乳房外パジェット病におけるマッピング生検の評価 ： 後ろ向き研究

加来，裕美子

<http://hdl.handle.net/2324/4475002>

出版情報：Kyushu University, 2020, 博士（医学），課程博士
バージョン：
権利関係：(c) 2017 by the American Academy of Dermatology, Inc.

Evaluation of mapping biopsies for extramammary Paget disease: A retrospective study

Yumiko Kaku-Ito, MD,^a Takamichi Ito, MD, PhD,^a Gaku Tsuji, MD, PhD,^{a,b} Takeshi Nakahara, MD, PhD,^{a,c}
Akihito Hagihara, DMSc, MPH,^d Masutaka Furue, MD, PhD,^{a,b,c} and Hiroshi Uchi, MD, PhD^a
Fukuoka, Japan

Background: Extramammary Paget disease (EMPD) sometimes shows an ill-defined border and an unexpectedly extended tumor spread beyond the clinical borders. Mapping biopsy is 1 approach for complete surgical removal, but its efficacy has remained controversial.

Objective: We sought to evaluate mapping biopsies for EMPD.

Methods: We performed a retrospective review of 133 patients with 150 primary EMPD lesions. We histopathologically examined 1182 skin biopsy specimens (975 from mapping biopsy and 207 from lesional biopsy).

Results: Only 1.6% of mapping biopsy specimens from well-defined EMPD (13 of 810) were positive. Moreover, 4.6% of mapping biopsy specimens from ill-defined EMPD (8 of 165) were positive, whereas all specimens taken from sites 2 cm or more from the clinical border were negative. For both well-defined and ill-defined EMPD, there was no significant difference in the margin status of surgical resection regardless of mapping biopsy.

Limitations: This was a retrospective study.

Conclusions: Mapping biopsies are unnecessary for well-defined EMPD or when 2-cm margins can be achieved, whereas surgical removal with predetermined margins (1 cm for well-defined EMPD and 2 cm for ill-defined EMPD) appears to be safe. Mapping biopsies can be considered when shortening of the safe surgical margin to less than 2 cm is required in ill-defined EMPD. (J Am Acad Dermatol 2018;78:1171-7.)

Key words: complete removal; extramammary Paget disease; mapping biopsy; Mohs micrographic surgery; recurrence; surgery; surgical margin; white macule.

Extramammary Paget disease (EMPD) is a rare malignant tumor mainly affecting the anogenital area of elderly people.^{1,2} Most EMPD cases develop slowly, being restricted to the epidermis as in situ lesions. However, once the tumor invades the dermis, the risk of lymph node or distant metastasis is increased, sometimes resulting in a dismal prognosis with a 5-year survival rate of less than 10% after systemic metastasis.³⁻⁵ Because no

fully effective treatment for metastatic EMPD has been established, complete surgical removal in the localized stage is the treatment of choice.⁶ EMPD, however, sometimes shows an ill-defined tumor border and an unexpectedly extended tumor spread beyond the clinical tumor border, making determination of the appropriate resection line difficult.^{7,8} Previous studies have produced varied findings on the estimated incidence of inadequate excisions

From the Division of Skin Surface Sensing,^c Department of Dermatology,^a and Department of Health Services Management and Policy, Graduate School of Medical Sciences,^d and Research and Clinical Center for Yusho and Dioxin, Kyushu University, Fukuoka.^b

Drs Kaku-Ito and Ito contributed equally to this article.

Funding sources: Supported in part by grants from the National Cancer Center, Japan; Ministry of Education, Culture, Sports, Science and Technology; and Ministry of Health, Labor and Welfare, Japan.

Conflicts of interest: None disclosed.

Accepted for publication December 17, 2017.

Correspondence to: Yumiko Kaku-Ito, MD, Department of Dermatology, Graduate School of Medical Sciences, Kyushu University, 3-1-1 Maidashi, Higashiku, Fukuoka 812-8582, Japan.

E-mail: kumiko@dermatol.med.kyushu-u.ac.jp.

Published online December 22, 2017.

0190-9622/\$36.00

© 2017 by the American Academy of Dermatology, Inc.

