Extramammary Paget's disease: Surgical treatment with Mohs micrographic surgery

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Background: Extramammary Paget's disease (EMPD) is an uncommon tumor that has a high rate of recurrence after conventional surgical treatments.

Objective: Our purpose was to establish the efficacy of Mohs micrographic surgery (MMS) in the treatment of EMPD, and to make treatment recommendations with regard to surgical margins. We also attempted to summarize the published recurrence rates of EMPD after standard surgical management.

Methods: In a retrospective chart review, pertinent demographic data, tumor data, treatment characteristics, and follow-up data were tabulated. A search of the literature for recurrence rates after MMS and non-MMS surgical treatment modalities was performed.

Results: The recurrence rate after treatment with MMS was 16% for primary EMPD and 50% for recurrent EMPD. The 5-year tumor-free rates (Kaplan-Meier analysis) were 80% for primary tumors and 56% for recurrent tumors. Using MMS, the salvage rate (and, hence, overall cure rate) was 100%. Margins of 5 cm were required to clear 97% of the tumors. The recurrence rate after non-MMS (from the literature) is 33% to 60%.

Conclusion: MMS is effective, and superior to standard surgical management in the treatment of EMPD. We recommend a 5-cm margin of normal skin if MMS cannot be offered. (J Am Acad Dermatol 2004;51:767-73.)

Extramammary Paget's disease (EMPD) is an uncommon malignancy that usually affects the genital skin, and less commonly the axilla, in elderly patients. It is thought to be an apocrine tumor, which arises within the epidermis from native stem cells that differentiate toward glandular cells.[1] EMPD is often undiagnosed for years as it can mimic contact or irritant dermatitis, seborrheic dermatitis, tinea cruris, candidiasis, inverse psoriasis, or Bowen's disease. There are reports of EMPD arising in the eyelids,[2] ear canal,[3] and the umbilicus.[4] Standard surgical management procedures with wide local excision, vulvectomy, or abdominoperineal resection can carry significant morbidity and deformity. The recurrence rates with these modalities are relatively high (up to 60%).[5] This is likely because of the characteristic microscopic extension of EMPD beyond the clinically visible margins.[1]

The use of Mohs micrographic surgery (MMS) in the management of EMPD has been documented in the medical literature.[6-11] However, there are no large cohorts evaluating the efficacy of MMS in the management of EMPD. MMS differs from routine excision with histologic margin examination by providing intraoperative microscopic evaluation of 100% of the tissue margin. The technique allows for the microscopically guided excision of tumors and preservation of normal tissue. In contrast, routine frozen sections, done without Mohs technique of enface sectioning, sample less than 0.1% of the surgical margin. To examine the entire margin of 1 cm of submitted specimen by serial vertical sectioning, as many as 1500 sections (7-μm thick) would be required.[12] The paucity of data from a large cohort, and our successful experience with treating EMPD with MMS, led us to review the cases performed during a period of 20 years.

METHODS

Daily surgical logs for all the cases performed by the authors (J. A. Z.: 1983-2003; D. G. B.: 1997-2003) were reviewed and all cases of EMPD were noted. Detailed review of each patient's medical record was undertaken and all relevant data collected (Table I).

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Funding sources: None.
Conflicts of interest: None identified.
0190-9622/$30.00

doi:10.1016/j.jaad.2004.07.004

Table I. Patient demographics, tumor and treatment characteristics, and follow-up data

