Intraoperative Immunostaining for Cytokeratin-7 During Mohs Micrographic Surgery Demonstrates Low Local Recurrence Rates in Extramammary Paget's Disease

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BACKGROUND Extramammary Paget's disease (EMPD) is a rare intraepithelial malignancy with high recurrence rates following standard surgical treatments, ranging from 22% to 60% in large retrospective reviews.

OBJECTIVE To evaluate the local recurrence rate of Mohs micrographic surgery (MMS) supplemented with intraoperative immunohistochemistry for cytokeratin-7 (MMS + CK-7) for primary and recurrent EMPD.

MATERIALS AND METHODS Retrospective, multi-center, cross-sectional study of patients treated using MMS + CK-7. Demographic, clinicopathologic, treatment, and follow-up data were obtained by chart review.

RESULTS The observed local recurrence rate for MMS + CK-7 is 3.3% (2/61 tumors) with a mean follow-up of 43.5 months (1–120 months). Local recurrence occurred in 2.3% (1/43) of primary tumors and 5.6% (1/18) of recurrent tumors. Kaplan–Meier 5-year tumor-free rates are 94.6% overall, 97.1% for primary tumors, and 80.0% for recurrent tumors. The Kaplan–Meier 5-year tumor-free rates for all EMPD tumors treated with MMS + CK-7 versus a historical cohort of MMS alone are 94.6% versus 72.0% (p = .012).

CONCLUSION MMS + CK-7 is an effective treatment for EMPD, demonstrating improved outcomes compared with historical controls.

The authors have indicated no significant interest with commercial supporters.

Extramammary Paget's disease (EMPD) is a rare intraepithelial malignancy typically occurring in the groin and axillary regions. Given its indolent growth pattern and clinical resemblance to inflammatory skin conditions, diagnosis of EMPD is often delayed. Reported recurrence rates for standard surgical treatments including wide local excision, vulvectomy, and abdominoperineal resection are high, ranging from 22% to 60% in the largest retrospective reviews.[1–6] Previously, the authors reported the largest cohort of patients with EMPD treated with Mohs micrographic surgery (MMS) demonstrating local recurrence rates of 26% overall, 16% for primary disease, 50% for recurrent disease, and a salvage rate for recurrent disease after MMS (overall cure rate) of 100%.[7]

The authors hypothesize that the increased recurrence rates for EMPD after MMS, as compared to other types of skin cancer, are due to difficulties in

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recognizing tumor cells on routine hematoxylin and eosin staining. Indeed, the authors have previously shown a case of EMPD in the axilla with irregular yet contiguous finger-like microscopic extensions that were not seen on H&E but identified on sections stained for cytokeratin-7 (CK-7).[8] The use of intraoperative immunohistochemistry for CK-7 during MMS for EMPD is described in case studies and small single-center cross-sectional studies.[3,8,9]

The primary objective of this study is to evaluate the local recurrence rate after using intraoperative immunohistochemistry for CK-7 during MMS (MMS + CK-7) for EMPD in a large, multicenter, retrospective cohort. In addition, this study compares the efficacy of MMS + CK-7 with the efficacy of the MMS without immunostaining.

Methods

A retrospective, multi-center, cross-sectional study of consecutive cases of MMS + CK-7 for EMPD performed by the authors (A.H.: Mayo Clinic, Jacksonville, Florida and private practice, Chevy Chase, Maryland 2006–2015; J.A.Z.: private practice, Pittsburgh, Pennsylvania 2004–2015; D.G.B.: private practice, Pittsburgh, Pennsylvania 2004–2015, C.J.M.: University of Pennsylvania, Philadelphia, Pennsylvania 2011–2015) was conducted. Inclusion criteria for patients included histopathologic confirmation of EMPD by permanent section pathology reviewed by a dermatopathologist before MMS + CK-7. Patients were identified for inclusion in the study by reviewing surgical logs and billing databases after approval from the MedStar Health Research Institute, Mayo Foundation, and University of Pennsylvania Institutional Review Boards. Thorough evaluation of each patient's medical record was conducted and pertinent medical, treatment, and follow-up information was collected (Tables 1 and 2). Follow-up visits were performed for all patients and examination of the surgical site by a physician was required to confirm the presence or absence of recurrence, defined as the persistence or reappearance of tumor at the scar margin confirmed by histopathology.

