Survival analysis of extramammary Paget’s disease (EMPD) in a tertiary hospital in Taiwan

Yu-Wei Chang¹,², Hsu Ma¹,² and Wen-Chieh Liao¹,²,³*

Abstract

Background: This study aimed to investigate the survival analysis of extramammary Paget’s disease (EMPD) in a Taiwanese population and to provide data for comparison with other studies in various locations and racial populations.

Methods: We retrospectively analyzed the medical records of 63 patients with EMPD who were surgically treated from 2002 to 2019 at a single institution. The primary endpoint was the 5-year overall survival rate of EMPD, and the secondary endpoint was recurrence-free 5-year survival. Independent variables included patients’ demographic data, concurrent malignancy (i.e., non-EMPD-related cancers), tumor size, distant metastasis, and surgery and/or radiation.

Results: Of all the 63 patients, 8 cases were excluded. A total of 43 patients (78.18%) were male, and 12 were female, with a mean age of 72.67 years (range 44–89 years). The most common affected anatomic site was the penoscrotal region (22 patients, 40.00%), followed by the perianal and perineal regions (17 patients, 30.91%). Among the 55 patients, 41 patients (74.55%) were diagnosed with at least one underlying disease, whereas the most common underlying disease was cardiovascular disease (30 patients, 54.55%). The overall survival rate was 80.00% at 36 months and 65.45% at the end of follow-up. EMPD with deep dermal invasion was a significant poor prognostic factor of overall survival in cause-specific hazard model (sub-hazard ratio (HR) 5.167, \( p = 0.0015 \), 95% confidence interval (CI) 1.876–14.230). Patients with regional metastasis or distant metastasis had poorer prognosis of 5-year survival (sub-HR 4.513, \( p = 0.0028 \), CI 1.683–12.103). The limitations of this study include its retrospective nature and sample size.

Conclusions: In our series, EMPD with metastasis and deep dermal invasion was the significant harmful factors in both overall 5-year survival and 5-year recurrence-free survival. The surgical excision is not associated with a low risk of local recurrence or overall survival, and long-term follow-up is still needed.

Keywords: Extramammary Paget disease (EMPD), Survival analysis, Metastasis wide excision
Background
Extramammary Paget’s disease (EMPD) is a rare intraepithelial neoplasm that most commonly affects individuals in their 60s to 80s [1, 2]. Given its slow growth and non-specific symptoms, EMPD is easily neglected and results in delayed diagnosis [2–4]. The disease affects sites rich in apocrine glands, including the vulva, scrotum, penis, and perineal and perianal regions and less frequently in the axilla, face, or trunk. High prevalence in Caucasians and predominance in female were reported in Western literature, whereas less frequent occurrence was reported for Asian populations [1–4].

Previous literatures have identified potential factors related to poor prognosis of EMPD; these factors include the dermis invasion, distant metastasis, concurrent malignancy, male gender, and tumor in the perianal anatomic region [2–6]. Karam et al. conducted a survival analysis of white people-predominant population with 2001 EMPD patients in 1973–2007 and concluded the high mortality in invasive EMPD patients with old age, advanced stage, and treatment modality [4].

Different characteristics and manifestations of EMPD in Asian population, including male predominance and low incidence of concurrent internal malignancy, have been identified [7, 8]. Nevertheless, given the relative rarity of EMPD in Asian population, limited literature reported findings on Taiwanese population [8–11], whereas a similar comprehensive survival analysis in Taiwan is still lacking.

In this study, we presented our 18-year experience of EMPD cases in a single center in Taiwan. We aimed to analyze the demographic characteristic of the disease and identify potential prognostic factors of overall survival and recurrence-free survival in Taiwanese population.

Methods
Patient selection and inclusion criteria
This retrospective cohort study was conducted by the plastic surgery department of Taipei Veterans General Hospital, Taiwan. The study was approved by the institutional review board of our hospital. Through the electronic patient record system, in January 2002 to January 2019, patients who received biopsy with final diagnosis of EMPD on pathological reports were included. The 5-year survival status was confirmed through electronic patient records. If the survival status cannot be confirmed, phone interview was performed.

