

Narrow-Margin Treatment with Modified Mohs Microsurgery for Extramammary Paget's Disease: A Retrospective Clinical Analysis

Jing Yang^{1,*}, Jianna Yan^{1,*}, Hao Luo¹, Liang Li¹, Long Jiang¹, Xuewen Chen¹, Ling Wu¹, Jingxiu Chai¹, Huan Xue¹, Leimeng Gan¹, Ye qiang Liu², Jia Chen³, Wu Fei², Yun Bai⁴, Quangang Zhu⁵, Zhongjian Chen⁵, Lehong Guo⁶, Yuchong Chen¹

¹Department of Surgery, Shanghai Skin Disease Hospital Affiliated to Tongji University, Shanghai, People's Republic of China; ²Department of Pathology, Shanghai Skin Disease Hospital Affiliated to Tongji University, Shanghai, People's Republic of China; ³Department of Rheumatology and Immunology, Shanghai Skin Disease Hospital Affiliated to Tongji University, Shanghai, People's Republic of China; ⁴Department of Central Laboratory, Shanghai Skin Disease Hospital Affiliated to Tongji University, Shanghai, People's Republic of China; ⁵Department of Pharmacy, Shanghai Skin Disease Hospital Affiliated to Tongji University, Shanghai, People's Republic of China; ⁶Department of Ultrasonography, Shanghai Skin Disease Hospital Affiliated to Tongji University, Shanghai, People's Republic of China

*These authors contributed equally to this work

Correspondence: Yuchong Chen, Department of Dermatologic Surgery Division, Shanghai Skin Disease Hospital Affiliated to Tongji University, Shanghai, People's Republic of China, Email 973309637@qq.com

Background: To investigate the clinical efficacy of narrow-margin modified Mohs microsurgery (mMMS) in the treatment of extramammary Paget's disease (EMPD).

Methods: A retrospective cohort review was conducted on 52 patients with EMPD who were treated at the Skin Disease Hospital of Tongji University in Shanghai between 2017 and 2023. The primary objectives of this study were to assess the long-term local recurrence rates of tumors treated with narrow-margin mMMS and to explore the final margin width as well as the factors that may influence postoperative recurrence.

Results: A total of 52 patients were included in this retrospective study. Most patients were male (n = 48, 92.3%) with a mean age of 69.5 years (SD:9.08, range:44–91). The follow-up rate was 78.7% (41/52), and the mean follow-up time was 36.17 months (SD:18.25, range 5.8–62.5). The recurrence rate was 9.7% (4/41) and the 5-year tumor-free rate was 85.9%. Approximate 95% of tumors with 1 cm of non-scrotal skin extension or 1.5 cm of scrotal skin extension could be completely cleared. Univariable analysis revealed that hypopigmented patches (HR=14.0, 95% CI=1.269,154.395, p = 0.031) correlated with tumors recurrence.

Conclusion: Narrow-margin mMMS is the ideal therapy combine a disease control rate with more satisfying functional results. Determination of tumor boundaries requires attention to skin lesions with hypopigmented macules. The initial resection margins width of the extension cut can be reduced in non-scrotal skin lesions at the time of surgery to minimize pointless margin expansion.

Keywords: extramammary Paget's disease, modified Mohs microsurgery, retrospective study, recurrence, hypopigmented patches

Introduction

Extramammary Paget disease (EMPD) is an uncommon intraepithelial adenocarcinoma which presents most commonly affects the genital skin of older Asian males and white female.¹ It usually presents as persistent erythematous, asymmetric and slowly enlarging plaques that may be accompanied by hypopigmentation.² The skin lesions of EMPD are prone to co-infection, making it difficult to define the clinical extent of the lesion. Moreover, the multifocal growth of the tumor and diffuse subclinical spread extend beyond the range visible to the naked eye, rendering the identification of the tumor margin of Paget's disease challenging.^{3,4} Classical wide local excision (WLE) has a postoperative tumor residual rate of 39.5% and a recurrence rate of up to 30–60%, increasing surgical trauma and economic burden.^{4,5} Additionally, generous initial resection margins can result in large defects and increased morbidity.⁶ Mohs surgery has

been proposed as an alternative surgical approach that can reduce the extent of surgical resection.⁷ However, there is no consensus on initial margins in most margin control procedures.

