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Prognostic analysis of patients with extramammary Paget's disease treated with conservative excision

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Structural Abstract

Background: Extramammary Paget's disease (EMPD) is a malignant skin tumor with a relatively good prognosis. The standard treatment is wide local resection or Mohs micrographic surgery. However, conservative excision may be a better option when radical wide local excision is difficult to perform due to the patients' mental or physical condition. There have been no studies on the prognosis of patients with EMPD who underwent conservative excision or wide local excision.

Objective: To compare the prognosis of conservative excision cases to wide excision cases of EMPD.

Materials & Methods: We retrospectively analyzed the clinical data of 69 cases of EMPD without metastases to lymph nodes or organs (11 cases treated with conservative excision, 58 cases treated with wide local excision) who underwent resection of the primary tumor from 2002 to 2022 in the Department of Dermatology at Hokkaido University Hospital.

Results: The log-rank test showed no significant differences in overall survival (OS) or metastasis-free survival (MFS) between the wide excision group and the conservative excision group, although conservative surgery was often chosen in elderly patients or patients with lower performance status.

Conclusion: The present study suggests that conservative surgery should be considered as a treatment option for EMPD.

Abstract (the journal style when we submit our final version)

Extramammary Paget's disease (EMPD) is a malignant skin tumor with a relatively good prognosis.

The standard treatment is wide local resection or Mohs micrographic surgery. However, conservative

excision may be a better option when radical wide local excision is difficult to perform due to the

patients' mental or physical condition. There have been no studies on the prognosis of patients with

EMPD who underwent conservative excision or wide local excision; thus, we retrospectively analyzed

the clinical data of 69 cases of EMPD without metastases to lymph nodes or organs (11 cases treated

with conservative excision, 58 cases treated with wide local excision). The log-rank test showed no

significant differences in overall survival (OS) or metastasis-free survival (MFS) between the wide

excision group and the conservative excision group, although conservative surgery was often chosen

in elderly patients or patients with lower performance status. The present study suggests that

conservative surgery should be considered as a treatment option for EMPD.

Introduction

Extramammary Paget's disease (EMPD) is a rare intraepithelial adenocarcinoma.¹ EMPD typically affects individuals over the age of 50, with the highest incidence among patients over age 65.² EMPD occurs at anatomical sites that have apocrine glands, mainly the vulva, axillae, and perineum.³ EMPD is usually confined to the epidermis, and the 5-year disease-specific survival rate exceeds 95%.^{4, 5} However, in a small number of cases with intra-dermal infiltration, metastasis to regional lymph nodes or organs occurs with an overall frequency of about 15%.⁶ Wide surgical resection or Mohs micrographic surgery (MMS) is generally carried out as the standard treatment for EMPD.³ Since EMPD lesions are mainly located in the genital region, the lesions can spread to nearby organs, including the vagina, urinary organs, and gastrointestinal tract in advanced EMPD cases. However, it is difficult for elderly patients to undertake wide excision that involves gastrointestinal tract construction or urinary tract modification. Hence, particularly among the elderly, conservative excision may be a better option when wide excision is difficult to perform due to the patients' mental or physical condition. To the best of our knowledge, there have been no studies analyzing the prognoses of patients with EMPD who underwent conservative excision. In this study, we retrospectively analyzed the clinical data from 69 cases of EMPD without metastases to lymph nodes or organs in order to compare conservative excision cases (11 patients) to wide excision cases (58 patients).

Methods

We retrospectively analyzed the clinical data from 69 patients with EMPD without metastasis to lymph nodes or organs who underwent resection of the primary tumor from 2002 to 2022 in the Department of Dermatology at Hokkaido University Hospital (institutional review board approval number: 021-0158). We divided the 69 patients into two groups: a conservative excision group and a wide excision group. The wide excision group was defined as cases in which surgical resection was performed with at least a 1-centimeter margin from the clinically presumed location of the lesion.^{7,8} All cases in the wide excision group showed pathologically negative margins, including inside the tumors. Other cases treated with any other surgery were included in the conservative excision group. All cases in the conservative excision group showed pathologically positive margins. The following clinical data were collected: age, sex, primary tumor site, tumor size, performance status (PS), histological infiltration, clinical stage, postoperative complications, hospitalization period, anesthesia method, overall survival (OS), and metastasis-free survival (MFS). PS was determined based on the Eastern Cooperative Oncology Group Performance Status (ECOG PS).⁹ Clinical stage was determined using the stage classification proposed by Ohara et al.¹⁰ The degree of histological invasion was divided into *in situ*; microinvasive, showing scattered and discrete invasion of the upper dermis; and invasive, showing extensive invasion of the deep dermis.¹¹ To compare the two groups in terms of age, tumor size and hospitalization period, a *t*-test was performed. Comparisons of sex, primary tumor site, histological

infiltration, anesthesia method, postoperative complications and margins were carried out by Fisher's exact test. For comparison of PS and clinical stage, the Mann–Whitney U test was conducted. A log-rank test was performed to estimate OS and MFS, and to determine *P*-values. For all analyses, *P*-values of less than 0.05 were considered statistically significant. All statistical analyses were performed using EZR (Saitama Medical Center, Jichi Medical University, Japan), which is a graphical user interface for the R software program (The R Foundation for Statistical Computing, Vienna, Austria).