All tumors <8 cm in size or those with histopathologic or clinical signs of invasion into subcutaneous tissue were processed using standard Mohs technique, whereas a portion of those >8 cm in size without clinical signs of invasion were managed by the peripheral Mohs technique as previously described.[7] Briefly, in this technique the peripheral margin of the tumor is cleared using MMS and the central tumor-bearing island is then excised at the level of the mid subcutaneous plane to remove all skin, adnexa, and superficial subcutaneous tissue and submitted for permanent section histopathological evaluation (Figure 1). Two sets of each Mohs section were prepared, 1 for H&E staining and the other for CK-7 immunostaining, for interpretation by the Mohs surgeon (Figure 2). Using the data tabulated above, the primary end points of the study including the rate of local recurrence and mean local recurrence-free survival (in months) after surgery were calculated. In addition, 5-year tumor-free rates for primary and recurrent tumors by Kaplan–Meier analysis were estimated.

The current cohort of patients treated with MMS + CK-7 was compared with the previously published retrospective cohort of patients with EMPD treated with MMS alone.[7] Fisher's exact test was used to determine whether local recurrence rates differed significantly between both treatment modalities. Kaplan–Meier analyses were conducted to determine the relative efficacy of the techniques and differences were estimated using log-rank tests. Data analyses were performed using VassarStats.net (Poughkeepsie, NY) and SAS Version 9.4 (SAS Institute, Cary, NC).

Results

Forty-nine patients with 61 biopsy-confirmed EMPD lesions, 70.5% (43/61) primary and 29.5% (18/61) recurrent, underwent MMS + CK-7. One patient with a local recurrence after MMS + CK-7 for primary EMPD underwent repeat treatment for a total of 62 tumors treated overall. Thirty patients were men presenting with 41 tumors and 19 were women presenting with 21 tumors. Seventy nine percent (49/62) of the tumors involved the groin and genital area, 9.7% (6/62) the perianal region, and 8.1% (5/62) the axilla, with the remaining tumors localized to the frontal scalp and upper cutaneous lip. The mean patient age at the time of surgery was 70.6 years (range: 30–87).

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TABLE 1. Patient, Tumor, Treatment, and Follow-Up Characteristics of Patients With Primary EMPD Treated Using MMS With Intraoperative Immunostaining for CK-7

				Primary Tumors							
Case No.	*Patient*	*Sex*	*Age*	*Site of EMPD*	*Preoperative Size, cm*	*Final Size, cm*	*Margins, cm*	*Stages/ Status/Days*	*Follow-Up, mo*	*Local Recurrence*	*Closure*
1	A	F	73	Left suprapubic	3.5 × 3.5	10.5 × 7	3.5	2/clear/1	22	No	AF
2	B	M	81	Right scrotum/right groin	9 × 4	12 × 7	1.5	1/clear/1	46	No	REF
3	C	M	73	Right scrotum	5 × 3	12 × 8	3.5	2/clear/1	65	No	REF
4	D	M	71	Left groin, left pubic	2 × 1.8	5 × 4	1.5	2/clear/1	43	No	AF
5	E	M	71	Left groin/left scrotum	13 × 7	10 × 22	4.5	1/clear/1	16	Yes	AF/PC
6	F	M	80	Right groin	9	20	5.5	2/clear/1	86	No	AF
7	G	M	66	Right suprapubic	2 × 3			2/clear/1	80	No	STSG, RF, PC
8	G	M	66	Left groin/left scrotum	2 × 4	15 × 12	6.5	9/clear/4	80	No	STSG, RF, PC
9	G	M	68	Left groin	2.9	8.9 × 4.6	3	7/clear/2	58	No	PC
10	G	M	68	Right pubic	1.8 × 3.8	14 × 12.8	6.1	13/clear/4	56	No	PC
11	H	F	69	Left upper lip	2.1	2.8	0.2	2/clear/1	7	No	BF
12	I	M	77	Right groin/Right scrotum	10 × 10	13 × 13	1.5	9/clear/4	22	No	AF, STSG
13	J	M	75	Left groin	5	4 × 6	0.5	1/clear/1	91	No	PC
14	K	M	86	Left penile shaft/right penile shaft/left scrotum/right scrotum	8	15	3.5	4/clear/1	24	No	PC
15	L	M	87	Left scrotum	7.6 × 5.2	10.3	2.55	2/clear/1	1	No	PC
16	M	M	86	Bilateral penile shaft, bilateral scrotum	10	15.8	2.9	4/clear/2	49	No	AF
17	N	M	77	Left groin	7	8.5	0.75	1/clear/1	50	No	AF
18	N	M	77	Right groin	6	8.0 × 4.5	1	2/clear/2	50	No	AF
19	N	M	77	Perineum	10.5	12.5	1	2/clear/1	50	No	AF
20	O	M	76	Left penile shaft/left pubic	10.3 × 4.3	11	3.35	4/clear/1	87	No	AF
21	P	F	56	Right suprapubic	8	10 × 10	1	2/clear/1	29	No	AF
22	Q	F	83	Right vulva	10 × 10			6/clear/3	60	No	AF, 2nd intention
23	R	M	73	Right groin	13.4 × 7.4	15 × 30	11.3	7/clear/2	68	No	AF
24	R	M	73	Left groin	14	10 × 25	5.5	5/clear/2	68	No	AF
25	R	M	74	Right axilla	3.5	11.4 × 4.8	3.95	7/clear/2	58	No	AF
26	R	M	74	Left axilla	0.7			2/clear/1	58	No	PC
27	S	M	83	Left scrotum	14 × 14	18 × 16	2	2/clear/1	109	No	STSG
28	S	M	84	Right Scrotum	5 × 5	13 × 8.5	4	3/clear/1	103	No	STSG

