

Prognostic Factors of Extramammary Paget's Disease: A Retrospective Study at a Medical Center in Taiwan

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Abstract. *Background/Aim:* Extramammary Paget's disease (EMPD) is a rare, slow growing intra-epidermal malignant neoplasm that arises in areas rich in apocrine glands. Several common sites of occurrence have been reported, including the vulva, perianal region, perineum, and scrotum. Most relevant studies rely on small data bases. Our objective was to evaluate prognostic factors of EMPD patients at a single medical center. *Patients and Methods:* We retrospectively analyzed 19 patients (8 males, 11 females) diagnosed with genital EMPD who were treated at the Taichung Veterans General Hospital between 2006/04 and 2022/08. Collected information included tumor location, margin condition in the case of surgical resection, recurrence rate, recurrence management, accompanied gastrointestinal malignancy, treatment details and survival data. *Results:* Among 19 cases, 4 with initial margin being positive, and 3 received second surgery (one refused surgery and another expired within a year). Tumor recurrence was found in 7 cases, with 6 of them later receiving second surgery, and the remaining one received radiation therapy. Median DFS was 7.57 years. During the 15-year follow-up, 2 patients expired. Overall survival rate was 87.5%. Among all factors we had analyzed, only those accompanied with GI

tract malignancy had significantly worse survival rate ($p=0.018$). Frozen sections taken at surgical margin during surgery significantly reduced cancer recurrence rate ($p=0.45$). Permanent pathology margins appeared to affect the recurrence rate, but that was not significant when comparing with intraoperative frozen sections. *Conclusion:* Local wide excision with skin flap reconstruction remains the major treatment option for genital EMPD. Following the standard-of-care procedure, the overall patient outcome was excellent. Among factors potentially associated with recurrence rate, intraoperative frozen biopsy was the most significant one. Performing intraoperative frozen biopsy is essential for recurrence-free rate elevation.

Extramammary Paget's disease (EMPD) is an intra-epithelial adenocarcinoma involving apocrine glands at the anatomic site. It develops most commonly at vulva, penis, scrotum, perineum, and perianal area (1, 2). It may have distant metastasis, deep dermal invasion (3), and concurrent malignancy, all of which are risk factors on both overall survival and recurrence free survival. Female patients appear to have a lower mortality rate than male. A recent study reported anatomic site related outcomes, specifically outcomes are better with vulvar/labial EMPD than with vaginal EMPD (4). Until now, early diagnosis with curative resection and reconstruction remains the mainstay of treatment (5). Multidisciplinary treatments including radiation and chemotherapy were implemented, but with a poor outcome (6). Herein, we retrospectively evaluated our EMPD patients to identify factors associated with clinical outcomes.

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Key Words: Paget's Disease, extramammary, EMPD, overall survival, recurrence free survival.

Patients and Methods

Case selection and pathological review. Between April 2006 and June 2021, we retrospectively analyzed 19 patients (8 male, 11 female) with the diagnosis of EMPD treated at our Taichung Veterans General Hospital. This study was approved by the Institute



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Review Board of Taichung Veterans General Hospital (number CE CE23073A). The EMPD diagnosis was confirmed by histological examination of the incised specimens for biopsy. The survival status was confirmed through both electronic patient records and phone interviews. The data extracted and recorded included: demographic information (sex, age of diagnosis, concurrent malignancy), pathological findings (maximal diameter of lesion, status of excision margin, upper dermis invasion or deep dermal invasion, metastasis status), and treatments (surgical excision, radiotherapy, or chemotherapy). Surgical outcomes, including status of excision margin, recurrence, and recurrence-free interval, were also recorded. CK7 and CK20 monoclonal antibodies were used by pathologists to distinguish primary EMPD from Paget's phenomenon of underlying adenocarcinoma.

Surgical procedures. Before surgery, inscribe the boundary of the lesions with a marker pen. Wide excision over the erythematous plaques with a safe resection margin of 2 cm. Frozen sections pathology was determined from ill-defined margin in some cases. Skin defects were mostly reconstructed by primary closure. For wounds difficult to handle with primary closure, split-thickness graft harvest was performed to cover skin defects. Regional lymph nodes dissections were not performed routinely without clinical evidence of nodal involvement.

Statistical analyses. Endpoint evaluation was performed using the Kaplan-Meier survival curve, and the log-rank tests were used to compare the overall survival (OS). Continuous values were analyzed by the Mann-Whitney *U*-test and Fisher's exact test. Analyses were performed using the SAS software, version 9.2 (SAS Institute, Inc., Cary, NC, USA). Statistical significance was set at $p < 0.05$.