Data extraction and selection
Patient demographic characteristics, including age of diagnosis, gender, concurrent malignancy, anatomic site of lesion, maximal diameter of lesion, and metastasis status, were extracted and recorded. Dermal invasion of the lesion was divided into upper dermis invasion and deep dermal invasion, and the metastasis status was further classified as regional or distant metastasis. The type of treatment was classified into four groups, including surgical excision alone, surgical excision with adjuvant therapy, nonsurgical treatment alone (radiotherapy, chemotherapy, or phototherapy), and without any treatment. In addition to wide local excision, simple or radical vulvectomy in vulva EMPD was included in the excision. Surgical outcomes, including status of excision margin, recurrence, and recurrence-free interval, were also recorded.

Primary and secondary endpoints
The primary endpoint was the 5-year overall survival rate of EMPD, which was defined as the interval between the date of diagnosis on pathology to the date of death of any cause. The poor prognostic factors of 5-year overall survival were identified. The secondary endpoint was recurrence-free 5-year survival, defined as the interval between the date of diagnosis on pathology to the date of recurrence or death of any cause. The related risk factors of recurrence were also analyzed.

Statistical analysis
All the data were analyzed by the SAS® 9.4 software. Discrete variables were presented in percentages, and the continuous variables were presented as mean and standard deviation. Competing risk analysis with cause-specific hazard model was applied to evaluate the variables individually to identify the potential factors of poor prognosis in both 5-year overall survival and recurrence. The proportional hazard assumption of the cause-specific hazard model would be tested. Significance was set at \( p \leq 0.05 \) for each test.

Results
Between January 2002 and January 2019, 63 patients were diagnosed with EMPD in our hospital. To evaluate the 5-year overall survival status, in addition to the electronic medical record, phone interviews were performed to twelve patients, whereas seven patients were lost to follow-up and one refused the phone interview (Fig. 1). Table 1 lists the demographic characteristics of 55 eligible patients. The mean age diagnosis was 72.67 years (range 44–89 years), with 30 (54.55%) patients diagnosed at 75 years old or older. The majority of the diagnosed patients were male (43 patients, 78.18%), and the most common affected anatomic site was the perianal region (22 patients, 40.00%). The second most affected region was the perianal and perineal region (17 patients, 30.91%). More than half of the patients were diagnosed with a lesion larger than 2 cm (36 patients, 65.45%). Among the 55 patients, 41 (74.55%) were diagnosed with at least one underlying disease, whereas the most
common underlying disease was cardiovascular disease (30 patients, 54.55%), followed by metabolic or endocrine diseases (15 patients, 27.27%).

Pathological results and surgical outcomes
Based on the pathological results of preoperative biopsy, among the 55 eligible patients, 17 had invasive lesions (30.91%), including 10 lesions with microinvasion of upper dermis (18.18%) and 7 lesions with deep invasion (12.73%). Due to lack of the detailed staining results in some patient’s electronic record, we analyzed the results of 3 immunohistochemical staining markers among 36 patients, including CK7, CK20, and GCDFP-15 (Fig. 2). Among the 36 immunohistochemically stained EMPD specimen, 33 were positive of CK7 (91.67%), 8 were positive of CK20 (22.22%), 5 were positive of GCDFP-15 (13.89%), and 8 were positive of Cdx2 (22.22%) (Table 1). Seven cases indicated metastasis (12.72%), including three unilateral lymph node metastases (5.45%), one bilateral lymph node metastasis (1.82%), and three distant metastases (5.45%). A total of 47 patients (85.46%) received surgical excision of the lesion, including 8 (14.55%) who received surgical treatment with adjuvant therapy. Four patients (7.27%) received radiotherapy or chemotherapy without surgical excision, whereas another four (7.27%) refused any treatment.