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TABLE 1. (Continued)

Primary Tumors											
Case No.	*Patient*	*Sex*	*Age*	*Site of EMPD*	*Preoperative Size, cm*	*Final Size, cm*	*Margins, cm*	*Stages/ Status/Days*	*Follow-Up, mo*	*Local Recurrence*	*Closure*
29	T	M	72	Left groin	4 × 3	8 × 7	2	1/clear/1	42	No	STSG
30	U	M	61	Left axilla	4.5 × 1.8	9 × 5	2.25	3/clear/1	98	No	PC
31	V	M	65	Left scrotum/left penile shaft	8 × 9	12 × 7	2	1/clear/1	6	No	STSG
32	W	M	58	Right scrotum	2 × 3	3 × 4	0.5	1/clear/1	46	No	PC
33	X	F	75	Right vulva	8 × 2.5	20 × 16	6.75	5/clear/1	55	No	RF, AF
34	Y	M	78	Right scrotum/Right groin	10 × 9	12 × 11	1	1/clear/1	52	No	REF
35	Z	M	63	Left penile shaft/right penile shaft/left scrotum/right scrotum	10 × 8.5	12.8 × 12	1.75	1/clear/1	37	No	REF
36	AA	M	71	Left scrotum	8.7 × 4.8	10.7 × 6.8	1	1/clear/1	21	No	REF
37	BB	M	78	Left scrotum	8.5 × 7	12 × 10	1.75	2/clear/1	12	No	REF
38	CC	F	77	Right axilla	4.9 × 2.6	9.2 × 4.5	2.15	1/clear/1	4	No	REF
39	CC	F	77	Right groin	5.8 × 7.4	8.2 × 12.3	2.45	1/clear/1	4	No	REF
40	DD	F	74	Right pubis	9 × 8.5	10.9 × 12.8	2.15	1/clear/1	2	No	RF
41	EE	F	64	Right perianal	9.5 × 5.5	12.5 × 7	1.5	1/clear/1	10	No	REF
42	FF	M	62	Left penile shaft/right penile shaft/left scrotum/right scrotum	9.6 × 7.2	15 × 9.5	2.7	1/clear/1	6	No	REF
43	GG	M	58	Right groin/right scrotum/right suprapubic area/perineum	13 × 7	20 × 15	4	8/clear/4	74	No	REF

AF, advancement flap; BF, bilobed transposition flap, EMPD, extramammary Paget's diesease; MMS, Mohs micrographic surgery; PC, primary closure; REF, referred; RF, rhombic transposition flap; STSG, split-thickness skin graft.

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TABLE 2. Patient, Tumor, Treatment, and Follow-Up Characteristics of Patients With Recurrent EMPD Treated Using MMS With Intraoperative Immunostaining for CK-7