Results

Basic characteristics of EMPD patients. Nineteen patients with genital EMPD received local wide excision. The median diagnosis age was 73 years (range=53-94 years) with a 6.05-year median follow-up period. Among these patients, the most common affected anatomic site was scrotum for males (8 patients, 72.72%), and vulva for females (8 patients, 100%). Nearly half of the patients had a lesion >5 cm (9 patients, 47.37%). For underlying disease, 2 patients were found with a history of GI malignancy. Tumor marker CEA evaluation for 13 patients during initial diagnosis showed a median level 2.63 (IQR=1.27-4.27) (Table I).

Pathological results and surgical outcomes. All 19 patients received surgical wide excision after initial diagnosis. Intraoperative frozen sections were obtained from 5 patients (26.32%). According to pathological results, 8 out of the 19 patients had dermal invasive lesions (42.11%), but no lymph node metastasis nor distant metastasis was reported. However, margin positive findings appeared in 11 patients (57.89%).

Overall survival rate and prognostic factors. The median follow-up period for 19 patients was 6.05 years and the overall survival rate was 89.47% at the end of follow up

Table I. Basic characteristics of extramammary Paget's disease patients.

	(n=19)	
Age	73.58	±9.17
Age (median, IQR)	73	(69-80)
Male	11	(57.89%)
DM	4	(21.05%)
HTN	8	(42.11%)
CAD	0	(0%)
Neurological disease	1	(5.26%)
Malignancy history	2	(10.53%)
Size (>5 cm)	9	(47.37%)
CEA (n=13)	2.79	±1.56
CEA (median, IQR) (n=13)	2.63	(1.27-4.27)
Dermal invasion	8	(42.11%)
GI tract cancer	2	(10.53%)
Frozen biopsy during surgery	5	(26.32%)
Surgical margin (+)	11	(57.89%)
Location		
Scrotum/vulva (n)	16	(84.21%)
Other area (y)	3	(15.79%)
Outcome		
Recurrence	8	(42.11%)
Recurrence management (operation)	7	(87.50%)
Recurrence time (years)	4.39	±3.64
Recurrence time (years) (median, IQR)	3.20	(0.86-6.05)
Death	3	(15.79%)
Follow-up time (years)	6.90	±4.55
Follow-up time (years) (median, IQR)	6.05	(3.2-8.99)

Continuous data were expressed as median (range). Categorical data were expressed as number and percentage. DM, Diabetes mellitus; HTN, hypertension; CAD, coronary artery disease; CEA, carcinoembryonic antigen; GI, gastrointestinal.

(Figure 1). Regarding causes of death, one patient expired from HCC complicated with liver failure; another two expired from EMPD recurrence with multiple metastases. Patients with concurrent GI tract malignancy had a worse prognosis (66.67% vs. 0%, $p=0.018$). Evaluation was performed on multiple factors, including whether frozen sections were obtained during surgery, anatomic site of lesion, size of lesion (> or <5 cm), surgical margin, and treatment options after tumor recurrence. No significant prognostic factor was found (Table II).

Recurrence-free rate and prognostic factors. During follow-up, 8 patients developed recurrence (57.89%), with a median recurrence interval of 5.16 years (range=0.15-11.31 years) (Figure 2). Marked differences were found when comparing prognostic factors between overall survival rate and progression free survival rate. Whether frozen sections were obtained during surgery turned out to be the only significant factor of progression free survival rate (45.45% vs. 0%, $p=0.045$) (Table III). No significant association was found between the margin status and recurrence (45.45% vs. 70%, $p=0.352$).