Overall survival rate and prognostic factors
After diagnosis, the overall survival rate declined over the years (Table 2). The overall survival rate was 80.00% at 36 months and 65.45% at the end of follow-up. Cause-specific hazard model of 5-year all-cause mortality was performed (Table 3) for each variable. Patients with regional metastasis or distant metastasis had poorer prognosis of 5-year survival compared with patients without metastasis (sub-HR 4.513, \(p = 0.0028, \text{CI} 1.683–12.103\)). Furthermore, patients with deep dermal invasion had worse prognosis compared with those without dermal invasion (sub-HR 5.167, \(p = 0.0015, \text{CI} 1.876–14.230\)), whereas no similar harmful effect was noted in the microinvasion of dermis (\(p = 0.6362\)). No other significant prognostic factor was found among the other variables, including age, anatomic site of lesion, size of lesion, type of treatment, or concurrent malignancy. Proportional hazard assumption was tested, and there was no indication of violating the assumption.

Recurrence rate and 5-year recurrence-free survival
During the 5-year follow-up, among the fifty-one patients who received any type of treatment, eight patients suffered from recurrence (15.69%), with a mean recurrence interval of 15.5 months (range 1.3–29.6 months). The recurrence-free survival rate declined more rapidly over the years than the overall survival rate (Table 2). The recurrence-free survival rate was 70.59% at 36
months and 60.78% at the end of the follow-up. Competing risk analysis with cause-specific hazard model (Table 4) of recurrence in the 5-year follow-up interval showed a similar outcome as the overall survival. Metastatic disease (sub-hazard ratio 9.103, \( p = 0.002, \text{CI} 2.249–36.849 \)) and deep dermal invasion (sub-HR 7.836, \( p = 0.0052, \text{CI} 1.848–33.449 \)) were significant factors leading to poor outcome of recurrence-free survival. No significant association was observed between the margin status and recurrence (\( p = 0.4338 \)). In the subgroup analysis of those with intraepithelial lesion, free-margin status revealed no significant benefit of recurrence-free survival compared with those without free excision margin (\( p = 0.3998 \)). No other significant risk factor of recurrence was found in other variables. Proportional hazard assumption was tested, and there was no indication of violating the assumption.

Concurrent malignancy

Concurrent or subsequent malignancy was noted in 21 patients (38.18%), including 3 patients (5.45%) with adnexal carcinoma and 18 patients (32.73%) with internal malignancy (Table 1). Among the 18 patients with internal malignancy, 10 were diagnosed with gastrointestinal tract malignancy, 4 with genitourinary tract malignancy, 2 with adenocarcinoma with unknown origin, and 2 with parotid cancer. When analyzed with anatomic site of lesion, among 17 patients with perianal EMPD, 8 patients were diagnosed with gastrointestinal tract malignancy (47.06%) compared with 2 gastrointestinal tract malignancy in 38 patients with EMPD (5.26%) in other sites. In the 29 patients with genitourinary EMPD, 3 patients with genitourinary tract malignancy was observed (10.34%), whereas a genitourinary tract malignancy was detected in the other 26 EMPD patients (3.85%). Logistic regression of EMPD anatomic site and internal malignancy revealed the strong association between gastrointestinal malignancy and perianal region EMPD (odds ratio = 16.00, \( p = 0.0015, \text{CI} 2.885–88.730 \)), whereas no similar association was noted in genital region EMPD and genitourinary malignancy (\( p = 0.3726 \)) (Table 5).