				Recurrent Tumors								
Case No.	*Patient*	*Sex*	*Age*	*Site of EMPD*	*Preoperative Size, cm*	*Final Size, cm*	*Margins, cm*	*Previous Treatment (MTR)*	*Stages/Status/ Days*	*Follow-Up, mo*	*Recurrence*	*Closure*
1	HH	M	78	Right groin/right scrotum/right buttock	8.5 × 8.5	16 × 3	3.75	Excision × 6 (3)	4/clear/2	3	No	AF
2	II	F	69	Right vulva	0	11 × 9		PV (43)	2/clear/1	32	No	REF
3	JJ	F	71	Perineum/bilateral perianal	8 × 10	7 × 12	1	PV and CO2 laser × 2 (9)	3/residual in anal canal/1	70	No	REF
4	KK	F	74	Right vulva	0	11 × 9		Excision × 2 (5)	2rResidual in vagina/1	31	No	REF
5	LL	F	30	Left axilla	0	6.7 × 2.8		Excision (1)	1/clear/1	14	No	PC
6	MM	M	71	Bilateral scrotum	3.0 × 2.0	6.6 × 5.0	1.8	Excision (118)	1/clear/1	1	No	AF
7	E	M	73	Left groin	3.5	5.5	1	MMS with CK-7 (16)	1/clear/1	90	No	PC
8	NN	F	63	Bilateral perianal	4	5	0.5	Excision (13)	2/residual in anal canal/1	48	No	REF
9	OO	F	46	Right buttock	5.7 × 3.4	8	2.3	Excision × 2 (3)	3/clear/1	11	No	PC
10	PP	F	69	Left perianal	0.4	11 × 14	6.8	V × 3 (9)	10/clear/2	21	No	PC
11	PP	F	69	Left vulva	2.1	8.6 × 6.9	3.25	V × 3 (9)	14/clear/5	20	No	PC
12	QQ	M	83	Right suprapubic, right penile shaft, and right scrotum	NR	16.2 × 13		5-FU (DNR)	7/clear/3	120	No	AF, PC
13	RR	F	73	Left vulva	10	Partially closed		CO2 laser (DNR)	5/residual in vagina and cervix/2	46	Yes	AF, PC, REF
14	SS	F	66	Right vulva	0	15 × 18		Excision × 6, MMS (34)	7/clear/2	76	No	AF, PC
15	T	M	72	Bilateral suprapubic	12 × 5.5	19 × 9	3.5	Excision, imiquimod (4)	2/clear/1	42	No	STSG
16	TT	F	52	Right vulva	7.7 × 3	12.5 × 8	2.5	Excision (8)	3/clear/1	36	No	REF
17	UU	M	64	Bilateral penile shaft and scrotum	10 × 5	18 × 7	4	MMS with + margin, excision × 3, radiation (24)	5/clear/3	37	No	REF
18	VV	F	61	Bilateral vulva	3.4 × 3	5 × 3.5	0.8	V (19)	1/clear/1	24	No	REF
19	WW	M	57	Left frontal scalp	1.9 × 2.2	3.4 × 3.2	0.75	LN2 × 2 (6)	1/clear/1	8	No	AF

5-FU - topical 5-fluorouracil treatment; AF, advancement flap; CO2 - ablative carbon dioxide laser; DNR, did not resolve; REF, referred; RF, rhombic transposition flap. EMPD, extramammary Paget's disease; LN2, liquid nitrogen cryotherapy; MMS, Mohs micrographic surgery MTR, months to recurrence; PC, primary closure; PV, Partial vulvectomy; STSG, split-thickness skin graft; V, Vulvectomy.

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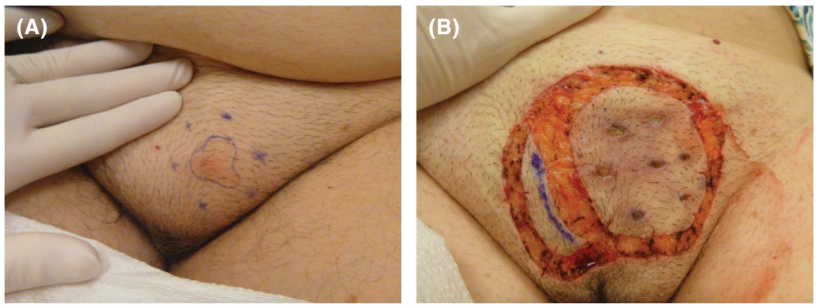

Figure 1. A representative case of vulvar EMPD treated with MMS + CK-7 using the peripheral Mohs modification. (A) Preoperative evaluation with the clinically visible lesion outlined and peripheral scouting biopsies planned. (B) Postoperative defect after clearance of the peripheral margin before excision of the central tumor-bearing islands. EMPD, extramammary Paget's disease; MMS, Mohs micrographic surgery.

Thirteen cases were treated using the peripheral Mohs modification due to large tumor size. Tables 1 and 2 display patient demographic, tumor, treatment, and follow-up data. The mean number of MMS stages to clear the tumor was 3.36 (range: 1–14 stages), with a mean peripheral surgical margin of 2.76 cm (range: 0.2–11.3 cm) for patients with clinically visible preoperative lesions, over a mean of 1.51 (range: 1–5 days) operative days. The mean tumor size (based on the largest postoperative diameter measurement) was 12.2 cm (range: 2.8–30 cm). Of the 62 cases in this cohort, 12 (19.4%) were reconstructed with complete or partial primary closures, 18 (29.0%) with local flaps, 5 (8.1%) with split-thickness skin grafts, 8 (12.9%) with a combination of the above methods, and 19 (30.6%) were referred to outside specialists for reconstruction.