<https://doi.org/10.1016/j.jaad.2017.12.040>

(resection with positive margins) of EMPD (4.8%-57.6%),⁹⁻¹² although relatively wide margins have been recommended (1-5 cm).^{4,6,8,9,12} Accordingly, certain methods have been proposed to achieve complete removal.⁹⁻¹⁶ Preoperative mapping biopsy (or scouting biopsy) is 1 such method, which several studies have reported to be useful; indeed, at our institute, preoperative mapping biopsy has been performed for nearly 20 years. However, those previous studies had relatively small sample sizes (range, 6-19 patients) and short follow-up periods (range, 1-75 months; median, 26 months).⁹⁻¹³

Preoperative mapping biopsy is typically performed by a standard skin punch biopsy procedure to evaluate the EMPD lesion spread before surgery. Such biopsies are carried out in several directions in each lesion. With application of this approach, reduced rates of positive resection margin and recurrence can be expected.⁹

However, mapping biopsy has a serious flaw, namely, its invasiveness. Patients are required to tolerate the pain of local anesthesia administration on numerous occasions and to undergo repeated skin biopsies from multiple sites. On the basis of our data, in patients undergoing mapping biopsy, an average of 8.3 biopsy specimens are taken.

A recent report suggested that EMPD with well-defined borders can be successfully removed with a predetermined surgical margin.⁶ The authors also suggested that mapping biopsy can be skipped in cases of well-defined EMPD. However, the efficiency of mapping biopsy for ill-defined lesions has not been fully elucidated. Against this background, here we have summarized our 19-year experience of treating patients with EMPD and re-evaluated the efficiency of mapping biopsy in an attempt to establish a better management strategy for EMPD. We have provided data from a relatively large number of patients and long-term follow-up (150 lesions from 133 patients, 975 mapping biopsies, and a median follow-up of 6.9 years). Here, we have divided the EMPD lesions into 2 groups, well-defined and ill-defined EMPD, and separately assessed the efficacy of mapping biopsy for each group.

METHODS

Patients

This study is a retrospective review of our patients that was conducted in accordance with the principles embodied in the Declaration of Helsinki and was approved by the Institutional Ethics Committee of Kyushu University (No. 26-1). We identified 133

patients with 150 EMPD lesions at the Department of Dermatology of Kyushu University (Fukuoka, Japan) between January 1997 and June 2016. All lesions were primary EMPD; cases of secondary EMPD were excluded. We retrieved clinical and demographic data on all patients from our prospectively maintained data bank and analyzed them. At least 3 experienced dermatopathologists confirmed the diagnosis of EMPD in each case. We performed mapping biopsy in

117 patients with 129 EMPD lesions. We also performed surgical excision without mapping biopsy in 16 patients with 21 EMPD lesions. These 16 patients did not undergo mapping biopsy, mainly because of their comorbidities (such as Alzheimer's disease) preventing patients from tolerating mapping biopsies with local anesthesia. Overall, we histopathologically examined 1182 biopsy specimens.

Classification as well-defined or ill-defined EMPD

In every case, all experienced dermatologists in our hospital undertook sufficient discussion of the patient and the therapeutic plan and reached a consensus about whether each lesion was well defined or ill defined. We judged a lesion to be well defined only when it had a clear, well-delineated border. Other lesions, including those having a mixed border, were judged to be ill-defined lesions.

A total of 13 lesions (10.1%) had a mixture of both well-defined and ill-defined borders in 1 lesion. When evaluating mapping biopsy for such lesions, we judged biopsy sites as well defined or ill defined from the nearest EMPD border of the biopsy sites.

Mapping biopsy

Mapping biopsy was achieved by the standard skin biopsy procedure as described previously.⁹

CAPSULE SUMMARY

- EMPD excisions often involve surgical margins and the disease frequently recurs.
- This study showed no utility for mapping biopsies with well-defined EMPD or when 2-cm surgical margins can be achieved.
- Mapping biopsies may be beneficial when the surgical margins need to be reduced to <2 cm for ill-defined EMPD.

Abbreviations used:

EMPD: extramammary Paget disease
MMS: Mohs micrographic surgery

Briefly, punch biopsy was performed at sites 0.5 to 4 cm beyond the clinical border of the lesion by using 4-mm circular blades. The biopsy wound sites were repaired with 5-0 nylon suture. Suture strings were not removed until surgery to facilitate identification of the biopsy sites at surgery. The lesion was resected depending on the results of preoperative mapping biopsy, in which the resection line was decided by linking the nearest marked sites without Paget cells. When Paget cells affected the specimens obtained from the first mapping biopsy, mapping biopsy was repeated at sites 1 to 2 cm beyond the affected sites until the Paget cells had disappeared. We examined 975 mapping biopsy specimens from 129 EMPD lesions in 117 patients. A representative image of mapping biopsy for EMPD is shown in Fig 1.