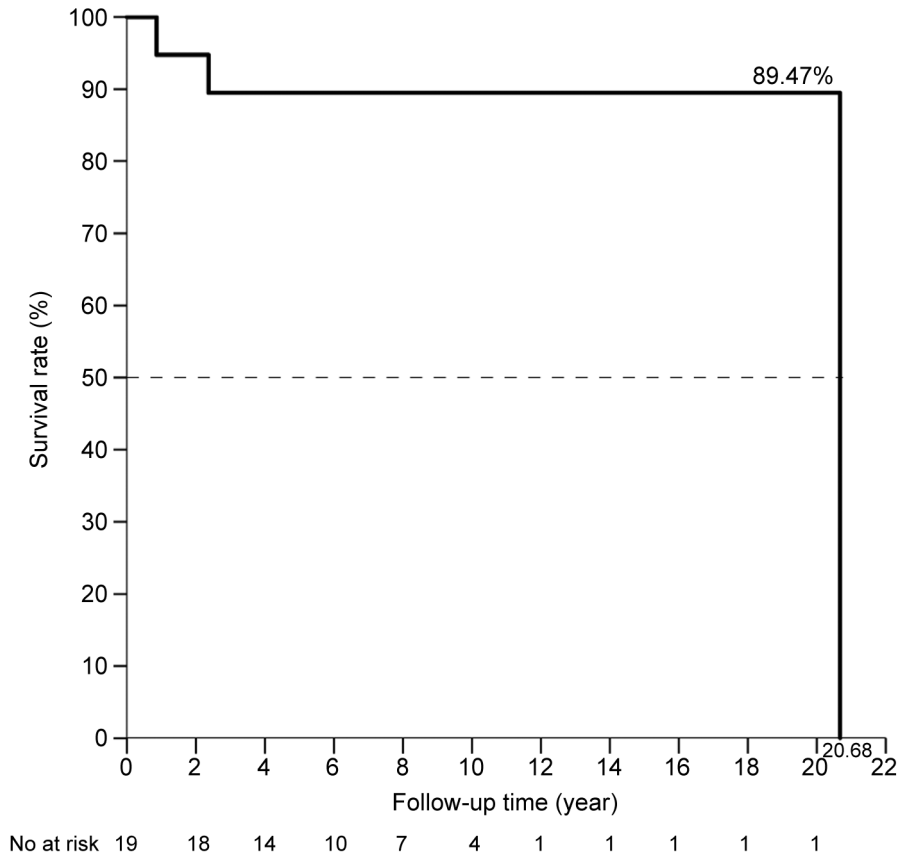


Figure 1. Kaplan-Meier curve for OS of extramammary Paget's disease patients was 89.47% after 20.68 months of follow-up. OS: Overall survival.

Discussion

EMPD typically presents ill-defined eczematous lesions. Several factors may lead to diagnostic delay, including a long-lasting asymptomatic phase, and slowly evolving lesions (7). Chief complaints of patients are usually non-specific, often like pruritus, erythema, and hyperpigmentation with ulcerative lesions. Patients on the average experience a diagnostic delay from 21 to 43 months. The definitive diagnosis of EMPD is based on histopathology. Therefore, biopsy is essential over recalcitrant lesions with poor response to expectant treatments.

According to statistics, almost all patients with Paget's disease at the breast have an underlying history of ductal breast carcinoma. However, even though they share the same histopathology presentation, the percentage of EMPD patients with underlying malignancy is between 21 to 29% (8). The relationship is also known between locations of EMPD and anatomic sites of the underlying malignancy (9). Penoscrotal EMPD is associated with malignancy of the male genitourinary tract (*e.g.*, prostate). Perianal EMPD is associated with malignancy of the gastrointestinal tract (*e.g.*,

rectal). Vulvar EMPD is associated with malignancy of the female genitourinary tract (*e.g.*, cervix, Bartholin glands) (8). In our study, similar percentage of patients with underlying malignancy (21.06%) was observed. Prostate adenocarcinoma and penoscrotal EMPD were found concurrent in one patient.

Treatment strategies for EMPD include the non-surgical approach, surgical approach, and systemic therapy. Non-surgical treatments include radiation, laser therapy or photodynamic therapy (photoreactive drugs, *e.g.*, aminolevulinic acid). Systemic therapy tends to use drug combinations, with FP (5-FU and cisplatin), FECOM (5-FU, epirubicin, carboplatin, vincristine, mitomycin C), and PET (cisplatin, epirubicin, and paclitaxel). Surgical treatments include wide local excision (WLE) and Mohs micrographic surgery (MMS) (7, 10). In the approach of wide local excision, a circumferential incision is typically made around an area >1.0 cm beyond the grossly visible abnormal region. Frozen section is necessary more recently and should be repeated until reaching margins of confirmed negativity. In the Mohs micrographic surgery, biopsy samples are taken 1 cm peripheral to the visible margin, marking and excising the tumor mass in the form of a horizontal layer using the

Table II. Prognostic factors for survival in extramammary Paget's disease patients.