Local recurrence rates for MMS + CK7 are shown and compared with a previously published cohort of patients with EMPD treated with MMS without CK-7 immunostaining in Table 3.[7] The Kaplan–Meier 5-year tumor-free rate is 97.1% for the primary tumor group, 80.0% for the recurrent group, and 94.6% overall. The Kaplan–Meier curves for primary and recurrent EMPD treated with MMS + CK-7 are shown in Figure 3. The Kaplan–Meier 5-year tumor-free rates for all EMPD tumors treated with MMS + CK-7 versus MMS alone are 94.6% versus 72.0% (p = .012). Kaplan–Meier 5-year tumor-free rates for all EMPD cases treated with MMS + CK-7 versus MMS alone are shown in Figure 4. The patient and disease-related factors of this cohort and the previously published retrospective cohort of patients with EMPD treated with MMS alone are similar with the exceptions of a substantially larger mean tumor size in the present cohort and longer follow-up period in the historical cohort (Table 4).[7]

In 4 of the patients treated with MMS + CK-7, histologically clear margins were not able to be achieved because of residual disease in the anal canal (2 patients) and vaginal wall/cervix (2 patients). After clearance of the peripheral cutaneous margin, these cases were referred for excision of the central tumor-bearing tissue and reconstruction by colorectal surgeons and gynecological oncologists, respectively. In cases of primary and recurrent EMPD for which clear margins were able to be established (i.e. cases which

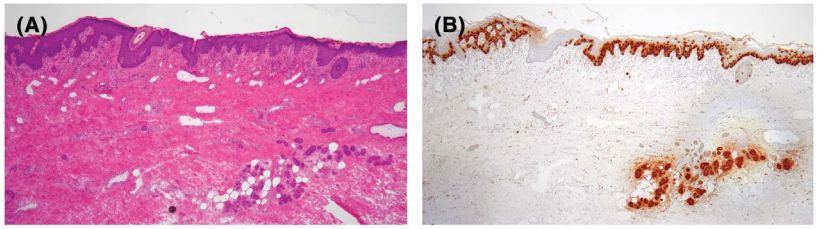

Figure 2. Low power views of adjacent sections of EMPD demonstrating increased visibility of tumor cells with immunostaining for CK-7. (A) Hematoxylin and eosin; ×40 magnification. (B) Immunohistochemistry for CK-7; ×40 magnification. Note the expected staining of the secretory coil of eccrine glands in the dermis. EMPD, extramammary Paget's disease.

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TABLE 3. Local Recurrence Rates for EMPD Treated With Mohs Surgery With CK7 Immunostaining With Comparison to Historical Cohort

	Local Recurrence Rate	*Mean Follow-Up, mo*	*Odds Ratio and 95% CI*	*p*
Primary EMPD				
MMS-CK7	2.3% (1/43)	46.9	Reference	—
MMS	15.8% (3/19)	59.2	7.88 (0.76–81.4)	.082
Recurrent EMPD				
MMS-CK7	5.6% (1/18)	35.6	Reference	—
MMS	50% (4/8)	55.4	17 (1.5–196.4)	.02
Total EMPD				
MMS-CK7	3.3% (2/61)	43.5	Reference	—
MMS	25.9% (7/27)	56.0	10.33 (1.98–53.8)	.0031

CI, confidence interval; EMPD, extramammary Paget's disease; MMS, Mohs micrographic surgery.

did not require further excision by an outside surgical specialist), the combined recurrence rate is 1.8% (1/57) with a mean and median follow-up of 43.2 and 42 months (range: 1–120 months [interquartile range 16–60 months]), respectively.

The single local recurrence in a primary tumor treated with MMS + CK7 occurred in a large tumor of the left groin and scrotum of an elderly man treated using the peripheral Mohs technique with immunostains to CK-7 in which the central tumor island was not evaluated by the Mohs surgeon but was instead submitted for permanent section histopathological analysis. At 16 months, the treating surgeon discovered a subcutaneous nodule within his surgical scar diagnosed histopathologically as an adenocarcinoma without overlying epidermal involvement but with positive staining for CK-7, focal positive staining for carcinoembryonic antigen (CEA), and negative staining for cytokeratin-20. After a negative staging work-up including a pelvic magnetic resonance imaging, computed tomography (CT), and colonoscopy, he underwent repeat surgery with MMS + CK-7 without evidence of recurrence at 90 months of follow-up. The single local recurrence in the group of recurrent EMPD treated with MMS + CK7 occurred in an elderly female with a large tumor affecting the left aspect of the vulva that was previously treated unsuccessfully with ablative carbon dioxide laser. After a total of 5 stages over 2 days, the central portion of the tumor could not be cleared because of residual disease involving the vaginal canal and