Statistical analysis

All statistical analyses were performed with the GraphPad Prism statistical software package (version 6, GraphPad Software, San Diego, CA). A *P* value less than 0.05 was considered to indicate statistical significance. To evaluate the association between the clinical features (well-defined or ill-defined EMPD) and the rate of positivity for Paget cells in mapping biopsy, the χ^2 or Fisher exact test and the Cochran-Mantel-Haenszel test were used as appropriate.

RESULTS

Demographic and clinical data

Comprehensive clinical data on all 133 patients with 150 EMPD lesions are shown in Table I. All patients were Japanese, with a mean age of 72.0 years. Tumors were predominantly localized in the genital area (85.7%). A total of 15 patients (11.3%) had a double primary EMPD and 1 had a triple primary EMPD (Supplemental Table I; available at <http://www.jaad.org>). The median follow-up period was 6.9 years (range, 1.2 months–17.1 years). All of the patients underwent lesional biopsy to confirm the EMPD diagnosis with or without mapping biopsy. Eleven patients underwent a repeat of the mapping biopsy.

Among 975 mapping biopsy specimens (117 patients, 129 EMPD lesions), 810 were taken from well-defined EMPD borders and 165 were from

Fig 1. A representative image of mapping biopsy for extramammary Paget disease. The dotted line indicates the clinical tumor border. X's around the line are mapping biopsy sites.

Table I. Demographic and clinical data on 150 EMPD lesions in 133 patients

Parameter	n (%)
Sex	
Male	86 (64.7)
Female	47 (35.3)
Age, y	
Range	42–88
Mean	72.0
Primary tumor site	
Genital	114 (85.7)
Perianal	2 (1.5)
Axillary	1 (0.8)
Double lesion	15 (11.2)
Triple lesion	1 (0.8)
Mapping biopsy	
Total patients	117 (88.0)
Total lesions	129 (86.0)
Total biopsies	975 (100)
From well-defined EMPD border	810 (83.1)
From ill-defined EMPD border	165 (16.9)
Treatment	
Surgical excision	133 (100)
Follow-up period, mo	
Range	1.2–205
Median	82.5

EMPD, Extramammary Paget disease.

ill-defined EMPD borders. Among all 129 lesions, 13 (10.1%) had borders involving a mixture of well- and ill-defined parts, and the remaining 116 (89.9%) had either a well-defined or ill-defined border.

Table II. Results of 975 mapping biopsies

Biopsy site from clinical border	Well-defined		Ill-defined	
	Biopsies (%)	Positive for tumor (%)	Biopsies (%)	Positive for tumor (%)
≤1 cm	201 (24.8)	4 (2.0)	58 (35.2)	8 (16.0)
2 cm	489 (60.4)	9 (1.8)	79 (47.9)	0 (0)
≥3 cm	120 (14.8)	0 (0)	28 (17.0)	0 (0)
Total	810 (100)	13 (1.6)	165 (100)	8 (4.6)

Results of mapping biopsy from well-defined EMPD borders

The detailed results of mapping biopsy are shown in Table II. Among the 810 mapping biopsy specimens from well-defined EMPD borders (Fig 2, A), 201 (24.8%) were taken at sites 1 cm or less away from the clinical border (a ≤1-cm biopsy), 489 (60.4%) at sites 2 cm from it (a 2-cm biopsy), and 120 (14.8%) at sites 3 cm or more from it (a ≥3-cm biopsy). Mapping biopsy specimens from well-defined EMPD rarely contained Paget cells, with positivity rates of 2.0% for ≤1-cm biopsy sites, 1.8% for 2-cm biopsy sites, and 0% for ≥3-cm biopsy sites ($P = .371$).

Results of mapping biopsy from ill-defined EMPD borders

Paget cells were more frequently present in the 165 biopsy specimens taken from ill-defined EMPD (Fig 2, B) than in those from well-defined EMPD ($P = .0024$). Notably, all of the affected mapping biopsy specimens were from a 1-cm biopsy; none of the specimens from a 2-cm biopsy or ≥3-cm biopsy site contained Paget cells, suggesting that we can skip mapping biopsy even for ill-defined EMPD when we set surgical resection lines 2 cm away from the clinical borders (Table II).