Results

The clinical information is summarized in Table 1 (detailed data of the conservative excision group are shown in Table S1). The median age at diagnosis was 76 years (range: 46–94). Of the 69 patients, 35 (51%) were male. PS was 0 for 48 of the patients (70%), 1 for 11 patients (16%), 2 for 6 patients (9%), 3 for 4 patients (6%) and 4 for no patients (0%). The median tumor diameter was 8.5 centimeters (range: 2–22). Histological infiltration was *in situ* for 35 patients (51%), microinvasive for 17 (25%) and invasive for 17 (25%). Clinical stage was 0 for 35 patients (51%), I for 6 (9%), and II for 28 (41%). The present study included no cases with clinical stage III/IV. The median hospitalization period was 34 days (range: 3–91). Postoperative complications were found in 17 patients (25%), 9 (13%) of which were wound infection. There were four postoperative complications in the conservative excision group,

all of them wound infections. All cases in the wide excision group showed pathologically negative margins, including inside the tumors. Other cases treated with different surgical procedures were included in the conservative excision group. In the conservative excision group, 7 of the 11 patients complained of symptoms such as itching and pain associated with the residual lesions after surgery. All of the residual lesions responded well to topical azulene or other topical agents. All cases in the conservative excision group showed pathologically positive margins, because all cases in that group were resected without surgical margins. There were no significant differences in primary site, tumor size, histological infiltration, clinical stage, hospitalization period, or frequency of postoperative complications between the wide and conservative excision groups. There were significantly more women in the conservative excision group. The age was significantly higher in the conservative excision group, as was the PS score and the frequency of postoperative wound infection. There was also a significant difference in anesthesia method: General anesthesia was more common in the wide excision group. The log-rank test showed no significant differences in OS or MFS between the wide excision group and the conservative excision group. Although some patients in the conservative excision group felt pain or itching around the residual tumor lesions, they were able to be treated with topical anti-inflammatory or antibiotic ointments. The median follow-up period for the wide excision group and the conservative excision group was 26.5 and 19 months, respectively. There was one death in each group, related to EMPD in the wide excision group but unrelated to EMPD in the conservative

excision group.

Further, we retrieved the cases with a follow-up period of at least 24 months in order to assess the long-term prognosis. There are 34 such cases in the study: 5 of them in the conservative excision group and 29 of them in the wide excision group. The clinical information is summarized in Table S2 (detailed data of the conservative excision group are shown in Table S3). There were no deaths in either group. The median follow-up period was 60 months for the wide excision group and 40 months for the conservative excision group. The Kaplan–Meier method and the log-rank test found no significant difference in OS between the wide excision group and the conservative excision group, since there had been no deaths. MFS was significantly shorter in the conservative excision group (Fig. S1).

Discussion

The prognosis of EMPD is relatively good⁶, and it has been reported that incomplete excision of primary tumors does not statistically correlate with worse disease-specific survival nor is such excision a poor prognostic factor, compared to complete removal.¹² In the present study, there were no significant differences in OS or MFS between the conservative excision group and the wide excision group, which suggests that local management of the primary tumor is not directly related to EMPD metastasis and prognosis. In addition, the subgroup analysis of the cases with a follow-up period of at least 24 months revealed that there were no significant differences in OS between the two groups,

although MFS was shorter for the conservative excision group. The advantages of conservative excision are less invasiveness, a shorter hospital stay, and fewer complications. Elderly patients often have cardiopulmonary complications; thus, general anesthesia increases the risk of perioperative complications. Considering the patient's physical condition and social background, conservative excision could be considered as a better treatment option. In performing conservative excision, skin wound care should be a primary concern because the risk of wound disruption and infection increases due to residual tumor cells at the margin.