To address these issues and reduce the recurrence rate while shortening surgical time, our team implemented a narrow-margin modified Mohs micro-surgery (mMMS) technique for the excision of EMPD skin lesions. We retrospectively analyzed the outcome of 52 patients treated with narrow-margin mMMS at our institution. The aim of this study was to summarize the recurrence rate, surgical margins, and recurrence influencing factors of narrow-margin mMMS and to increase the clinical experience in the treatment of EMPD.

Patients and Methods

Study Design

This was a retrospective, single-center study conducted at department of dermatologic surgery division, skin disease hospital of Tongji University in Shanghai. Patients who underwent histopathological diagnosis of EMPD and underwent mMMS between 2017 and 2023 were included in this retrospective analysis. The clinical data used in this study were approved by the Ethics Committee of Shanghai Dermatology Hospital. The approval number is 2023–03. We reviewed the clinical and histopathological data in the patients' medical records. This research did not reveal personal information.

Follow-up visits were conducted in the clinic or by the telephone (every 3 months). We defined surgical margins as the sum of initial margins and subsequent section margins. Recurrence was defined as the development of a clinically or histologically similar lesion at the previously treated site after achieving a negative margin. The period of recurrence (in months) was recorded in the follow-up column. Recurrence-free survival (RFS) is the time from treatment response to the date of relapse or in the absence of relapse to the date of the last follow-up visit.

Narrow-Margin Modified Mohs Microsurgery

Prior to surgery, the boundaries of the tumors were determined by photodynamic fluorescence diagnosis (PDD) and Wood's lamp and dermoscopy. Surgical margins were marked along the outer edges of the preoperatively identified tumors, with these margins sectioned and numbered on a pattern map. The initial margins of mMMS were expanded by 0.5 cm in the non-scrotal skin and 1 cm in the scrotal skin. Then, we cut a strip of about 2 mm from the marked initial margins, the so-called "noodle", and labeled the outer edge of this strip a biological dye. The "noodle" is further divided into segments according to the markers and sent for examination by dermatopathologist. If any segment on the "noodle" is positive for tumor, the step is repeated by continuing the extranodal expansion by 5 mm outside the corresponding involved segment. The procedure is repeated as often as necessary until the last segment of "noodle" is found to be tumor free. Considering the patient's advanced age and poor tolerance to prolonged surgery, we usually intraoperative extended resection twice. If the margin is still positive after the second extended resection, we will continue the extended resection while preparing paraffin sections to clarify the margin status. Neither intraoperative frozen sections nor postoperative paraffin sections used CK7 to assist in diagnosis. The minimal peripheral area free of tumor is outlined by the outermost margins of a continuous "noodle" procedure, which defines the central area to be resected. The surgical procedure is shown in [Figure 1](#).

Under general anesthesia or local anesthesia, the skin is incised along the marked surgical margins. If the excision area reaches the pubic symphysis, the depth of excision reaches the middle and deep layers of the fat to the point where no obvious hair follicle structure is seen. In the genital section, the depth of excision reaches the middle layer of the meatus at the scrotum and penis. The wounds were repaired by direct suture, flap repair, and skin grafting, and the enlarged lymph nodes were subjected to lymph node biopsy. In addition, previous study had shown that patients are often associated with hypopigmented patches in Asian populations, hypopigmentation often obscures the margins of the tumor leading to incomplete resection.³ When hypopigmented patches are present at the border, we use a Wood's lamp to determine the exact margins and always consider them as "latent lesions" and biopsy them, so that the hypopigmented patches are usually thereby included within the tumor border.