Margin status of complete resection

Next, we examined whether patients who underwent preoperative mapping biopsy achieved complete EMPD removal after surgery. Among the 117 patients with mapping biopsy, only 4 (3.4%), each with well-defined EMPD, had a surgical margin positive for tumor at the time of surgical resection. Detailed data on these 4 patients are shown in Table III. All 4 patients had EMPD arising in the genital area, and the resection lines were determined by preoperative mapping biopsy. Interestingly, no mapping biopsy specimens taken from these 4 patients were affected by Paget cells, and the number of biopsy sites of these 4 patients

was similar to that of other patients with a clear surgical margin. There were no remarkable differences in EMPD clinical properties between these 4 patients and those of the other patients with EMPD.

Patients who did not undergo mapping biopsy

We identified 16 patients who underwent surgical resection without preoperative mapping biopsy (15 with well-defined EMPD and 1 with EMPD with a mixture of well- and ill-defined borders). All patients underwent lesional biopsies to establish the diagnosis. Among these patients, only 1 (6.3%) had a surgical margin positive for tumor, whereas the remaining 15 patients achieved complete EMPD removal without mapping biopsy. There was no significant difference in the rate of positivity for Paget cells between the 2 groups (3.4% in the mapping biopsy group vs 6.3% in the non-mapping biopsy group [$P = .48$]).

DISCUSSION

In the current study, we re-evaluated the efficacy of mapping biopsy and made several important findings. First, we detected Paget cells in only 21 (2.2%) of 975 mapping biopsy specimens. This rate of positivity for tumor seems to be extremely low and may indicate the limited importance of mapping biopsy in a clinical context. When we focused on mapping biopsy for well-defined EMPD, only 1.6% of biopsy specimens were affected by Paget cells, suggesting that mapping biopsy should be skipped for such cases. This fits well with the current recommendations of the Japanese Skin Cancer Society, in which the predetermined 1-cm margin resection is suggested for well-defined EMPD and mapping biopsy can be considered for ill-defined EMPD.¹⁷ When we focused on mapping biopsy for ill-defined EMPD, we found 8 specimens (4.6%) containing Paget cells. Notably, all specimens from ill-defined EMPD that were positive for Paget cells were from a ≤1-cm biopsy, and no specimens among the 2-cm biopsy and ≥3-cm biopsy groups

Fig 2. **A**, A well-defined example of extramammary Paget disease expressed as a sharp, reddish brown patch. **B**, An ill-defined example of extramammary Paget disease presenting as an ill-defined white patch.

Table III. Patients with positive surgical margins

Case	Age, y	Sex	Primary site	Border	TT, mm	Mapping biopsy	Size, cm	Resection margin, cm	Recurrence	Follow-up, mo
1	73	M	Genital	W	In situ	N (8 sites)	10 × 8	1	—	83
2	72	M	Genital	W	In situ	N (8 sites)	7 × 6.5	1-2	—	138
3	77	M	Genital	W	1.75	N (6 sites)	4 × 4	3	—	122
4	69	F	Genital	W	In situ	N (9 sites)	8.5 × 7	2	—	40

N, Negative for tumor; TT, tumor thickness; W, well defined.

contained Paget cells. This suggests that Paget cells are unlikely to extend 2 cm beyond the clinical tumor border, suggesting that mapping biopsy can be safely skipped for surgical resection with 2-cm or larger margins in ill-defined EMPD. In contrast, the ≤ 1 -cm biopsy for ill-defined EMPD showed a non-negligible proportion of specimens positive for tumor (16.0%). We also investigated the background factors that influenced the difference between patients with negative biopsy results and those with positive biopsy results and found that patients with positive biopsy results had a significantly higher proportion of small (≤ 3 cm) primary lesions (Supplemental Table II; available at <http://www.jaad.org>). Caution is thus required when assessing the tumor border, even when a primary EMPD is small.