Case no.	Patient	Sex	Site of EMPD	Size (cm)	P/R (previous treatment) MTR	Stages/margins (cm)	Closure	Follow-up (mo)	Recurrence
Primary tumors treated with MMS									
1	A	M	Perianal	7	P	3/2.0	REF	4*	No
2	B	M	Perineum	15 × 15	P	2/1.8	AF	9	Yes
	B	M	Perineum	4	R (MMS)	2/1.2	AF	76	No
3	C	F	Perineum	8	P	4/3.8	REF	29	Yes
	C	F	Vulva	3.5	R (MMS)	1/0.7	AF	15	No
4	D	M	Scrotum	4 × 10	P	2/1.6	AF	96	No
5	E	F	Pubic	6	P	3/1.8	2°	12	No
6	F	F	Vulva	3.5	P	4/1.8	AF	101	No
7	G	M	Scrotum	8	P	2/1.5	REF	108	No
8	H	F	Perianal	10	P	2/1.5	REF	97	No
9	I	M	Perineum	15 × 8	P	2/0.9	REF	21	No
10	J	M	Scrotum	6 × 7	P	3/2.5	AF	40	No
11	K	F	Left axilla	5	P	1/1.0	AF	38	No
12	L	F	Vulva	12.5	P	2/1.8	REF	59	No
13	M	M	Perineum	6 × 11	P	2/2.5	REF	54	No
14	N	M	Left groin	12	P	4/3.5	AF	42	Yes
	N	M	Left groin	2 × 7	R (MMS)	2/1.8	AF	37	No
15	N	M	Right groin	1.5	P	5/5.0	AF	59	No
16	O	F	Perianal	2.8	P	2/1.3	AF	16	No
17	P	F	Left axilla	5	P	1/0.6	AF	72	No
18	Q	M	Right perineum	15	P	3/5.0	REF	106	No
19	Q	M	Left perineum	13	P	4/3.5	REF	106	No
Recurrent tumors (after non-MMS) treated with MMS									
1	R	F	Vulva	3 × 8	R (excision ×5) 4	5/3.6	AF	26	No
2	S	F	Vulva	5	R (CO_2 laser) 15	6/3.5	2°	104	No
3	T	M	Perineum	20	R (excision)	5/4.0	2°	57	Yes
	T	M	Suprapubic	1	R (MMS)	1/0.6	AF	84	No
4	U	M	Pubic+Penis	4	R (Efudex) 6	4/2.0	STSG	7	Yes
	U	M	Scrotum	3.5	R (MMS)	2/2.0	STSG	174	No
5	V	F	R axilla	4	R (LN_2) 12	1/0.6	AF	116	No
6	W	M	Scrotum	2.5	R (excision) 10	9/11.0	AF	99†	Yes
	W	M	Perirectral	3	R (MMS)	3/1.8	AF	71	No
7	X	F	Vulva	10	R (PV) 84	3/2.2	AF	8	Yes
	X	F	Vulva	1	R (MMS)	5/2.8	2°	NA‡	NA
8	Y	F	Vulva	5	R (V) 42	4/3.5	AF	26	No

AF, Advancement flap; *CO_2*, carbon dioxide laser destruction; *EMPD*, extramammary Paget's disease; *F*, female; *LN_2*, liquid nitrogen destruction; *M*, male; *MMS*, Mohs micrographic surgery; *MTR*, months to recurrence after non-MMS; *NA*, not applicable; *P*, primary; *PV*, partial vulvectomy; *R*, recurrent; *REF*, referred; *STSG*, split-thickness skin graft; *V*, vulvectomy; *2°*, second intention healing.

*Patient died of unrelated cause.

†Patient with perirectal recurrence distant to the site of first MMS on the scrotum.

‡Patient with positive margins after last stage of MMS and refused further surgery to clear margins; asymptomatic at time of submission.

Follow-up visits and telephone surveys were performed for all patients. Examination of the affected area by a physician was required to establish the presence or absence of recurrence. Recurrence was defined as the persistence/reappearance of tumor at the surgical margin (ie, marginal recurrence). For patients who had a recurrence, repeated MMS of the tumors was undertaken. The recurrence-free period is noted (in months) in the follow-up column.

Technical aspects of performing MMS are reviewed elsewhere.[13,14] All patients had histologic diagnosis of EMPD on permanent sections before undergoing MMS of the tumors. The margins taken for the initial stage of MMS were based on the visible extent of the lesion, and in some cases mapping biopsy specimens of the lesion. Small lesions (ie, <8 cm) or those with histologic or clinical signs of invasion into subcutaneous tissue were processed using standard Mohs techniques, ie, the entire

peripheral and deep margins were evaluated by frozen sections. Large lesions of EMPD (>8 cm) that were superficial and had no evidence of invasion were managed with a modified technique, which we refer to as "peripheral Mohs." In this modification, the peripheral margin of the tumor was demarcated and excised using MMS. The remaining central island of tumor (containing skin, all adnexa, and superficial subcutaneous tissue) was then excised at the level of the midsubcutaneous tissue. This assured removal of the epidermal tumor, along with any potential Paget's cells extending down the adnexa. Histologic evaluation of the entire deep margins of indicated lesions was not undertaken. This modification was performed to save time and expense of microscopic examination of extremely large tissue areas.