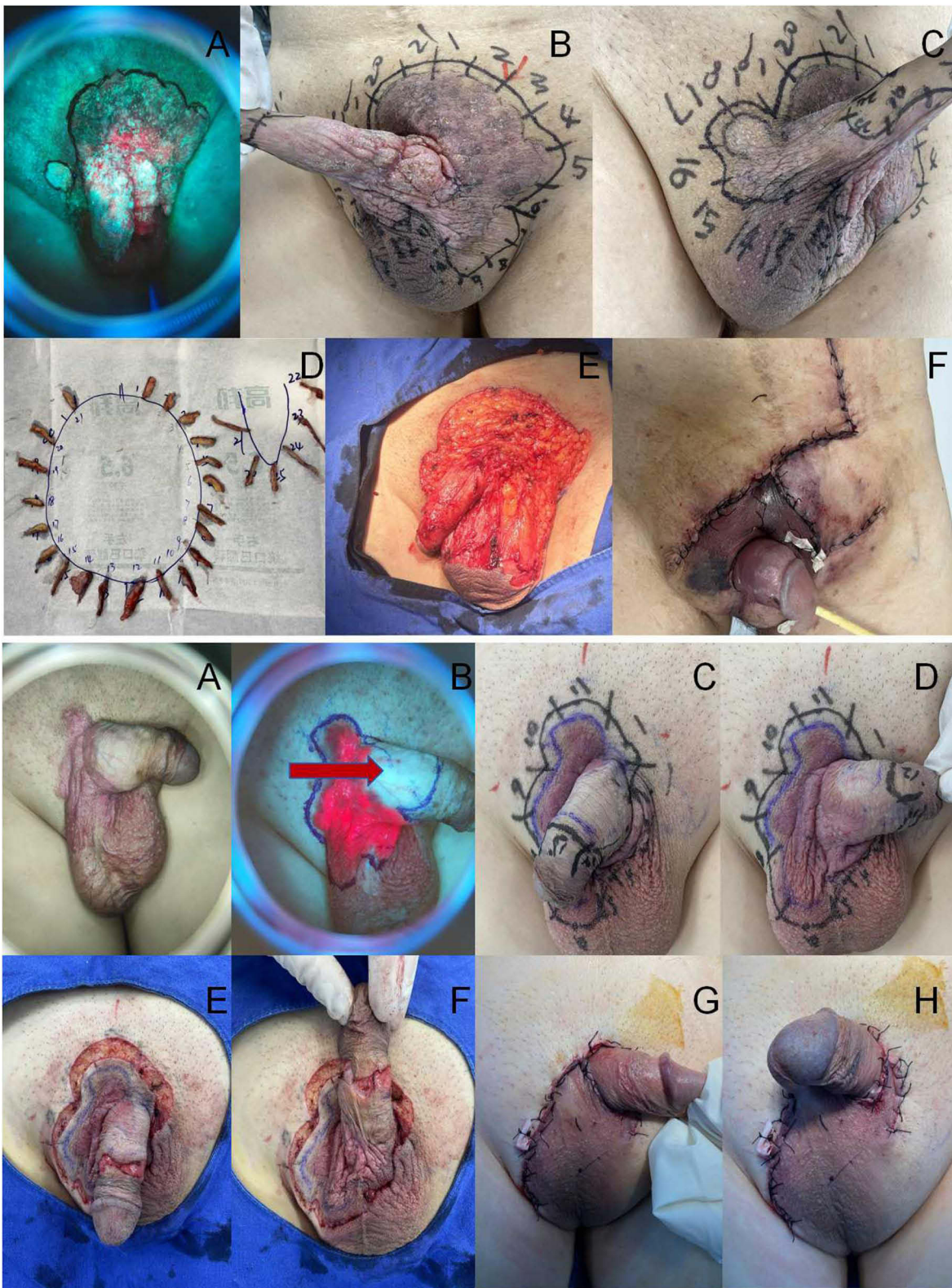


Figure 1 Two patient who underwent the Narrow-Margin Modified Mohs Microsurgery. Case 1 (A–H): preoperative wood lamp and 20% ALA-assisted determination of tumor margins, subclinical lesions of skin are visible at the penis (red arrow); surgical margins; excision of peripheral tissue for pathologic examination; arbitrary flap repair of the wound. Case 2 (A–F): preoperative wood lamp and 20% ALA-assisted determination of tumor margins, surgical margins; cutting edge sent for examination; clean cut edge; arbitrary flap repair of the wound.

