains a debate among caregivers with some studies claiming that MMS is superior to wide excision in obtaining negative margins, while others claiming that both approaches are comparable in achieving adequate cancer control.<sup>16,17</sup> Several studies have demonstrated that wide excision can be performed safely and effectively and yields equally satisfactory results to MMS.<sup>18,19</sup>

EMPD is insidious in nature such that margin status cannot always reliably be determined intraoperatively via gross examination. Malignant cells are capable of extending microscopically beyond the grossly evident lesion in an irregular and multifocal pattern.<sup>20</sup> Rates of positive margins for MMS and wide local excision ranged from 8% to 26% and 20% to 50%, respectively.<sup>16,17,19-25</sup> Obtaining negative margins is crucial since positive surgical margins are associated with a higher risk of local recurrence and less durable cure in noninvasive disease.<sup>5,6,10</sup> Techniques such as excising wider margins, performing preoperative mapping biopsies, and obtaining intraoperative immunohistochemical staining and frozen

**Table 2.** Patient demographics and treatment history

ID	Age at Diagnosis	Gender	Presenting Symptom	Area of Presentation (Primary Site)	Symptom Duration Prior to Diagnosis (Months)	Largest Lesion Diameter (cm)	Metastatic Disease	Number of Surgeries Required to Achieve Negative Margins	Total Number of Surgeries Including Reconstruction	Time Between First and Last Surgery (days)	Reconstruction Method	Follow-Up (months)	Recurrence	Status	Survival Time (months)
1	85, M		Rash	Penis, Scrotum, Suprapubic	24	16	No	2	3	7	STSG	18	1	Alive	—
2	72, M		Rash	Scrotum, Suprapubic	6	20	No	3	4	9	STSG	17	0	Alive	—
3	62, M		Rash	Perineum, Scrotum	36	20	Lymph node	1	2	7	STSG	10	—	Passed	12
4	69, M		Rash	Groin, Scrotum	24	15	No	1	2	5	STSG	30	0	Alive	—
5	71, M		Erythema	Groin	6	20	Lymph node	1	2	4	STSG	5	—	Passed	29
6	55, M		Rash	Groin, Perineum, Scrotum	6	17	No	1	2	2	STSG	18	0	Alive	—
7	71, F		Itching	Perianal, perineum	24	10	No	4	4	20	Secondary intention	7	0	Alive	—
8	58, M		Rash	Penis, Suprapubic	60	30	No	2	3	6	STSG	13	0	Alive	—
9	66, M		Rash	Groin, Scrotum	3	10	No	3	4	13	STSG	10	0	Alive	—
10	88, M		Rash	Perineum, Scrotum, Suprapubic	12	21	No	2	3	7	STSG + abdominal advancement flap	7	0	Alive	—

EMPD, extramammary Paget's disease; STSG, split thickness skin graft.



**Figure 2.** An 88-year-old male (ID 10) presents with a pruritic rash after a skin biopsy confirmed the diagnosis of extramammary Paget's disease. Erythematous lesions with ill-defined borders are seen in the suprapubic (A), inguinal, scrotal (B), and perineal (C) regions. The arrow in C shows a concomitant sebaceous gland carcinoma. (Color version available online.)

sections have been described to combat the issue with positive margins.<sup>11</sup> However, a recent case series by Long et al described a high incidence of positive margins despite the use of intraoperative frozen sections. This is because when only a limited number of pathology sections are assessed intraoperatively, microscopic projections of EMPD may be potentially missed. For this reason, we prefer to perform wound closure when and only after final pathology has been reviewed and finalized.<sup>26</sup>

Wide local excision is the preferred surgical approach for patients at our institutions and is performed with a 2-cm margin to help overcome the insidious nature of EMPD. A study analyzing 46 EMPD patients who underwent wide excision found that the distance between the last lesional cell on histopathology to the resected edge measured 1.02 cm on average. This, together with surgeon preference, justified our approach for obtaining 2-cm margins when managing our EMPD patients.<sup>27</sup> Most of the patients in our series were referred by a dermatologist with large lesions less amenable to MMS (average diameter 18 cm, largest diameter 30 cm). In a review of MMS studies for EMPD, 72% of patients had lesion sizes less than 10 cm and 97% had lesion sizes less than 15 cm.<sup>19,28,29</sup> Our protocol is to delay complex closure until negative margins have been confirmed. Patients requiring complex wound closure (90% of patients in this series) are admitted for wound care with xenografts or wet-to-dry dressings as permanent specimens are being expeditiously reviewed. If positive margins are identified (60% in our series), the patient is returned to the operating room for further excision. In our series, patients required a median of 2 trips to the operating room to achieve negative margins, despite the use of 2 cm margins, prior to undergoing wound closure. This systematic approach has allowed us to achieve negative surgical margins for this challenging malignancy.

We believe this utilization of physician effort and hospital resources is worthwhile and beneficial in providing the best possible outcomes for patients. We achieve negative margins, which have been associated with a 4% recurrence rate compared to positive margins with a 53%-56% recurrence.<sup>5,6</sup> Furthermore, in

contrast to MMS, which is an outpatient procedure performed under local anesthesia, our patients benefit from inpatient care and are discharged home only when wound closure has been performed.

Our study is limited by a retrospective review of a small patient cohort with limited follow-up; however, we believe this work will help to increase awareness of this rare disease. Urologists with reconstruction training, may be valuable in caring for these patients due to gained experience in genital reconstruction and complex wound closure. In the absence of such experience, working with a plastic surgeon comfortable with genital grafting is recommended. This study provides an initial foundation to managing patients suffering from EMPD. Further studies involving a multi-institutional cohort and coordination amongst other specialties who may treat EMPD will hopefully lead to the development of future treatment guidelines and recommendations.

## CONCLUSION

Our experience for the surgical management of EMPD is as follows: due to the high prevalence rate of positive margins and its association with disease recurrence, physicians should not perform flap wound closure or complex grafts in patients until final pathology margins are confirmed to be negative. Patients may best be served with inpatient care between these surgeries. We also recommend that these patients be referred to centers of excellence to ensure homogeneity in treatment and follow-up which would potentially improve and standardize care. Although our techniques to managing EMPD may not be novel, we believe this study will increase awareness, educate providers, decrease delay in care, and improve prognosis for this rare disease.

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