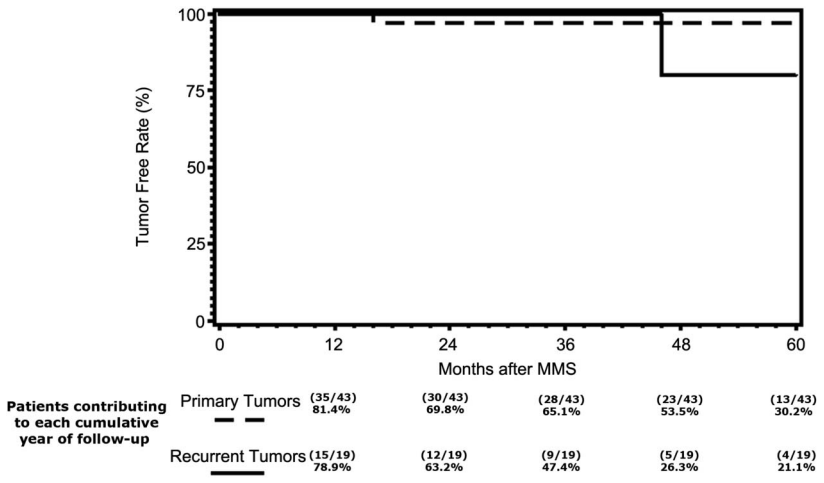

Figure 3. Kaplan–Meier 5-year recurrence-free survival curves for primary versus recurrent EMPD tumors treated with MMS with intraoperative immunostaining for CK-7. EMPD, extramammary Paget's disease; MMS, Mohs micrographic surgery.

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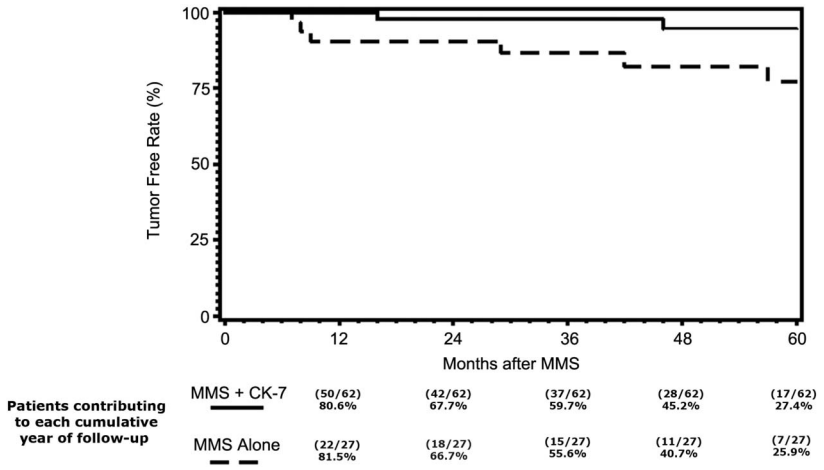

Figure 4. Kaplan–Meier 5-year recurrence-free survival curves for all EMPD tumors treated with MMS alone versus MMS with intraoperative immunostaining for CK-7. EMPD, extramammary Paget's disease; MMS, Mohs micrographic surgery.

cervix. The patient was referred for vaginectomy and transvaginal hysterectomy, which achieved negative non-Mohs surgical margins, but she developed a local recurrence at 46 months identified and managed by her gynecological oncologist.

Of the 49 patients treated in this study, 5 (10.2%) had a history of a preceding internal carcinoma including a patient with a remote history of endometrial adenocarcinoma with EMPD of the right groin and right axilla, patients with remote histories of ovarian adenocarcinoma and breast adenocarcinoma with EMPD of the right vulva, a patient with a remote history of bladder transitional cell carcinoma with EMPD of the groin, scrotum, and suprapubic areas, and a patient with a history of adenocarcinoma in situ of the rectum resected 3 years before the diagnosis of perianal EMPD. One patient with EMPD of the left scrotum had a nearly simultaneous diagnosis of prostate adenocarcinoma without metastasis and underwent treatment of his underlying prostate adenocarcinoma with radiation and hormonal therapy. Two patients had subsequent development of seemingly unrelated cancers including fatal non-Hodgkins lymphoma a year after surgical treatment of EMPD involving the right groin, scrotum, and buttock, and an advanced head and neck squamous cell carcinoma diagnosed several years after the successful treatment of EMPD of the left groin and pubic areas.