Statistical Analysis

Descriptive statistics were reported as numbers (percentages) or means (SD). Kaplan-Meier was used to predict the 5-year Tumor-free rate. Cox proportional risk models were applied to identify factors independently associated with recurrence. Correlations were summarized using hazard ratios (HR) and corresponding 95% CIs. All analyses were performed using Stata/BE version 17.0, and a P value 0.05 was considered statistically significant.

Results

Description of the Study Population

A total of 52 patients were included in this retrospective study. There were 48 males and 4 females. All patients were Chinese, with a mean age of 69.5 years (SD:9.08, range:44–91). Most of the tumor located in scrotum ± penile shaft (47/52,90.4%). There were also 3 cases located in axillary (3/52,5.6%), and 2 cases located in vulva (2/52,3.8%)(Figure 2). The main demographic and clinical information are summarized in Table 1.

The average tumor size was 34.11 (SD:34.16, range:4–199) cm². We observed a total of 12 patients (23.0%) with hypopigmented patches at the edges of the lesions. In addition, a total of 7 patients (13.4%) had a pathological diagnosis of secondary EMPD, 21 patients (40.4%) had dermal invasion, and 3 patients (5.6%) had lymph node abnormalities detected on lymph node ultrasound. Regarding previous treatment, 6 patients had relapsed after undergoing WLE, and one patient had received seven times of photodynamic therapy (PDT) and still relapsed.

Surgical and Follow-Up Results

The follow-up rate was 78.7% (41/52), with a mean follow-up duration of 36.17 months (SD: 18.25, range: 5.8–62.5). All patients had histological margin status data, and 80.8% (42/52) achieved tumor-free resection margins. Overall, 9.7% (4/41) of patients relapsed, and among the 42 who underwent radical resection, 7.1% (3/42) had recurrence. No deaths occurred during follow-up, with a median time to relapse of 14.5 months.

Surgical Margins and Tumor Positivity

We further investigated surgical margins and tumor positivity in Supplementary Table 1. In the axillary region, no tumor cells were observed in the margins of both patients after outgrowth of 0.5 cm and 1 cm, respectively. One patient achieved complete tumor cell clearance with a 0.5 cm extravasation from the vulval tumor margin. However, two other

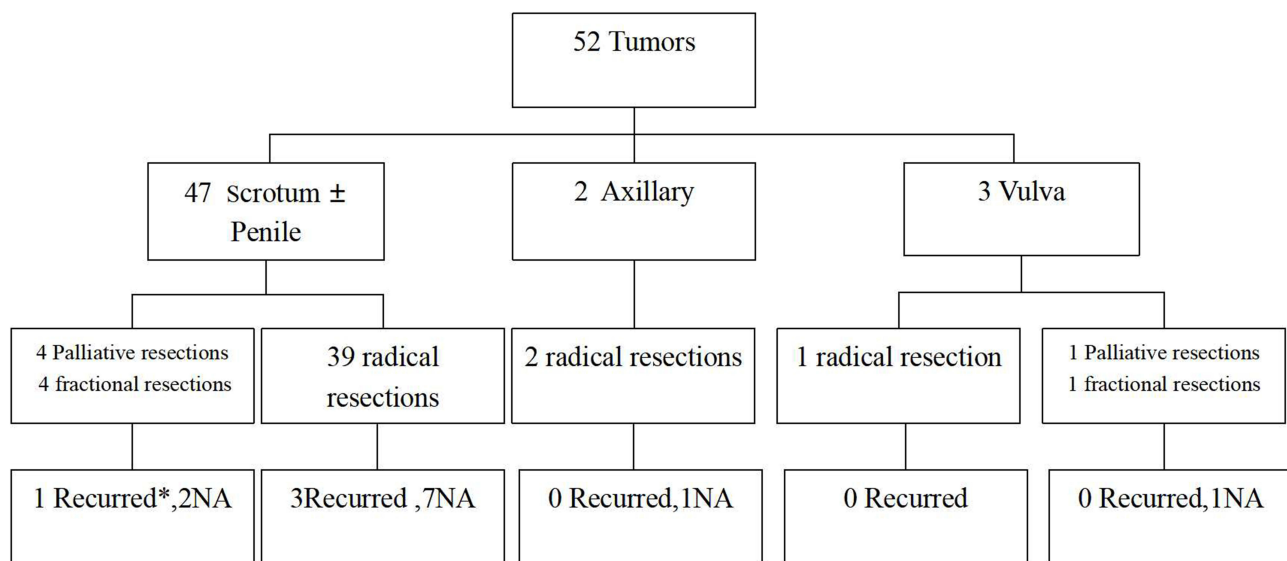


Figure 2 Graph of narrow-margin mMMS and recurrence at different sites of EMPD in this retrospective study.