To determine the efficacy of standard surgical management for EMPD, a search of the English-language literature was performed. Standard operation is defined as excision of the visible tumor plus a margin by the surgeon and histologic examination (frozen and/or permanent sections) of the tissue, processed by standard bread-loaf sectioning, by a pathologist. Examples include local excision, wide local excision, vulvectomy, and abdominoperineal resection. Case reports and series with less than 10 patients were excluded. As our goal was to compare the local recurrence rate after MMS and standard operation, only such data were pulled from each study. Hence, if the study did not otherwise specify that the recurrence was a local recurrence, these data were omitted.

RESULTS

In all, 25 patients with 27 lesions of EMPD were referred for MMS. There were 12 male and 13 female patients. All patients were Caucasian. Of the tumors, 52% (14/27) involved the male gentialia/groin (including one perianal). The remaining 13 tumors were in women and consisted of 26% (7/27) vulvar, 11% (3/27) axillary, 7% (2/27) perianal, and 4% (1/27) pubic.

A total of 34 cases of MMS were performed on 19 primary tumors, 8 tumors recurrent after non-MMS, and 7 tumors recurrent after MMS. Table I tabulates the patient demographic data, tumor and treatment characteristics, and follow-up data. Mean age at time of MMS was 68.8 years (range: 56-82 years). The mean size of all lesions (based on largest diameter in centimeters) was 7.3 cm (range: 1-20 cm). The mean number of MMS stages was 3.1 (range: 1-9 stages). The mean margin needed to clear all tumors was 2.5 cm (range: 0.6-11 cm). The outlier margin of 11 cm was in a case of scrotal EMPD that had been previously excised before MMS. A total of 5 cm of normal-appearing skin from the visible tumor margin was needed to obtain microscopically clear margins in 97% of the cases.

There were 3 recurrences among the 19 primary tumors treated with MMS. Hence, the recurrence rate for primary EMPD was 16% (3/19), with a cure rate of 84% (mean follow-up 59.2 months, median follow-up 56.5 months). The Kaplan-Meier 5-year tumor-free rate is 80% (Fig 2). In this group, the median recurrence time was 29 months.

There were 4 recurrences in the 8 tumors that were previously treated with non-Mohs surgical and nonsurgical modalities. The recurrence rate for recurrent tumors was 50% (mean follow-up 56.6 months, median follow-up 41.5 months). The Kaplan-Meier 5-year tumor-free rate for this group was 56% (Fig 2). The median time to recurrence in this group was 32.5 months.

The composite recurrence rate for primary and recurrent tumors was 26% (7/27) with a mean follow-up of 58 months and median follow-up of 55.5 months (range: 7-116). The 7 recurrences after MMS were retreated with MMS, and there were no recurrences in this group (mean follow-up 76.2 months, median follow-up 73.5 months). One patient (X) is excluded from this group as she deferred completion of the MMS procedure. Hence, the salvage rate and the overall cure rate for treatment of EMPD with MMS is 100%. Fig 1 summarizes the above data.

In this cohort 3 patients had or developed other internal malignancy. Patient S had cervical cancer. Patient P developed breast cancer on the contralateral side of the axillary EMPD. Patient O, at age 76 years, developed lung cancer 9 years after being given the diagnosis of EMPD. Two patients had metastatic EMPD. Patient M developed metastasis to the right inguinal lymph nodes 2 years after operation and underwent lymph node dissection and radiation therapy. He had no evidence of marginal recurrence and was well 54 months after MMS. Patient I developed lymph node metastasis 19 months after MMS, and died of metastatic disease 2 months later. He had no evidence of recurrence at the margin. Of note, patients I and M were the only two patients in the cohort who had clinical evidence of invasive disease (plaques and nodules) and, hence, the entire deep margin was evaluated at time of MMS (in contrast to peripheral Mohs) and neither developed local recurrence. One patient (A) had involvement of the rectal mucosal margin after the last stage of MMS. He was referred for excision of the rectal margin and closure of the defect.