Discussion

In the present study, the characteristics of EMPD patients in one single institution were analyzed. As

### Table 1 Demographics and clinical data of 55 study patients with EMPD

| Variable                                | Patients |
|-----------------------------------------|----------|
| **Patient characteristics**             |          |
| Gender (male)                           |          |
| Male                                    | 43 (78.18%) |
| Female                                  | 12 (21.82%) |
| Age (year) (mean= 72.67, range 44–89)  |          |
| Age < 65 years old                      | 14 (25.45%) |
| Age = 65–74 years old                   | 11 (20.00%) |
| Age = 75 years old or more              | 30 (54.55%) |
| **Anatomic site of lesion**             |          |
| Scrotum or penis                        | 22 (40.00%) |
| Vulva or labia                          | 7 (12.73%) |
| Perianal or perineal region              | 17 (30.91%) |
| Trunk or others                         | 9 (16.36%) |
| **Types of treatment**                  |          |
| Surgical excision only                  | 39 (70.91%) |
| Surgical excision with adjuvant therapy | 8 (14.55%) |
| Radiotherapy or chemotherapy only       | 4 (7.27%) |
| Refused any treatment                   | 4 (7.27%) |
| Recurrence (N=51)                       | 8 (15.69%) |
| Concurrent malignancy (N=21, 38.18%)    |          |
| Adnexal carcinoma                       | 3 (5.46%) |
| Internal malignancy                     | 18 (32.73%) |
| **Underlying diseases**                 |          |
| Without any underlying diseases         | 14 (25.45%) |
| Cardiovascular diseases                 | 30 (54.55%) |
| Respiratory diseases                    | 5 (9.09%) |
| Metabolic or endocrine diseases         | 15 (27.27%) |
| Nephrology disease                      | 3 (5.45%) |
| Gastrointestinal disease                | 8 (14.55%) |
| **Pathological parameter**              |          |
| Size of lesion (length of maximal diameter) |    |
| 2 cm or less than 2 cm                  | 19 (34.55%) |
| More than 2 cm                          | 36 (65.45%) |
| Depth of invasion                       |          |
| Intraepithelial                         | 38 (69.09%) |
| Micro-invasion of upper dermis          | 10 (18.18%) |
| Deep invasion                           | 7 (12.73%) |
| **Immunohistochemical staining (N=36)** |          |
| Positive of CK7                         | 33 (91.67%) |
| Positive of CK20                        | 8 (22.22%) |
| Positive of GCDFP-15                    | 5 (13.89%) |
| Positive of Cdx2                        | 8 (22.22%) |

### Table 1 Demographics and clinical data of 55 study patients with EMPD (Continued)

| Variable                                | Patients |
|-----------------------------------------|----------|
| Metastasis status (N=7, 12.72%)         |          |
| Unilateral lymph node metastasis        | 3 (5.45%) |
| Bilateral lymph node metastasis         | 1 (1.82%) |
| Distant metastasis                      | 3 (5.45%) |
revealed in other Asian population-based studies [7, 12],
the predominance of male gender in the distribution of
EMPD patients was also noted in our cases. The most
common affected site was the penoscrotal region (40%),
similar to the findings of other studies [13–15]. The
average size of lesion, the mean age of diagnosis, and
rate of metastasis (12.72%) were also in compatible range
with previous literature [4, 5, 7, 12]

The overall survival rates in our study were 80.00%
(36-month follow-up) and 65.45% (60-month follow-up)
(Table 2), which were compatible with those of previous
male-predominant or Asian-predominant study [12, 13].
Previous studies had identified several potential risk fac-
tors of poor prognosis of EMPD, including the level of
tumor invasion, lymph node metastases, elevated CEA,
perianal lesion, old age, and male gender [5, 12, 13, 16].
In our study, based on the results of cause-specific haz-
ard model (Table 3), metastatic diseases and deep der-
mal invasion were identified as significant harmful
factors of the overall 5-year survival, showing similar
outcomes with two population-based studies and previ-
ous reviews [6, 12, 17]. The relationship between sur-
vival and microinvasive disease remains controversial,
whereas deeply invasive EMPD was linked to poorer
prognosis than the non-invasive counterpart [12, 17].
The association between prognosis and site of lesion had
been reported, suggesting that anorectal EMPD has a
statistically significantly decreased mean disease-specific
survival compared with those without anorectal involve-
ment [4]. However, no significant difference in overall
survival was observed between the different groups of le-
sion site in our study (Table 3).