Table 1 Clinical and Demographic Features of Study Population

Characteristic	Total (N=52)
Gender	
Female, n (%)	4 (7.6%)
Male, n (%)	48 (92.3%)
Age (years)	
Mean (SD)	69.5 (9.08)
Range	44-91
Race	
Asian, n (%)	52 (100.0%)
Site of presentation	
Axillary, n (%)	3 (5.6%)
Vulva, n (%)	2 (3.8%)
Scrotum ± penile Shaft, n (%)	47 (90.4%)
Lesion size, cm (range)	
Mean (SD)	34.11 (34.16)
Range	4-199
With PDD	36 (69.2%)
With hypopigmented patches, n (%)	12 (23.0%)
Underlying malignancy, n (%)	7 (13.4%)
Lymphovascular invasion, n (%)	3 (5.6%)
Dermal invasion, n (%)	21 (40.4%)
Initial treatment	
Wide local excision, n (%)	6 (11.5%)
Photodynamic therapy, n (%)	1 (1.9%)
Reconstruction, n (%)	
Skin graft, n (%)	38 (80.8%)
Locoregional flap, n (%)	8 (15.4%)
Locoregional flap with skin graft, n (%)	2 (3.8%)
Follow-up rate, n (%)	41/52 (78.7%)
Follow-up time (months)	
Mean (SD)	36.17 (18.25)
Range	5.8–62.5
Recurrence, n (%)	4/41 (9.7%)
Median recurrence time (months)	14.5

Abbreviations: SD, standard deviation; PDD, photodynamic fluorescence diagnosis.

patients, managed with palliative and staged surgery, still had tumor cells present after a 0.5 cm external expansion ([Supplementary Table 1](#)).

We provide a detailed summary of the extension width and margin positivity in narrow-margin modified Mohs microsurgery of the scrotal area. In non-scrotal skin, a 0.5 cm tumor margin excision showed a positivity rate of 15% (48/319), while a 1 cm excision had a positivity rate of 3.9% (13/232). In scrotal skin, the positivity rates were 19.7% (67/340) for a 1 cm extension, 4.7% (16/340) for a 1.5 cm extension, and 1.5% (5/340) for a 2 cm extension ([Table 2](#)).

Factors Associated with Tumor Recurrence

To compare recurrence-free survival (RFS) rates among subgroups, we constructed stratified Kaplan-Meier survival curves and conducted Log rank tests. The Kaplan-Meier analysis revealed a 5-year RFS of 85.9% in the study cohort ([Figure 3](#)). Patients without hypopigmented patches exhibited a significantly higher RFS compared to those with hypopigmented patches ($P = 2e-04$). Additionally, patients with lymphovascular invasion had a significantly higher recurrence rate than those without lymph node involvement ($P = 0.0094$) ([Supplementary Figure 1](#)). However, no

Table 2 Surgical Margin for Narrow-Margin mMMS and Marginal Positive Data in the Scrotum ± Penile Shaft

Resection Margins (cm)	Non-Scrotal Area	Scrotal Area
0.5	15.0% (48/319)	
1	3.9% (13/332)	19.7% (67/340)
1.5		4.7% (16/340)
2		1.5% (5/340)
Negative margin width(cm)		
Mean (SD)	0.71 (0.25)	1.26 (0.39)
Median (quartiles)	0.5 (0.5,1)	1(1,1.5)
Range	0.5-1	0.5-2

significant difference in RFS was observed between patients with primary tumors and those with recurrent tumors ($P = 0.93$). Higher RFS values were noted in the intraepidermal and primary EMPD groups, but these differences were not statistically significant ([Supplementary Figure 2](#)).