	No (n=16)		Yes (n=3)		p-Value
Age	72.50	±8.39	79.33	±13.05	0.247
Age (median, IQR)	72.50	(69-79.5)	78		0.247
Male	9	(56.25%)	2	(66.67%)	1.000
DM	3	(18.75%)	1	(33.33%)	0.530
HTN	6	(37.50%)	2	(66.67%)	0.546
CAD	0	(0%)	0	(0%)	–
Neurological disease	1	(6.25%)	0	(0%)	1.000
Malignancy history	2	(12.50%)	0	(0%)	1.000
Size (>5 cm)	8	(50.00%)	1	(33.33%)	1.000
CEA (n=12 vs. 1)	2.94	±1.54	1.09		0.273
CEA (median, IQR) (n=12 vs. 1)	2.64	(1.58-4.47)	1.09	(1.09-1.09)	0.273
Dermal invasion	6	(37.50%)	2	(66.67%)	0.546
GI tract cancer	0	(0%)	2	(66.67%)	0.018*
Frozen biopsy during surgery	4	(25.00%)	1	(33.33%)	1.000
Surgical margin (+)	9	(56.25%)	2	(66.67%)	1.000
Location					1.000
Scrotum/vulva (n)	13	(81.25%)	3	(100%)	
Other area (y)	3	(18.75%)	0	(0%)	

Values are from *t*-test and Fisher's Exact test. **p*<0.05. Continuous data were expressed as median (range). Categorical data were expressed as number and percentage. DM, Diabetes mellitus; HTN, hypertension; CAD, coronary artery disease; CEA, carcinoembryonic antigen; GI, gastrointestinal.

Table III. Prognostic factors for recurrence in extramammary Paget's disease patients.

	No (n=11)		Yes (n=8)		p-Value
Age	71.55	±8.71	76.38	±9.62	0.269
Age (median, IQR)	73	(64-78)	71.05	(69.25-85.25)	0.269
Male	6	(54.55%)	5	(62.50%)	1.000
DM	1	(9.09%)	3	(37.50%)	0.262
HTN	3	(27.27%)	5	(62.50%)	0.181
CAD	0	(0%)	0	(0%)	–
Neurological disease	1	(9.09%)	0	(0%)	1.000
Malignancy history	1	(9.09%)	1	(12.50%)	1.000
Size (>5 cm)	7	(63.64%)	2	(25.00%)	0.170
CEA (n=6 vs. 7)	2.52	±1.51	3.03	±1.68	0.576
CEA (median, IQR) (n=6 vs. 7)	2.31	(1.04-4.06)	2.63	(1.45-4.87)	0.576
Dermal invasion	3	(27.27%)	5	(62.50%)	0.181
GI CA	1	(9.09%)	1	(12.50%)	1.000
Frozen biopsy during surgery	5	(45.45%)	0	(0%)	0.045*
Surgical margin (+)	5	(45.45%)	6	(75.00%)	0.352
Location					0.546
Scrotum/vulva (n)	10	(90.91%)	6	(75.00%)	
Other area (y)	1	(9.09%)	2	(25.00%)	

t-test. Fisher's Exact test. **p*<0.05. Continuous data were expressed as median (range). Categorical data were expressed as number and percentage. DM, Diabetes mellitus; HTN, hypertension; CAD, coronary artery disease; CEA, carcinoembryonic antigen; GI, gastrointestinal.

Mohs technique (11). In our study, all patients had received a wide local excision as their initial treatment, but frozen sections were obtained only from some patients.

The 5-year recurrence rate (33%) in our study was much higher compared with other EMPD studies that treated patients initially with wide local excision (2, 12, 13). Intra-

operation frozen sections being performed only in 5 patients (26.32%) is considered to be the main cause. In our study, margin status and frozen sections during operation were the two major factors that were associated with local recurrence. The relationship between margin status and recurrence risk was also observed in a previous study (13). Frozen sections