The 5-year recurrence rate (15.69%) and the mean re-
currence interval (15.5 months after diagnosed) in our
study were similar to those of other EMPD studies that
treated patients with wide local excision [14, 15, 18].
The recurrence-free survival rate was 70.59% at 36-month follow-up and 60.78% at 60-month follow up (Table 2), consistent with those of other wide local excision studies [15, 18]. Based on the results of competing risk analysis (Table 4), metastatic diseases and deep dermal invasion were identified as potential risk factors of recurrence. The results of our study coincided with that of a previous study [10], whereas another population-based study reported no relationship between dermal invasion and local recurrence [7]. Previous literature observed a strong association between margin status and recurrence risk [15], whereas in our study (Table 4) no similar significant association was found. In the sub-group analysis of those with intraepithelial lesion, free-margin status revealed no improvement in recurrence-free survival compared with those without free excision margin (p =0.3998), which was in conflict with previous literature [19].

Table 3 Competing risk analysis of 5-year mortality

| Variate                        | Mortality rate | Sub-HR  | 95% CI          | p-value |
|--------------------------------|----------------|---------|-----------------|---------|
| Gender                         |                |         |                 |         |
| Female                         | 16.67%         | Reference | Reference | Reference |
| Male                           | 39.53%         | 2.737   | 0.632–11.859   | 0.1784  |
| Age                            |                |         |                 |         |
| Age less than 75 years old     | 24.00%         | Reference | Reference | Reference |
| Age= 75 years old or more      | 43.33%         | 2.127   | 0.808–5.600    | 0.1265  |
| Lesion site                    |                |         |                 |         |
| Genital region or others       | 26.32%         | Reference | Reference | Reference |
| Perianal or perineal region    | 52.94%         | 2.338   | 0.948–5.765    | 0.0651  |
| Size of lesion                 |                |         |                 |         |
| Lesion = 2 cm or less          | 26.32%         | Reference | Reference | Reference |
| Lesion larger than 2 cm        | 38.89%         | 1.624   | 0.584–4.514    | 0.3527  |
| Invasion of dermis             |                |         |                 |         |
| No dermal invasion             | 28.95%         | Reference | Reference | Reference |
| Micro-invasion                 | 20.00%         | 0.695   | 0.154–3.137    | 0.6362  |
| Deep dermal invasion           | 85.71%         | 5.167   | 1.876–14.230   | 0.0015  |
| Metastasis status              |                |         |                 |         |
| Without metastasis             | 27.08%         | Reference | Reference | Reference |
| Metastatic diseases            | 85.71%         | 4.513   | 1.683–12.103   | 0.0028  |
| Recurrence (N=51)              |                |         |                 |         |
| No recurrence                  | 27.91%         | Reference | Reference | Reference |
| With recurrence                | 62.50%         | 2.587   | 0.907–7.382    | 0.0756  |
| Concurrent malignancy          |                |         |                 |         |
| No concurrent malignancy       | 29.41%         | Reference | Reference | Reference |
| Adnexal carcinoma              | 33.33%         | 1.180   | 0.151–9.225    | 0.8744  |
| Internal malignancy            | 44.44%         | 1.595   | 0.629–4.044    | 0.3249  |
| Types of treatment             |                |         |                 |         |
| With surgical excision         | 31.91%         | Reference | Reference | Reference |
| Without surgical excision      | 50.00%         | 1.642   | 0.544–4.950    | 0.3787  |
| Margin status (N=47)           |                |         |                 |         |
| Margin not free                | 33.33%         | Reference | Reference | Reference |
| Margin free                    | 31.03%         | 0.911   | 0.324–2.561    | 0.8596  |
| Intraepithelial lesion (N=31)  |                |         |                 |         |
| Margin not free                | 37.50%         | Reference | Reference | Reference |
| Margin free                    | 21.74%         | 0.528   | 0.126–2.211    | 0.3822  |