Next, we utilized Cox proportional hazards models to identify factors associated with tumor recurrence. Univariate analysis showed that hypopigmented patches were significantly associated with disease recurrence ($HR = 14.0$, 95% CI = 1.269–154.395, $p = 0.031$). Other factors, including tumor size, invasive EMPD, primary EMPD, and lymphovascular invasion, did not significantly correlate with recurrence ([Table 3](#)).

Discussion

EMPD is a rare malignant tumor primarily affects the genital area of Asian males and the standard treatment has not yet been established.⁸ MMS is regarded as a promising therapeutic alternative for EMPD, yet its clinical application is limited due to its specialized requirements and time-consuming nature.^{6,9} In this study, we employed narrow-margin mMMS for EMPD treatment and analyzed the recurrence rate and risk factors for recurrence in Asian Chinese patients.

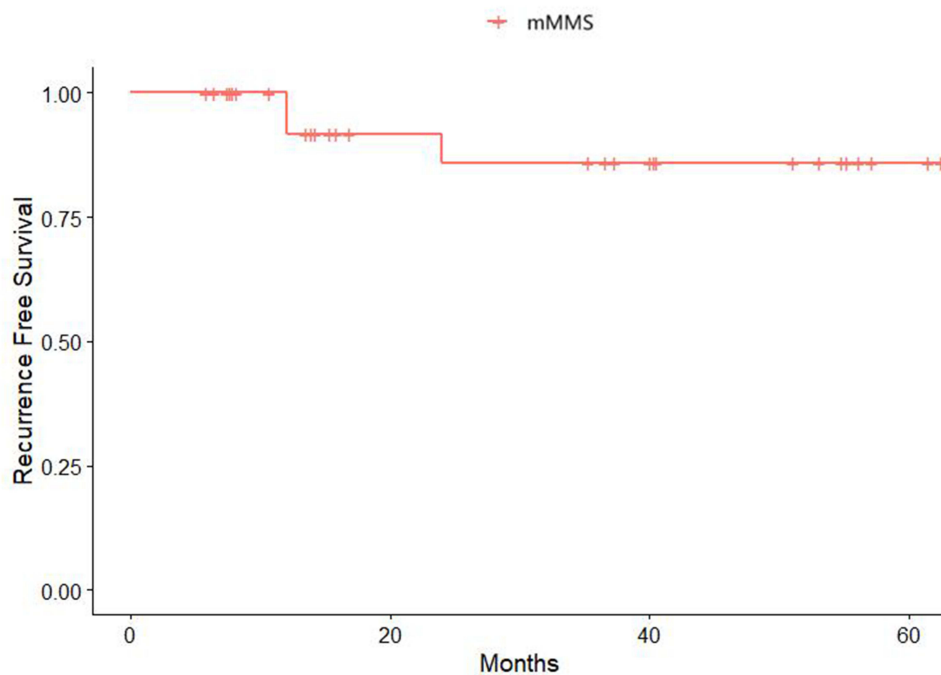


Figure 3 Kaplan-Meier survival analysis showing the Recurrence -Free Survival with narrow-margin mMMS in the study population.

Table 3 Univariable Analysis of Disease-Free Survival by Cox Regression in the Radical Cohort. (Event: Recurrence)

	HR (95% CI)	p-value
With hypopigmented patches	14.0 (1.269, 154.395)	0.031
Primary EMPD	0.112 (0.01, 1.253)	0.076
Invasive EMPD	0.3 (0.027, 3.308)	0.326
Lymphovascular invasion	15.50 (0.970, 247.806)	0.053
Tumor size	1.002 (0.921, 1.091)	0.964

Note: The p-value of univariate Cox regression less than 0.05 was considered significant.

Abbreviations: HR, Hazard Ratio; CI, Confidence Interval.

Our findings revealed a local recurrence rate of 7.1%, an estimated 5-year tumor-free rate of 85.9%, and identified hypopigmented plaques as a significant risk factor for recurrence.