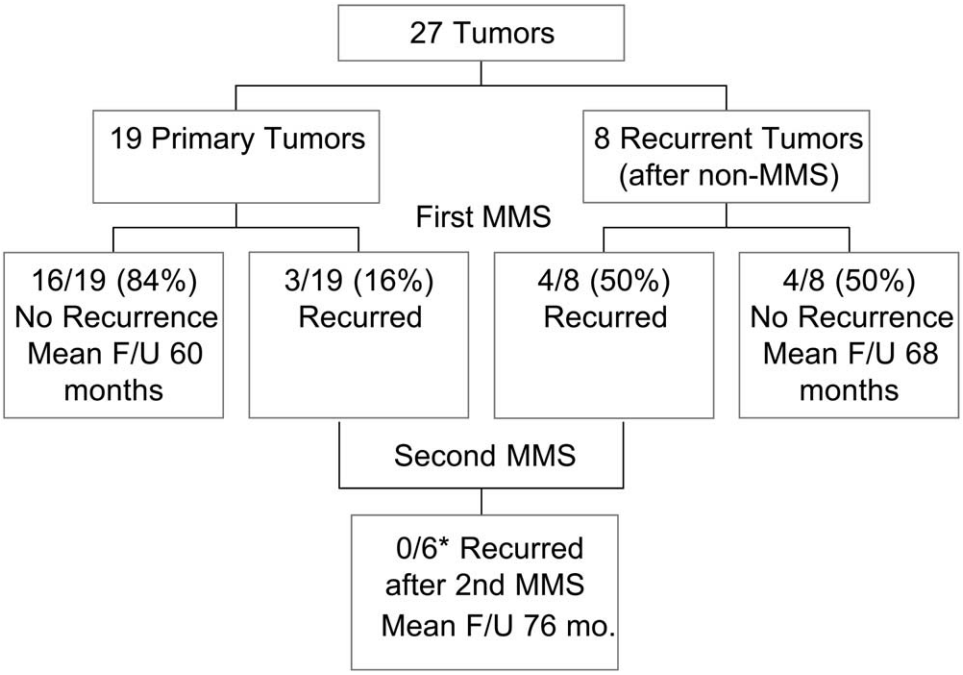

Fig 1. Patient treatment, recurrence, and follow-up (*F/U*) data. Two patients (I and M) developed nodal metastasis with no evidence of local recurrence, and are not included. One patient* (T) deferred subsequent stages to obtain clear margins during second Mohs micrographic surgery (MMS) and is excluded from total.

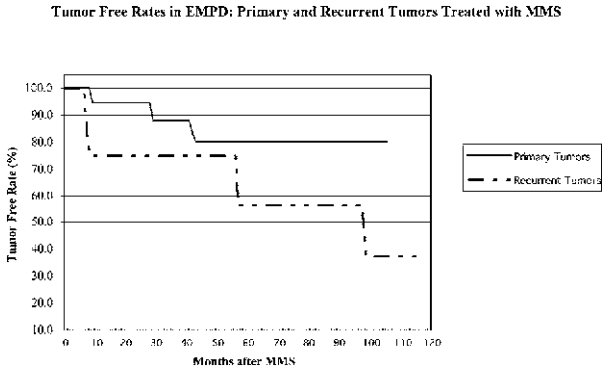

Fig 2. Kaplan-Meier graph of tumor-free rates for primary and recurrent tumors treated with Mohs micrographic surgery (MMS). Five year tumor-free rates for primary and recurrent tumors are 80% and 56%, respectively.

The frozen-section slides from all cases recurrent after MMS were reviewed. They were evaluated for any missed tumor cells during initial evaluation of the horizontal frozen sections. Only one case (patient C), showed an error in interpretation of the frozen sections. Histologic examination of this case was complicated by the inflammatory infiltrate involving the epidermis with widening of the rete ridges in the area of recurrence.

With regard to the reconstruction of the defects after the 34 cases of MMS, 19 (56%) were reconstructed with advancement flaps, two (6%) with split-thickness skin grafts, and 4 (12%) were allowed to heal by secondary intention. In all, 8 patients (27%) were referred for reconstruction, and most were repaired by split-thickness skin grafts.

A literature search was performed for recurrence rates of EMPD treated by standard surgical management. These data are presented in Table II. Variabilities in study design and tumor characteristics preclude statistical comparison of the data. Table III summarizes the range of recurrence rates for MMS and standard operation.

DISCUSSION

It is clinically difficult to distinguish the margins of EMPD from normal skin. Standard surgical management of EMPD are associated with an inherently high recurrence rate, and repeated operations lead to significant morbidity and deformity. MMS offers an alternative to blind excision of EMPD, or excision with frozen-section sampling of a fraction of the margins. It offers the ability to microscopically visualize the entire margin and remove only the affected tissue and, hence, a lower recurrence rate.