Abbreviation: CI confidence interval, Sub-HR sub-hazard ratio
The rates of concurrent malignancy (38.18%), adnexal carcinoma (5.45%), and internal malignancy (32.73%) in our study were in compatible range with previous reviews [2, 5, 15, 20]. Several Asian population-based studies revealed a low concurrent internal malignancy rate in Asian EMPD patients [7, 12, 14] which is in contrast with the result of our study. The potential relationship between the anatomic site of EMPD lesion and internal malignancy was proposed in another study [20]. We determined the perianal EMPD as a significant risk factor of gastrointestinal malignancy (odds ratio = 16.00, \( p = 0.0015 \), CI 2.885–88.730), whereas no similar association was observed between the genital region EMPD and genitourinary malignancy (\( p = 0.3726 \)) (Table 5).

Our study had several limitations. First, all the data were retrospectively extracted from the electronic patient record system, which may lead to potential bias in data extraction or misinterpretation. Inadequate description of pathology reports and outpatient department follow-up may also lead to underestimation of the actual rate of dermis invasion and recurrence. In addition,

### Table 4 Competing risk analysis of recurrence (N=51)

| Variate                        | Recurrence rate | Sub-HR | 95% CI          | p-value |
|--------------------------------|-----------------|--------|-----------------|---------|
| Gender                         |                 |        |                 |         |
| Female (N=12)                  | 16.67\%         | Reference | Reference | Reference |
| Male (N=39)                    | 15.38\%         | 0.884  | 0.178–4.381     | 0.8799  |
| Age                            |                 |        |                 |         |
| Age less than 75 years old (N=25) | 20.00\%       | Reference | Reference | Reference |
| Age= 75 years old or more (N=26) | 11.54\%       | 0.673  | 0.161–2.818     | 0.5878  |
| Lesion site                    |                 |        |                 |         |
| Genital region or other (N=36) | 16.67\%         | Reference | Reference | Reference |
| Perianal or perineal (N=15)    | 13.33\%         | 0.835  | 0.169–4.138     | 0.8253  |
| Size of lesion                 |                 |        |                 |         |
| Lesion = 2 cm or less (N=16)   | 6.25\%          | Reference | Reference | Reference |
| Lesion lager than 2 cm (N=35)  | 20.00\%         | 3.743  | 0.460–30.454    | 0.2171  |
| Invasion of dermis             |                 |        |                 |         |
| No dermal invasion (N=45)      | 11.11\%         | Reference | Reference | Reference |
| Deep dermal invasion (N=6)     | 50.00\%         | 7.863  | 1.848–33.449    | 0.0052  |
| Metastasis                     |                 |        |                 |         |
| Without metastasis (N=44)      | 9.09\%          | Reference | Reference | Reference |
| With any metastasis (N=7)      | 57.14\%         | 9.103  | 2.249–36.849    | 0.0020  |
| Concurrent malignancy          |                 |        |                 |         |
| No concurrent malignancy (N=32) | 12.50\%         | Reference | Reference | Reference |
| Adnexal or Internal malignancy (N=19) | 21.05\%    | 1.955  | 0.488–7.828     | 0.3436  |
| Excision margin status (N=47)  |                 |        |                 |         |
| Margin not free (N=18)         | 22.22\%         | Reference | Reference | Reference |
| Margin free (N=29)             | 13.79\%         | 0.575  | 0.144–2.300     | 0.4338  |
| Intraepithelial lesion (N=31)  |                 |        |                 |         |
| Margin not free (N=8)          | 25.00\%         | Reference | Reference | Reference |
| Margin free (N=23)             | 13.04\%         | 0.463  | 0.077–2.779     | 0.3998  |