Previous studies have shown that MMS is a treatment modality that reduces recurrence rates relative to WLE, with reported recurrence rates ranging from 7.3% to 26%.^{4,10–12} A retrospective study on Mohs surgery showed a postoperative recurrence rate of 26% (7/27), mainly due to the inclusion of recurrent cases and a small sample size. Moreover, the multicentricity and jumping nature of tumors increase the difficulty of practical operation of traditional MMS, which is not suitable for patients with extensive skin lesions. A retrospective study revealed that WLE is still the primary treatment for EMPD, with resection margins ranging from 1 to 5 cm, yet positive margins were observed in 57.6% of patients.¹³ From a therapeutic point of view, the surgical goal is to pursue pathologically negative surgical margins while considering the patient's postoperative quality of life. From our previous experience with Mohs surgery, we have found a low positive rate of choosing an initial flaring width of 5 mm, with a 1-cm flaring of the scrotal area, taking into account the contractile nature of the scrotal skin. Therefore, we designed narrow-margin mMMS with varying margins tailored to different tumor sites. An initial margin of 0.5–1 cm was implemented to prioritize rapid tumor resection while ensuring comprehensive margin assessment through MMS.

In our study, the final cut edge to achieve complete tumor clearance was 0.5 (0.5, 1) cm in non-scrotal skins and 1 (1, 1.5) cm in scrotal skins. In the initial external excision, positivity rates were 15% (48/319) in non-scrotal skin and 19.7% (67/340) in scrotal skin with a 1 cm margin. An unexpected finding was that approximately 95% of tumors with extensions of 1 cm in non-scrotal skin or 1.5 cm in scrotal skin could be completely cleared. Furthermore, a significant proportion of tumors could be largely removed with a single expansion during narrow-margin mMMS. Therefore, we suggest that surgeons consider selecting different initial margin widths based on the tumor site. Narrow-margin mMMS offers comprehensive margin assessment, rapid tumor removal, and maximum tissue preservation. The higher margin clearance rate observed in our study may be attributed to the use of photodynamic diagnosis (PDD) and Wood's lamp for delineating tumor margins, particularly for hypopigmented patches, which were consistently identified as tumors and confirmed by postoperative pathology to contain Paget cells. Surgery for EMPD tumors focuses on finding the tumor border, so we focus on margin monitoring. Usually, the depth of surgical resection reaches the mid-depth fat layer, and a negative base margin can be obtained in the mid-sarcolemmal layer. To minimize surgery time, we abandoned the traditional Mohs bread slice method and adopted the postoperative bottom margin biopsy method for evaluation.

In the present study, 7.1% (3/42) of EMPD tumor cases recurred after narrow-margin mMMS. A pooled analysis of the 90 cases treated with MMS by Bae et al found a 5-year tumor-free rate of 83.6%.⁶ Another cohort study of MMS found a 5-year tumor-free rate of 91%.⁵ Our result is comparable with this, with 5-year tumor-free of 85.9%. The most obvious factor influencing recurrence in our study was the hypopigmented patches, similar to previous findings.³ This suggests that surgeons should be cautious about subclinical lesions such as hypopigmentation before mapping surgical margins. Furthermore, intra-operative CK7 staining has been shown to enhance 5-year tumor-free survival to 94.6% during MMS.¹⁴ In our study, we found a lower RFS rate for combined lymph node abnormalities, but it was not statistically significant in the COX analysis, possibly due to the infrequency of the lymph node subgroup for regression analyses. Other previously reported well-known risk factors for the recurrence including dermal invasion, type of surgery,

tumor size, were not observed in our study. The limitations of this study are mainly related to its retrospective nature, which may have resulted in some missing or incomplete data. As a specialist hospital, we were unable to screen for other potential tumors. Despite the small size of this cohort, we represent a larger cohort of the Asian population due to the rarity of the disease.

Conclusions

Narrow-margin mMMs enhances treatment efficiency by achieving 100% margin detection while preserving a greater amount of normal tissue. Depending on the skin lesion's location, the surgeon can adjust the procedure's extension, enabling complete clearance of approximately 95% of tumors with either 1 cm of non-scrotal skin extension or 1.5 cm of scrotal skin extension. This approach maximizes skin preservation, facilitating easier reconstruction.

Patient Consent

All the patients signed informed consent after being informed that their clinical information will be used anonymously for research.