The MMS technique requires a frozen-section laboratory and skilled histotechnologists. The formal training of a histotechnologist typically does not

Table II. Local recurrence rates and follow-up after standard surgical management

Study	LE	WLE	APR	Total	Mean follow-up (mo)
1991[8]	Literature review: conventional excision with frozen/fixed margin control			33% (37/112)	54
1997[5]*	100% (2/2)	50% (4/8)		60% (6/10)	96
1997[17]*	83% (5/6)	20% (1/5)	0% (0/2)	46% (6/13), 61% 5 y	80
1999[15]†				31% (31/100)	84
2000[6]‡		43% (3/7)		43% (3/7)	44
2003[16]*		43% (9/21)	0% (0/5)	35% (9/21)	91

APR, Abdominoperineal resection (for perianal EMPD only); *LE*, local excision; *WLE*, wide LE.
*Perianal disease only.
†Primary vulvar EMPD only; nonlocal recurrence excluded.
‡Vulvar EMPD; unspecified or distant recurrence excluded (18 patients with 8 recurrences).

Table III. Local recurrence rates after Mohs micrographic and standard surgeries

Mohs micrographic surgery	Standard surgical management
8%-26%[8,11, current study]	33%-60%[5,6,8,15-17]

include horizontal sectioning of tissue. Hence, the histotechnologist needs to be trained in mounting and cutting horizontal frozen sections. In addition the Mohs surgeon should have advanced training, and be experienced in performing MMS on such rare tumors as EMPD. It should be noted that the training of the Mohs surgeon provides the skills to not only remove cutaneous tumors, but to perform the histologic evaluation of the tissue. In a multidisciplinary approach, the Mohs surgeon can delineate tumor-free margins, and a gynecologic, urologic, colorectal, oncologic, or plastic surgeon can repair the resultant defect.

To perform MMS on large tumors, the peripheral Mohs modification was instituted for large tumors that did not have clinical or histologic evidence of invasion. With this technique, the peripheral margin of the epidermal EMPD was defined using MMS, and the central tumor-bearing island of tissue was excised at the level of the mid subcutaneous tissue. This assured the removal of the Paget's cells in the epidermis and adnexa. It should be noted that the most common type of EMPD is one in which the Paget's cells appear to be of epidermal origin and only invade the adnexa at a late stage.[1] When Paget's cells are confined to the epidermis and adnexal structures, metastatic disease never occurs.[1]

Although cutaneous EMPD can uncommonly invade beyond the basement membrane, or rarely affect the skin by extension from a noncutaneous internal neoplasm, it is believed that many cases reported as having an underlying adnexal carcinoma may have simply been because of the "incidental downward invasion of the Paget's cells into the adnexa."[8] In addition, it has been shown that dermal invasion of less than 1 mm is associated with a good prognosis, with no cases of metastasis in a series reported by Crawford et al.[18] In this series, all patients with dermal invasion greater than 1 mm had nodal metastasis. Of note, the margins in these cases were clear at the time of excision. This supports the notion that dermal invasion and lymph node metastasis are a result of the aggressive nature of the tumors and unrelated to the surgical treatment.

Only two patients (I and M) had evidence of invasion (ie, nodules on examination) and the entire deep margins were examined despite large tumor sizes. The fact that these patients went on to develop nodal metastasis without evidence of marginal recurrence alludes to the presence of metastatic disease at the time of operation. Without evidence of marginal recurrence, nodal recurrence is a reflection of the aggressive nature of the tumor, and not failure of operation. The effectiveness of a surgical modality in removing a tumor can be assessed by looking at the local recurrence rate. Marginal recurrence is indicative of failure of the excision to remove the entire tumor. This is the recurrence definition used within this study.

Patients with clinical evidence of nodal involvement may benefit from therapeutic regional lymph node dissection. There is no evidence that elective lymph node dissection, in absence of palpable nodes, improves survival. Patients with tumors invading through the basement membrane should be followed up closely for signs and symptoms of metastatic disease. Extension of Paget's cells along

the adnexa should not be confused for invasive disease unless the basement membrane has been violated.

MMS has been described in the literature as an effective means of treating EMPD.[6-11] Coldiron et al[8] reported a recurrence rate of 23% (11/48; with 42/48 cases from a survey) with a follow-up of 39 months. This consisted of a recurrence rate of 27%, 17%, and 28% after using MMS to treat EMPD of the female genitalia, male genitalia, and perianal skin, respectively. These data reflect the recurrence rate after MMS treatment of primary and recurrent lesions of EMPD (personal communication, Brett M. Coldiron, MD, October 2003). O'Connor et al[11] recently reported a recurrence rate of 8% (1/12) with a follow-up of only 24 months.