**Abbreviation:** CI confidence interval, Sub-HR sub-hazard ratio

### Table 5 Logistic regression analysis of EMPD and internal malignancy

| Variate                                        | Odds ratio | 95% confidence interval | p-value |
|------------------------------------------------|------------|-------------------------|---------|
| Perianal EMPD and gastrointestinal malignancy  | 16.00      | 2.885–88.730            | 0.0015  |
| Genital region EMPD and genitourinary malignancy | 2.884 | 0.281–29.609            | 0.3726  |
given the long follow-up period of up to 5 years, phone interview was performed as an alternative way of evaluation, in which only limited information can be accessed. Finally, with the rarity of EMPD in Asian population, the present single-center study included 55 illegible patients. A multicenter, larger sample size study in Taiwanese population is still needed for further evaluation.

To the best of our knowledge, this research is the first study in the English language literature about the comprehensive survival analysis of EMPD in Taiwan population. Our report also identified similar disease characteristics and prognostic factors in Taiwan population, similar to other Asian population-based studies, and their differences.

Conclusion
EMPD is commonly observed among aged people. The presence of metastatic EMPD and deep dermal invasion are significant harmful factors of the overall 5-year survival and 5-year recurrence-free survival. In most cases, EMPD is not associated with cancer, whereas perianal EMPD is accompanied with a high risk of gastrointestinal malignancy. Regardless of treatment method, long-term follow-up is recommended.

Abbreviations
EMPD: Extramammary Paget's disease; sub-HR: Sub-hazard ratio

Acknowledgements
The authors would like to thank Y. L. LIN HUNG TAI Education and Culture Charity Trust and Y. L. LIN HUNG TAI Education Foundation for kindly funding the article-processing charge of this article and the Enago academy (www.enago.tw) for their expertise and assistance in professional language editing of the manuscript.

Authors’ contributions
WL collected the data and assisted with manuscript editing. YC analyzed the data and wrote the manuscript. HM designed and supervised the study. All authors participated in final revision and approved the manuscript.

Funding
Not applicable.

Availability of data and materials
The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations
Ethics approval and consent to participate
This study was approved and supervised by the institutional review board of Taipei Veterans General Hospital (Approval number:2020-03-021CC).

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

Author details
1Division of Plastic and Reconstructive Surgery, Department of Surgery, Taipei Veterans General Hospital, 19F, No.201 Shih-Pai RD Sec 2, Taipei, Taiwan. 2School of Medicine, National Yang-Ming University, Taipei, Taiwan. 3Institute of Environmental and Occupational Health Sciences, School of Medicine, National Yang Ming Chiao Tung University, Taipei, Taiwan.

Received: 13 November 2020 Accepted: 3 April 2021
Published online: 12 April 2021