Another important finding is that among patients who underwent mapping biopsy, 4 (3.4% [all with well-defined EMPD]) had resected margins at surgery that contained Paget cells, but preoperative mapping biopsy of all 4 of these patients failed to detect these cells. This reveals 2 important points: (1) mapping biopsy is not 100% reliable to detect the spread of Paget cells because the biopsy sites are randomly chosen around EMPD lesions and the space between biopsy sites is not histopathologically examined, and (2) Paget cells could spread beyond the biopsy sites while the patient is awaiting surgery after preoperative mapping biopsy. Alternatively, when we focus on the 16 patients who did not undergo preoperative mapping biopsy (15 with well-defined EMPD and 1 with ill-defined EMPD), only 1 patient (6.3%), whose EMPD was well

Fig 3. A white patch (arrow) adjacent to an erosive extramammary Paget disease lesion (arrowhead). It is difficult to determine clinically whether the white patch is extramammary Paget disease.

defined, had a surgical margin positive for tumor. The rate of margin positivity among these patients approximately corresponded to that of the patients who underwent mapping biopsy (3.4%), with no significant difference between the 2 rates of positivity for Paget cells. Routine mapping biopsy for all EMPD lesions is not necessary. Considering that EMPD lesions sometimes appear as a faint white patch (Fig 3) that is clinically indistinguishable from a white patch with other causes (such as vitiligo vulgaris and postinflammatory depigmentation), biopsy from the center of the macule might be more important than mapping biopsy to achieve histopathologic confirmation that a lesion is EMPD.

Besides the bias inherent in a retrospective study, 1 limitation of this study is that we exclusively assessed the efficacy of mapping biopsy taken from skin areas around EMPD lesions and could not apply it to the mucosa. Paget cells sometimes affect the mucosal area (anal canal, vaginal mucosa, and urethral mucosa) and spread deeply toward internal organs (rectum, uterus, and urinary bladder). Histopathologic evaluation of the mucosal sites is imperative because when Paget cells extend near the viscera, a more radical surgical procedure (proctectomy, hysterectomy, and total cystectomy) may well be required. In our data on mucosal

Fig 4. Schematic flowchart of the treatments of extramammary Paget disease (EMPD).

lesions, we experienced a high rate of tumor positivity (52.8%) at surgery, although the rate of mucosal biopsy results positive for tumor was relatively low (1.8% from well-defined borders and 7.1% from ill-defined ones) (Supplemental Tables III and IV; available at <http://www.jaad.org>). These results suggest that mucosal biopsy is of limited importance for detecting tumor spread and achieving complete removal at surgery, yet we should perform it for proof of tumor invasion before radical surgery. In addition, mucosal biopsy should be taken from a specific site (dentate line, etc) regardless of clinical tumor spread. The purpose of mucosal biopsy is therefore different from that of skin mapping biopsy; the former aims to determine whether the tumor has invaded the deep viscera and to examine the need for subsequent radical surgery (proctectomy, etc), whereas the latter aims to achieve complete removal at surgery.

In seeking complete tumor eradication, several approaches have been proposed.^{8,15,18,19} Bae et al systematically reviewed published reports and found a significantly lower recurrence rate in Mohs micrographic surgery (MMS) than in wide local excision (0-9.1% and 21.7-50.0%, respectively).^{7,8,15,16,20} MMS provides complete microscopic margin control of entire periphery of the excised tumor. On the other hand, MMS is sometimes time-consuming and requires more training and experience than mapping biopsy or excision with predetermined margins. Because many EMPD lesions are relatively large, MMS may not always be feasible. Alternatively, linear strip skin biopsy (also known as the “spaghetti” or “collerette” technique) has also been reported for margin control of

malignant melanoma, which sometimes has an ill-defined border.^{18,19} In this 2-step technique, a narrow strip of skin around the tumor is harvested and histopathologically examined before surgery. This technique is simple and can be applied to EMPD management, allowing complete microscopic examination of lateral margins. Its use for large EMPD lesions, however, can be more invasive to patients than mapping biopsy. After all, we need to make a case-by-case decision for the optimal approach, depending on tumor factors, patient factors, and medical environment.

In conclusion, our data obtained from 1182 biopsy specimens indicate the limited importance of mapping biopsy for EMPD. For well-defined EMPD, we may be able to skip mapping biopsy, whereas surgical removal with a predetermined 1-cm margin appears to be a safe, reliable procedure for this condition. For ill-defined EMPD, mapping biopsy can be considered when we need to shorten the safe surgical margin to less than 2 cm (Fig 4). We also urge caution when deciding on the surgical resection line, even after negative results of a mapping biopsy.