TABLE 4. A Comparison of Patient, Tumor, Treatment, and Follow-Up Characteristics of Patients With EMPD Treated Using MMS With Intraoperative Immunostaining for CK-7 Versus Patients With EMPD Treated With MMS Alone

	Current Cohort	*Hendi Colleagues*
Sex	30 men (61.2%), 19 women (38.8%)	12 men (48%), 13 women (52%)
Mean age	70.6 yrs (range: 30–87)	68.8 yrs (range: 56–82)
Tumor site	Groin and genital (79.0%), perianal (9.7%), axilla (8.1%), other (3.2%)	Groin and genital (79.4%), perianal (11.8%), axilla (8.8%), other (0%)
Mean tumor size	12.2 cm (range: 2.8–30 cm)	7.3 cm (range: 1–20 cm)
Primary or recurrent	43 primary (69.4%), 19 recurrent (30.6%)	19 primary (55.9%), 15 recurrent (44.1%)
Mean stages and margin	3.36 stages (range: 1–14), 2.76 cm (range: 0.2–11.3 cm)	3.1 stages (range 1–9), 2.5 cm (range: 0.6–11 cm)
Mean follow-up	44.1 months (1–120 months)	61.7 months (range: 7–174 months)
Local recurrences	1 primary (2.3%), 1 recurrent (5.3%), 2 overall (3.2%)	3 primary (16%), 4 recurrent (50%), 7 overall (26%)

EMPD, extramammary Paget's disease; MMS, Mohs micrographic surgery.

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Five (8.1%) of the 62 cases of EMPD treated had documented adnexal involvement of the tumor, whereas 9 (14.5%) demonstrated invasive disease either on initial biopsy or on review of debulking or Mohs sections ranging from foci of microinvasion into the papillary dermis to frank primary adnexal adenocarcinoma extending into the subcutaneous tissue plane. As described above, one of these patients had a dermal adenocarcinoma diagnosed as a recurrence after MMS + CK-7 on the left groin and has been disease free since repeat treatment of the site for more than 7 years. In addition, patient R was initially diagnosed with EMPD in association with primary apocrine carcinoma of the left groin. He underwent treatment of 4 biopsy-confirmed disease sites including his bilateral groin and axillae without local recurrence of his disease in the groin or axillary sites in more than 4 and 5 years of follow-up, respectively. He did, however, subsequently develop metastatic disease involving bone treated with a combination of capecitabine, lapatinib, and denosumab without evidence of residual disease evident on positron emission tomography/CT for more than 2 years. To date, none of the remaining 7 patients with known invasive tumors have developed local recurrences or metastatic spread of their disease.

Discussion

Here, the authors report the largest retrospective, multicenter cohort of patients with EMPD treated with MMS and the largest cohort of patients treated using intraoperative immunohistochemistry to CK-7. The local recurrence rate for primary and recurrent tumors of 2.3% and 5.3%, respectively, represents a composite local recurrence rate of 3.3% (mean follow-up time of 44.1 months) which is the lowest local recurrence rate of a substantial cohort with adequate follow-up reported to date. The 5-year tumor-free rates of 97.1% for primary tumors, 80.0% for recurrent tumors, and 94.6% overall by Kaplan–Meier analysis are also the highest reported to date. Indeed, these data represent a clinically substantial and statistically significant incremental improvement over the previously reported cohort of patients treated with MMS alone.

The average time to recurrence in this cohort was 34.2 months, which is in line with the previously reported average time to recurrence for MMS without special stains of 29 months.[7] Interestingly, both recurrences occurred in patients for whom the entire surgical specimen was not evaluated by the Mohs technique. In the primary tumor recurrence, the central island was processed by the peripheral Mohs protocol and submitted for permanent sections to be evaluated by a board certified dermatopathologist, whereas the local recurrence in the recurrent EMPD tumor occurred after vaginectomy and transvaginal hysterectomy by a gynecologic oncologist. If one considers only tumors that were excised by the Mohs surgeon and fully evaluated with intraoperative immunohistochemistry to CK-7, the recurrence rate is 0% representing a surgical cure rate of 100% in this cohort.

The chief explanation for the high recurrence rates after wide local excision of EMPD offered in the literature is that the high frequency of wide subclinical spread seen in this tumor makes empiric surgical margins, even those wide enough for other types of cutaneous carcinomas, unreliable and frequently inadequate.[7,10] To address this, the authors and others have previously reported on the use of MMS in the treatment of EMPD to allow for 100% margin evaluation and therefore more complete tumor removal. Indeed, the results have been promising with an overall recurrence rate of 12.2% corresponding to an estimated 5-year tumor-free rate of 83.6% by Kaplan–Meier analysis in pooled data from 8 studies of MMS for EMPD including 81 patients and 90 cases.[11] Yet, despite the precise nature of the MMS technique, the recurrence rates for EMPD still remain substantially higher than those of other cutaneous tumors routinely treated with MMS.[12]