References
1. Adaskin JJ, Leonard A, Nealon SW, Krishnan A, Mosiello GC, Dhillon J, et al. Extramammary Paget's disease: what do we know and how do we treat? Can J Urol. 2019;26(6):10012–21.
2. Asel M, LeBoeuf NR. Extramammary Paget's disease. Hematol Oncol Clin North Am. 2019;33(1):73–85. https://doi.org/10.1016/j.hoc.2018.09.003.
3. Meritt BG, Degesys CA, Brodland DG. Extramammary Paget disease. Dermatol Clin. 2019;37(3):261–7. https://doi.org/10.1016/j.det.2019.02.002.
4. Karam A, Dorigo O. Treatment outcomes in a large cohort of patients with invasive Extramammary Paget’s disease. Gynecol Oncol. 2012;125(2):346–51. https://doi.org/10.1016/j.ygyno.2012.01.032.
5. Yao H, Xie M, Fu S, Guo J, Peng Y, Cai Z, et al. Survival analysis of patients with invasive extramammary Paget disease: implications of anatomic sites. BMC Cancer. 2018;18(1):408. https://doi.org/10.1186/s12885-018-4257-1.
6. Cohen JM, Granter SR, Werchniak AE. Risk stratification in extramammary Paget disease. Clin Exp Dermatol. 2015;40(5):473–8. https://doi.org/10.1111/ced.12690.
7. Chan JY, Li GK, Chung JH, Chow VL. Extramammary Paget disease: 20 years of experience in Chinese population. Int J Surg Oncol. 2012;2012:16418.
8. Cheng PS, Lu CL, Cheng CL, Lai FJ. Significant male predisposition in extramammary Paget disease: a nationwide population-based study in Taiwan. Br J Dermatol. 2014;171(1):191–3. https://doi.org/10.1111/bjd.12851.
9. Wang YC, Li AF, Yang SH, Ma HH, Liang WY. Perianal Paget's disease: the 15-year-experience of a single institution in Taiwan. Gastroenterol Res Pract. 2019;2019:2603279.
10. Lai YL, Yang WQ, Tsay PK, Swei H, Chuang SS, Wen CJ. Penoscrotal extramammary Paget disease: a review of 33 cases in a 20-year experience. Plast Reconstr Surg. 2003;112(4):1017–23. https://doi.org/10.1097/01.PR.S.0000076193.6701A.
11. Chiu CS, Yang CH, Chen CH. Extramammary Paget's disease of the unilateral axilla: a review of seven cases in a 20-year experience. Int J Dermatol. 2011;50(2):157–60. https://doi.org/10.1111/j.1365-4632.2010.04604.x.
12. Ito Y, Igawa S, Ohishi Y, Uehara J, Yamamoto AI, Izuka H. Prognostic indicators in 35 patients with extramammary Paget's disease. Dermatol Surg. 2012;38(1):1938–44. https://doi.org/10.1111/j.1524-4725.2012.02594.x.
13. Herrell LA, Weiss AD, Goodman M, Johnson TV, Osunksya AO, Delman KA, et al. Extramammary Paget disease in males: survival outcomes in 495 patients. Ann Surg Oncol. 2015;22(5):1625–30. https://doi.org/10.1245/s10434-014-4139-y.
14. Chiu TW, Wong PS, Ahmed K, Lam SC, Ying SY, Burd A. Extramammary Paget's disease in Chinese males: a 21-year experience. World J Surg. 2007;31(10):1941–6. https://doi.org/10.1007/s00268-007-9189-x.
15. Long B, Schmitt AR, Weaver AL, McGree M, Bakkum-Gamez JN, Brewer J, et al. A matter of margins: surgical and pathologic risk factors for recurrence in extramammary Paget’s disease. Gynecol Oncol. 2017;147(2):358–63.
16. Leong JY, Chung PH. A primer on extramammary Paget’s disease for the urologist. Transl Androl Urol. 2020;9(1):93–105. https://doi.org/10.21037/tau.2019.07.14.
17. Hatta N, Yamada M, Hirano T, Fujimoto A, Morita R. Extramammary Paget’s disease: treatment, prognostic factors and outcome in 76 patients. Br J Dermatol. 2008;158(3):313–8. https://doi.org/10.1111/j.1365-2133.2007.08314.x.
18. Lee KY, Roh MR, Chung WK, Chung KY. Comparison of Mohs micrographic surgery and wide excision for extramammary Paget’s disease: Korean experience. Dermatol Surg. 2009;35(1):34–40. https://doi.org/10.1111/j.1524-4725.2008.34380.x.
19. Hegarty PK, Suh J, Fisher MB, Taylor J, Nguyen TH, Ivan D, et al. Penoscrotal extramammary Paget's disease: the university of Texas M. D. Anderson cancer center contemporary experience. J Urol. 2011;186(1):97–102. https://doi.org/10.1016/j.juro.2011.02.2685.
20. Lam C, Funaro D. Extramammary Paget's disease: summary of current knowledge. Dermatol Clin. 2010;28(4):807–26. https://doi.org/10.1016/j.dcl.2010.06.002.

Publisher's Note
Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.