Acknowledgment

This study is thanks to all the patients. We are grateful to our colleagues in the department of pathology for the technical expenditure on frozen sections in modified Mohs surgery. We thank our colleagues in the department of surgery at the skin disease hospital of Tongji University in Shanghai for their help in completing the surgery and follow-up. We thank our colleagues in the pharmacy and ultrasound and rheumatology departments for their help in the evaluation of the tumor. We thank the central laboratory of Shanghai Dermatological Hospital for advice and help in data compilation and article writing.

Funding

There is no funding to report.

Disclosure

The authors report no conflicts of interest in this work.

References

- Lloyd J, Flanagan AM. Mammary and extramammary Paget's disease. *J Clin Pathol*. 2000;53(10):742–749. doi:10.1136/jcp.53.10.742
- Yang CC, Lee JY, Wong TW. Depigmented extramammary Paget's disease. *Br J Dermatol*. 2004;151(5):1049–1053. doi:10.1111/j.1365-2133.2004.06223.x
- Choi S, Oh Y, Chung KY, Oh BH, Roh MR. Hypopigmentation in extramammary Paget disease is an important prognostic factor for high recurrence rate and poor surgical outcome. *Dermatol Surg*. 2021;47(5):613–617. doi:10.1097/DSS.0000000000002950
- Hendi A, Brodland DG, Zitelli JA. Extramammary Paget's disease: surgical treatment with Mohs micrographic surgery. *J Am Acad Dermatol*. 2004;51(5):767–773. doi:10.1016/j.jaad.2004.07.004
- Kim SJ, Thompson AK, Zubair AS, et al. Surgical treatment and outcomes of patients with extramammary Paget disease: a cohort study. *Dermatol Surg*. 2017;43(5):708–714. doi:10.1097/DSS.0000000000001051
- 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(4):632–637. doi:10.1016/j.jaad.2012.12.960
- Long B, Schmitt AR, Weaver AL, et al. A matter of margins: surgical and pathologic risk factors for recurrence in extramammary Paget's disease. *Gynecol Oncol*. 2017;147(2):358–363. doi:10.1016/j.ygyno.2017.09.008
- Kanitakis J. Mammary and extramammary Paget's disease. *J Eur Acad Dermatol Venereol*. 2007;21(5):581–590. doi:10.1111/j.1468-3083.2007.02154.x
- Li Q, Zhang G, Yao X, Yang S, Tu P, Li H. Prediction of surgical margin width using Mohs micrographic surgery for extramammary Paget's disease based on clinicopathological parameters: classification tree analysis of 150 cases. *Eur J Dermatol*. 2022;32(1):107–112. doi:10.1684/ejd.2022.4204
- Thomas CJ, Wood GC, Marks VJ. Mohs micrographic surgery in the treatment of rare aggressive cutaneous tumors: the Geisinger experience. *Dermatol Surg*. 2007;33(3):333–339. doi:10.1111/j.1524-4725.2007.33069.x
- O'Connor WJ, Lim KK, Zalla MJ, et al. Comparison of mohs micrographic surgery and wide excision for extramammary Paget's disease. *Dermatol Surg*. 2003;29(7):723–727. doi:10.1046/j.1524-4725.2003.29184.x
- Kim GY, Campbell EH, Brewer JD. Local recurrence rates of extramammary Paget disease are lower after mohs micrographic surgery compared with wide local excision: a systematic review and meta-analysis. *Dermatol Surg*. 2023;49(1):8–12. doi:10.1097/DSS.0000000000003601

13. Escola H, Llombart B, Escola-Rodriguez A, et al. Therapeutic outcomes and survival analysis of extramammary Paget's disease: a multicentre retrospective study of 249 patients. *J Am Acad Dermatol.* 2024;90(1):66–73. doi:10.1016/j.jaad.2023.08.088
14. Damavandy AA, Terushkin V, Zitelli JA, et al. Intraoperative immunostaining for cytokeratin-7 during mohs micrographic surgery demonstrates low local recurrence rates in extramammary Paget's disease. *Dermatol Surg.* 2018;44(3):354–364. doi:10.1097/DSS.0000000000001355

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