The authors thank all of the patients, as well as the members of our laboratory for their helpful advice.

REFERENCES

1. Shepherd V, Davidson EJ, Davies-Humphreys J. Extramammary Paget's disease. *BJOG*. 2005;112:273-279.
2. Kanitakis J. Mammary and extramammary Paget's disease. *J Eur Acad Dermatol Venereol*. 2007;21:581-590.
3. Ito T, Kaku Y, Nagae K, et al. Tumor thickness as a prognostic factor in extramammary Paget's disease. *J Dermatol*. 2015;42:269-275.
4. Hatta N, Yamada M, Hirano T, et al. Extramammary Paget's disease: treatment, prognostic factors and outcome in 76 patients. *Br J Dermatol*. 2008;158:313-318.
5. Ohara K, Fujisawa Y, Yoshino K, et al. A proposal for a TNM staging system for extramammary Paget disease: retrospective analysis of 301 patients with invasive primary tumors. *J Dermatol Sci*. 2016;83:234-239.
6. Murata Y, Kumano K. Extramammary Paget's disease of the genitalia with clinically clear margins can be adequately resected with 1 cm margin. *Eur J Dermatol*. 2005;15:168-170.
7. Mohs FE, Blanchard L. Microscopically controlled surgery for extramammary Paget's disease. *Arch Dermatol*. 1979;115:706-708.
8. Hendi A, Brodland DG, Zitelli JA. Extramammary Paget's disease: surgical treatment with Mohs micrographic surgery. *J Am Acad Dermatol*. 2004;51:767-773.
9. Kato T, Fujimoto N, Fujii N, et al. Mapping biopsy with punch biopsies to determine surgical margin in extramammary Paget's disease. *J Dermatol*. 2013;40:968-972.
10. Kim BJ, Park SK, Chang H. The effectiveness of mapping biopsy in patients with extramammary Paget's disease. *Arch Plast Surg*. 2014;41:753-758.
11. Jung JH, Kwak C, Kim HH, et al. Extramammary Paget disease of external genitalia: surgical excision and follow-up experiences with 19 patients. *Korean J Urol*. 2013;54:834-839.
12. Nagai Y, Kazama S, Yamada D, et al. Perianal and vulvar extramammary Paget disease: a report of six cases and mapping biopsy of the anal canal. *Ann Dermatol*. 2016;28:624-628.
13. Choi JH, Jue MS, Kim EJ, et al. Extramammary Paget disease: minimal surgical therapy. *Ann Dermatol*. 2013;25:213-217.
14. Appert DL, Otley CC, Phillips PK, et al. Role of multiple scouting biopsies before Mohs micrographic surgery for extramammary Paget's disease. *Dermatol Surg*. 2005;31:1417-1422.
15. Bae JM, Choi YY, Kim H, et al. Mohs micrographic surgery for extramammary Paget disease: a pooled analysis of individual patient data. *J Am Acad Dermatol*. 2013;68:632-637.
16. Lee KY, Roh MR, Chung WG, et al. Comparison of Mohs micrographic surgery and wide excision for extramammary Paget's disease: Korean experience. *Dermatol Surg*. 2009;35:34-40.
17. Tsuchida T, Koga H, Uhara H, et al. Japanese Dermatological Association: guidelines for skin cancer practice 2nd edition. *Jpn J Dermatol*. 2015;125:5-75 [in Japanese].
18. Gaudy-Marqueste C, Perchenet AS, Taséi AM, et al. The "spaghetti technique": an alternative to Mohs surgery or staged surgery for problematic lentiginous melanoma (lentigo maligna and acral lentiginous melanoma). *J Am Acad Dermatol*. 2011;64:113-118.
19. Kassi K, Vanwijck R, Kanga JM. The "collerette" technique for skin excision and biopsy: an efficient method for managing lentigo maligna of the head and neck. *Int J Dermatol*. 2014;53:899-903.
20. Hegarty PK, Suh J, Fisher MB, et al. Penoscrotal extramammary Paget's disease: the University of Texas M. D. Anderson Cancer Center contemporary experience. *J Urol*. 2011;186:97-102.