MMS is generally recommended as the standard treatment for EMPD, as is wide excision. Because EMPD sometimes involves unclear tumor borders and can unexpectedly spread beyond the clinical boundaries, MMS may be ideal for determining the surgical margins and minimizing the sacrifice of normal tissue. However, MMS requires a frozen-section lab, skilled histotechnologists, highly trained and experienced surgeons who have performed MMS on rare tumors such as EMPD, and a multidisciplinary approach by many specialized departments to repair the resultant defect.¹³ Therefore, the number of facilities where MMS is available is limited, so it is not always a feasible method. MMS has not been performed in our department because of constraints associated with the medical environment. MMS has the advantage of removing the lesion so that symptoms associated with residual lesions do not remain. However, in this study, symptoms associated with residual lesions caused by conservative excision were controlled by topical ointments. We believe that conservative

excision may be well worth considering when assessing the functional limitations of excision, depending on lesion size and location.

Local non-surgical treatment options for EMPD include local radiation therapy,¹⁴ and topical imiquimod, a local immunostimulating agent.¹⁵ For unresectable cases, local radiation therapy is the main treatment option as an alternative or adjuvant therapy. In first-line treatment, the median irradiation dose is 60 Gy (range: 45–80.2), and local progression-free rates were reported to be 82% at 5 years, disease-free rates were 46% at 5 years, and the cause-specific survival rates were reported to be 84% at 5 years.¹⁴ In adjuvant therapy for patients with positive margins, the 3-year and 5-year survival rates were reported to be 92% and 62%, respectively.¹⁵ Further, a review of 70 cases of EMPD treated with topical imiquimod reported the pooled rates of complete remission and partial remission as 71% and 16%, respectively.¹⁶ Therefore, even for patients who are not able to be treated with radical wide local resection, the lesions may be treated with a combination of conservative surgery, local radiation, and topical imiquimod.

There are several limitations to the present study. First, it is a retrospective study; thus, designing the control group was difficult. Second, the number of patients in the conservative excision group is small (11 cases). Third, there were several significant differences in background factors between the two groups. Finally, the present study included no cases with clinical stage III/IV.

In conclusion, our study found no statistically significant difference in OS or MFS between

the conservative and wide excision groups, suggesting that in some cases, conservative treatment should be considered as a treatment option.

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Table 1. Clinical features of the 69 cases of extramammary Paget's disease in the present study.

	Total (n = 69)	Wide excision (n = 58)	Conservative excision (n = 11)	P-value
Age, median (range)	76 (46-94)	73.9 (46-92)	82.8 (73-94)	< 0.01
Sex				
male	35	33	2	0.023
female	34	25	9	
Primary tumor site				
genital area	63	52	11	0.99
perianal	1	1	0	
groin	1	1	0	
axillae	4	4	0	
Tumor size in cm: median (range)	8.5 (2-22)	7.75 (2-22)	10.3 (7-15)	0.0814
ECOG PS				
0	48	46	2	< 0.01
1	11	8	3	
2	6	3	3	
3	4	1	3	
Histological infiltration				
<i>in situ</i>	35	31	4	0.57
microinvasive	17	14	3	
invasive	17	13	4	
Clinical stage				
0	35	31	4	0.29
I	6	5	1	
II	28	22	6	
Hospitalization period (days)				
median (range)	34 (3-91)	35 (3-91)	24 (3-79)	0.16
mean (SD)	35.5	36.9 (18.3)	27.8 (24.1)	
Anesthesia method				
general	59	55	4	< 0.01
local	10	3	7	
Postoperative complications	17	13	4	0.445
wound infection	9	5	4	0.03
urinary tract infection	3	3	0	0.99
neurogenic bladder	1	1	0	0.99
dementia	1	1	0	0.99
intestinal perforation	1	1	0	0.99
postoperative delirium	1	1	0	0.99
atelectasis and aspiration pneumonia	1	1	0	0.99
pseudomembranous enteritis	1	1	0	0.99
Postoperative margins	58	58	0	
positive	11	0	11	< 0.01
negative	58	57	1	
Outcome				
Alive	67	57	10	0.295
Dead	2	1	1	

ECOG PS, Eastern Cooperative Oncology Group Performance Status; SD, standard deviation

Table S1. Details of patients treated with conservative excision.

Table S2. Clinical features of the 34 EMPD cases with a follow-up period of at least 24 months in the present study.

Table S3. Details of patients in the conservative excision group with a follow-up of at least 24 months.

Fig. S1. The results of prognostic analysis of extramammary Paget's disease treated with surgical resection. Patients with a follow-up of at least 24 months were analyzed.

a, b) Kaplan–Meier curves display overall survival (OS: a) and metastasis-free survival (MFS: b) for extramammary Paget's disease patients treated with conservative excision (N = 5) or wide excision (N = 29). (OS: $P = 0.99$, MFS: $P = 0.016$, log-rank test).

Table 1.

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pseudomembranous enteritis	1	1	0	0.99
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