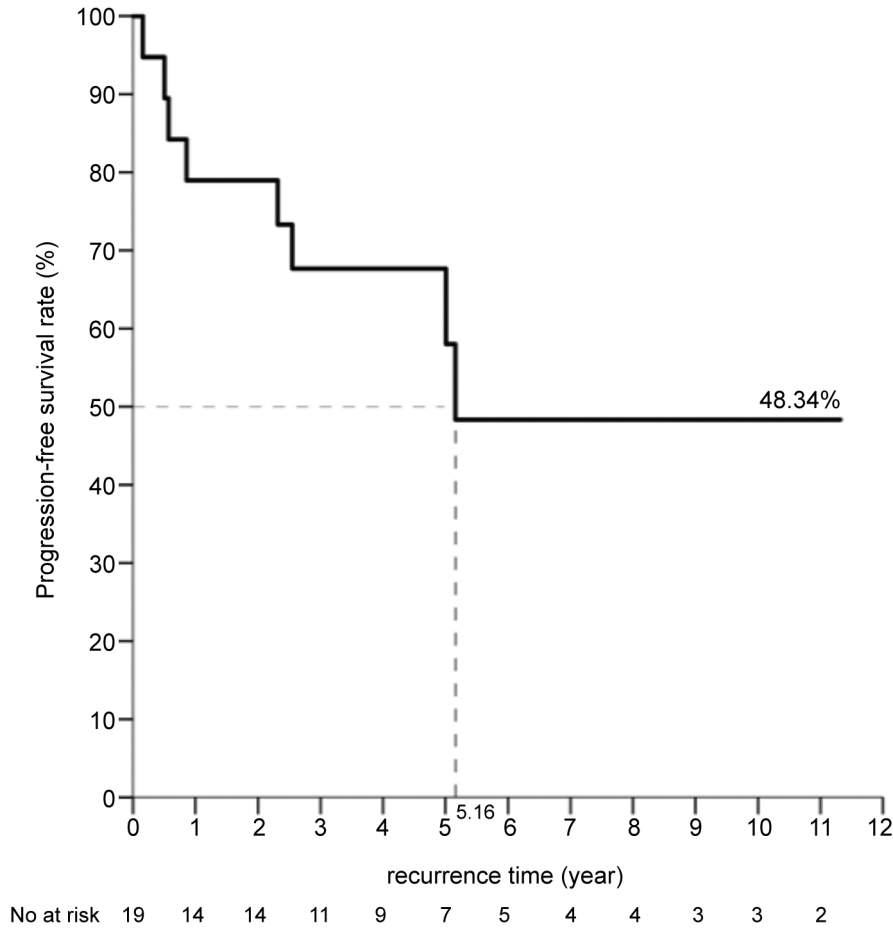


Figure 2. Kaplan-Meier curve for median recurrence interval of extramammary Paget's disease patients was 5.16 years (range=0.15-11.31 years).

are regarded as standard procedure in wide excision procedure, but their association with recurrence rate was seldom discussed in recent literature. A previous study also discussed the relationship between dermal invasion and local recurrence and like our study, revealed no obvious association (5).

In another study, the overall 5-year survival rate was 89.47%, and that percentage remained at the end of follow-up. This finding is consistent with previous Asian-predominant studies (10, 12, 14). Different risk factors were analyzed in previous studies (10, 12). They included clinically palpable lymph nodes, existence of dermal invasion, and lymph node metastases. However, only concurrent GI tract malignancy was found to be a significant prognostic factor in our study. Different from studies with similar Asian populations (10, 12), dermal invasion was not a significant prognostic factor in our patient population.

There are several limitations of our study. First, all data were retrospectively collected from electronic records and therefore had a potential bias in data extraction. Besides,

some patients were followed-up by phone interviews, leading to limited information and the possibility of misinterpretation. In addition, our study was conducted on a small population of the EMPD patients (n=19) at a single medical center. A larger sample size study in the Asian population is needed for further evaluation.

Conclusion

Even though non-surgical and systemic therapy are options for genital EMPD, local wide excision with skin flap reconstruction remains the major treatment approach. Among factors associated with recurrence-free rate, the intraoperative frozen biopsy is the most significant one. Besides, margin-negative status during initial surgery also has certain benefits. Ensuring the performance of intraoperative frozen sections, and surgical margin negativity during surgery or arranging secondary surgery as soon as possible are likely essential steps for recurrence-free treatment.

Conflicts of Interest

The contributing Authors have no conflicts of interest, including specific financial interests or relationships and affiliations relevant to the subject matter or materials discussed in the manuscript.

Authors' Contributions

Hsueh-Fen Ni and Jian-Ri Li conceived the presented idea. Hsueh-fen Ni developed the theory and performed the computations. Cheng-Kuang Yang and Chuan-Shu Chen verified the analytical methods. All Authors discussed the results and contributed to the final manuscript. Hsueh-Fen Ni wrote the manuscript with support from Shian-Shiang Wang and Sheng-Chun Hung.

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