Supplemental Table I. Patients with multiple primary lesions

Case	Age, y	Sex	Primary site	TT, mm	Mapping biopsy	Resection margin, cm	Recurrence	Follow-up, mo
S1-1	72	M	Bil A	In situ, in situ	N	2, 2	—	73.3
S1-2	76	M	Bil A	In situ, 0.85	—	1, 1	—	128.8
S1-3	88	M	Bil A	In situ, in situ	—	1, 1	—	82.5
S1-4	69	M	A + G	In situ, in situ	N	3, 3	—	149.3
S1-5	69	M	A + G	In situ, in situ	N	0.5, 1.2-2.0	—	32.5
S1-6	64	F	A + P	In situ, in situ	N	2, 2	—	68.6
S1-7	73	F	G + P	In situ, 1.5	N	2, 2	—	135.1
S1-8	76	M	G + P	In situ, 0.62	N	0.5, 2	—	86.5
S1-9	85	F	G + P	In situ, 1.2	N	2, 2	—	84.0
S1-10	66	F	G + P	In situ, 1.8	N	2, 2	—	25.9
S1-11	85	F	G + P	In situ, 1.7	N	1, 1	—	56.8
S1-12	76	F	G + P	In situ, in situ	N	0.5-1, 1	—	11.7
S1-13	83	F	G + P	In situ, in situ	—	1, 1	—	49.4
S1-14	73	F	G + P	In situ, 1.0	N	1, 1	—	21.0
S1-15	63	F	G + P	In situ, in situ	N	2, 2	—	143.3
S1-16	68	M	G + Bil A	In situ, 0.27, in situ	—	2, 2	—	110.8

A, Axillary; Bil A, bilateral axillary; F, female; G, genital; M, male; N, negative for tumor; P, perianal; TT, tumor thickness.

Supplemental Table II. Patients with a 1-cm biopsy sites from ill-defined EMPD borders

Case	Age, y	Sex	Primary site	TT, mm	Mapping	Size, cm	Follow-up, mo
S2-1	72	F	Genital	In situ	P	2.5 × 1.5	5.2
S2-2	76	F	Genital	In situ	P	1 × 1	49.0
S2-3	68	F	Genital	In situ	P	3 × 3	44.8
S2-4	83	F	Genital + perianal	In situ, in situ	P	16 × 5, 4.5 × 4	28.7
S2-5	73	F	Genital + perianal	In situ, 1.0	P	16.5 × 7	12.7
S2-6	68	M	Genital	In situ	N	7 × 6	187.3
S2-7	42	F	Genital	0.6	N	4 × 4	81.4
S2-8	79	M	Genital	5.5	N	6 × 6	32.7
S2-9	82	M	Genital	4.8	N	5 × 5	19.4
S2-10	67	M	Genital	0.2	N	9 × 7	11.9
S2-11	76	F	Genital	In situ	N	6 × 4	11.0
S2-12	76	M	Genital	6.8	N	14 × 9	53.0

EMPD, Extramammary Paget disease; F, female; M, male; N, negative for tumor; P, positive for tumor; TT, tumor thickness.

Supplemental Table III. Demographic and clinical data of 36 EMPD lesions in 30 patients with mucosal lesions

Parameter	n (%)
Sex	
Male	4 (13.3)
Female	26 (86.7)
Age, y	
Range	42-87
Mean	70.4
Primary tumor site	
Genital	22 (73.3)
Perianal	2 (6.7)
Genital + perianal	6 (20.0)
Total patients	30 (100)
Total lesions	36 (100)
Total biopsies	210 (100)
From well-defined EMPD border	168 (80.0)
From ill-defined EMPD border	42 (20.0)
Treatment	
Surgical excision	30 (100)
Resection margin	
≤1 cm	13 (36.1)
2 cm	21 (58.3)
≥3 cm	2 (5.6)
Surgical margin positive for tumor	19 (52.8)
Recurrence	4 (13.3)
Follow-up period, mo	
Range	20.1-200.4
Median	90.1

EMPD, Extramammary Paget disease.

Supplemental Table IV. Distance from clinical border of mucosal lesions

Biopsy site from clinical border	Well-defined		Ill-defined	
	Biopsies (%)	Positive for tumor (%)	Biopsies (%)	Positive for tumor (%)
≤1 cm	43 (25.6)	0 (0)	20 (47.6)	3 (7.1)
2 cm	116 (69.0)	3 (1.8)	19 (45.2)	0 (0)
≥3 cm	9 (5.4)	0 (0)	3 (7.1)	0 (0)
Total	168 (100)	3 (1.8)	42 (100)	3 (7.1)