In our study the raw data total recurrence rate for all primary cases of EMPD treated with MMS was only 16% (3/19). If recurrent cases of EMPD are included in this tabulation, a recurrence rate of 26% (7/27) is obtained. The 5-year Kaplan Meier recurrence rate was 20% for primary tumors and 44% for recurrent tumors (Fig 2). MMS can be used as a method to salvage patients after recurrences from standard surgical management. In this group the salvage rate was 100%, with no recurrences at a median follow-up of 73.5 months and mean follow-up of 76.2 months. Although this was a small group, the long-term follow-up of this group lends further support to the salvage rate of 100%, which is rare in the setting of managing recurrent tumors of any type.

The median time to recurrence after MMS (for both primary and recurrent tumors) was 29 months. This is consistent with that of previous studies, which report a period of 30 to 36 months.[8,15] This underscores the importance of long-term follow-up in evaluating patients with EMPD. To our knowledge, this series is the largest cohort of EMPD cases treated with MMS, and with the longest follow-up.

It is well known that recurrent tumors treated with MMS have a higher recurrence rate compared with primary tumors. The fragmentation of the primary tumor by standard excision may, in part, explain the higher recurrence rate after Mohs excision of recurrent tumors. For example, patient W had a recurrent scrotal lesion excised with MMS, which recurred adjacent to the scar line from initial standard excision in the perirectal area.

Recurrence rates for MMS treatment of EMPD are high compared with results of MMS for other cutaneous cancers. This may in part be because of multifocal disease in some cases and difficulty in recognizing EMPD microscopically. Means of improving the visualization of Paget's cells include obtaining thinner, more complete sections; quality staining of section; and the use of markers such as cytokeratin 7[19] and carcinoembryonic antigen.[20] All the tumors treated in our series were excised without the use of any markers. As immunohistochemical procedures become more standardized and easier to perform, the widespread use of such markers as cytokeratin 7 may lower the recurrence rate after MMS even further.

The literature has perpetuated the notion that there is an association between EMPD and other internal cancers. This has been based on reports of internal cancers for patients with EMPD, who are generally older. The reported incidence of cancers for patients with EMPD has not been compared with an age-matched control group. In the largest review of the topic, Chanda[21] reported a 12% rate of concurrent internal malignancy. As most reported cases of internal malignancy appear to be in the proximity of the cutaneous EMPD, a directed internal malignancy search may be warranted. Patients with perianal EMPD should be evaluated for cancers of the lower gastrointestinal system, and those with EMPD on the genital skin should be evaluated for genitourinary malignancies.[21]

Our summary of the published data on the recurrence rate of EMPD after standard surgical management finds a 33% to 60% local recurrence rate. Table II summarizes the data from the literature. The study by Fanning et al[15] is the only one limited to primary tumors only; in most of the remaining studies primary and recurrent tumors were included or otherwise unspecified. Table III compares the range of recurrence after MMS and standard surgical management. The statistical significance of these rates cannot determined as a result of study design and tumor (ie, site and size) variabilities.

In this study, 97% of cases were cleared with a margin of 5 cm from the visible tumor margins. This finding is consistent with that of Mohs[22] who noted that clinically unapparent microscopic tumor often extends for 2 to 5 cm beyond clinical margins. A 5-cm margin may not be feasible or practical when operating on the male or female genitalia. In this study, surgical margins of 2 cm would have cleared only 59% of the tumors. It is easy to see why tumors excised with 2-cm margins would recur in approximately 40% of patients. The MMS technique provides the means to take the extra margins only for patients who need it, and only in the affected areas, hence, potentially sparing such important genitourinary anatomic structures as the urethra and clitoris.

Our retrospective review lends further support for the efficacy of MMS in treating EMPD. We also use the data from this study to recommend 5-cm margins

of normal skin when MMS cannot be offered and standard excision must be done. This is twice the 2.5-cm average margin needed using MMS in this study. MMS provides the means to map the microscopic extension of tumor, so the surgeon can customize the excision to include only the involved skin. With a lower recurrence rate, high salvage rate, and critical tissue conservation, MMS is a better alternative to standard excision in treatment of cutaneous EMPD.

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