Previously, the authors suggested that a portion of the recurrences noted in EMPD lesions treated with MMS was due to difficulty in visualizing tumor cells on hematoxylin and eosin-stained frozen section slides and hypothesized that the introduction of immunohistochemical markers for CK-7 would lower tumor recurrences rates further.[8] For example, the addition of immunostains targeting melanoma antigen recognized by T-cells 1 (MART-1) to MMS of malignant melanomas of the head and neck has led to local recurrence rates that are far lower than those observed

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in conventional surgical management.[13] Although the options for cellular markers available for EMPD include CEA, it is a less sensitive and specific marker than CK-7.[14]

Previously, the only cohort of patients treated with MMS using intraoperative immunostains to CK-7 for EMPD included 4 patients, in which 2 cases also used the use of immunostains to CEA.[3] Interestingly, in this study which included a total of 12 patients with EMPD managed with MMS (8 without immunostains), the only recurrence was observed at 12 months in a patient who underwent MMS with immunostains to both CK-7 and CEA leading to a local recurrence rate for EMPD after MMS of 8% but a local recurrence rate of 25% when special stains were used.[3] Further details of the case including anatomical site, tumor extent, and primary versus recurrent status are not provided making it difficult to identify factors that may have contributed to local surgical failure despite the use of intraoperative immunohistochemistry.

In addition, the authors have hypothesized that EMPD may grow in a discontinuous or multifocal pattern, especially within the vulvar and perianal regions.[15,16] Although the presence of distant microscopic extension beyond what is visible to the clinician has been repeatedly observed and is widely accepted, the multifocality of EMPD remains controversial because of the lack of a formal study using confirmatory immunostaining techniques to improve the sensitivity of tumor cell identification.[8,10,17] Although the authors suspect previous incomplete treatment with partial surgical excision or topical chemotherapeutic or immunomodulatory agents that could fragment tumors leading to challenges in treating recurrent disease, it is their implicit understanding that EMPD grows contiguously, as do other tumors, that allows MMS to "track out" residual tumor extensions. Previously, the auhtors examined this issue and reported a case of primary axillary EMPD treated with MMS + CK-7 which demonstrated a highly irregular yet contiguous subclinical growth pattern.[8] The low local recurrence rate and hence high surgical success rate reported here supports the concept of EMPD as a contiguous growth rather than a multifocal disease process.

The limitations of this study include its retrospective nature and the lack of an alternative treatment arm with which to compare the efficacy of this treatment technique. A simultaneous comparison of MMS + CK-7 staining to MMS alone or wide local excision would not have been possible as all authors abandoned other treatment strategies for EMPD in favor of MMS + CK-7. To overcome this challenge, statistical comparison was conducted using the previously-published cohort of patients treated with MMS alone given its substantial size, adequate follow-up time, and similarity to the present cohort as approximately half of the cases in this study were performed by the same surgeons who performed the cases in the historical cohort.[7] In addition, the Kaplan–Meier 5-year tumor-free rate estimates are limited in that only 30.2% (13/43) of primary tumor cases and 21.1% (4/19) of recurrent tumor cases had at least 5 years of follow-up (Figure 3). The distribution of follow-up was similar between the current and historical cohorts allowing for a fair comparison in their respective Kaplan–Meier 5-year tumor-free rates (Figure 4).

Despite the low rates of local recurrences observed when EMPD is treated with MMS + CK-7 staining, the availability of this treatment option is limited. The number of Mohs laboratories with expertise in immunostaining and surgeons with experience interpreting these sections is growing, but this technique is currently offered by a small fraction of academic and private Mohs surgery practices. Aside from technical capability, there are practical and financial considerations that limit the uptake of this therapeutic modality. As seen in this cohort, EMPD tumors are typically large and occupy delicate anatomic regions which make them technically difficult and time-consuming tumors to treat for the surgeon and histotechnologist alike. Furthermore, given the current reimbursement models, practices using immunostains during Mohs surgery may not be adequately compensated for reagent costs when treating challenging tumors with tissue blocks that can number in dozens. It is the hope of the authors that future reimbursement models will consider the resource-intensive nature of this surgery and allow for adequate payment to make this highly effective form of treatment economically feasible.

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Intraoperative immunohistochemistry to CK-7 aids in the frozen section evaluation of tumor margins for EMPD during MMS and achieves the lowest reported local recurrence rates to date for EMPD. It represents a statistically significant and clinically substantial incremental improvement from Mohs surgery alone and far exceeds the reported local recurrence rates for wide local excision. The success of this technique supports the integral role of the Mohs micrographic surgeon in achieving the highest cure rates for patients with skin-limited EMPD, whether working independently or as a member of an interdisciplinary treatment team with other oncological surgical subspecialists.

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