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Original Article

Outcomes and prognostic factors of surgically treated extramammary Paget's disease of the vulva

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ABSTRACT

Objective: Extramammary Paget's disease (EMPD) of the vulva is a rare disease which predominantly presents in postmenopausal Caucasian women. As yet, no studies on Asian female patients with EMPD have been performed. This study aimed to identify the clinical features of patients with vulvar EMPD in Korea, and to evaluate the risk factors of recurrence and postoperative complications in surgically treated EMPD.
Methods: We retrospectively reviewed 47 patients with vulvar EMPD who underwent wide local excision or radical vulvectomy. The clinical data and surgical and oncological outcomes following surgery were extracted from medical records and analyzed. Univariate and multivariate analyses for predicting recurrence and postoperative complications were performed.
Results: 21.3% of patients had complications after surgery, and wound dehiscence was the most common. 14.9% of patients experienced recurrence, and the median interval to recurrence from initial treatment was 69 (range 33–169) months. Vulvar lesions larger than 40 mm was the independent risk factor of postoperative complications (odds ratio [OR]=7.259; 95% confidence interval [CI]=1.545–34.100; p=0.012). Surgical margin status was not associated with recurrence in surgically treated vulvar EMPD patients (OR=0.83; 95% CI=0.16–4.19; p=1.000).
Conclusion: Positive surgical margin is a frequent finding in the patients with vulvar EMPD, but disease recurrence is not related with surgical margin status. Since EMPD is a slow growing tumor, a surveillance period longer than 5 years is required.

Keywords: Vulvar disease; Vulvar neoplasm; Surgical margin

Synopsis

After surgical treatment of vulvar extramammary Paget's disease, 14.9% of patients experienced recurrence, and the median interval to recurrence from initial treatment was 69 months. Surgical margin status was not associated with recurrence in vulvar EMPD. Vulvar lesions larger than 40 mm was the independent risk factor of postoperative complications.

Conflict of Interest
No potential conflict of interest relevant to this article was reported.

Author Contributions
Conceptualization: C.A., P.J.Y.; Data curation: K.D.Y., S.D.S., K.J.H., K.Y.M., K.Y.T.; Formal analysis: C.A., P.J.Y.; Investigation: K.D.Y., S.D.S., K.J.H., K.Y.M., K.Y.T.; Supervision: P.J.Y.; Writing - original draft: C.A.; Writing - review & editing: C.A., K.D.Y., S.D.S., K.J.H., K.Y.M., K.Y.T., P.J.Y.

INTRODUCTION

Extramammary Paget's disease (EMPD) is a rare neoplasm of the skin which predominantly develops in the apocrine-gland bearing regions, such as the vulvar and perineal skin [1]. Primary EMPD is thought to originate within the epidermis or apocrine glands while secondary EMPD, the less common form of the disease, appears to develop from the epidermotropic spread of malignant cells from an underlying malignancy [2]. Pruritis is the most common symptom, occurring in approximately 70% of patients, and the average time interval from symptom onset to diagnosis is two years [3]. Noninvasive EMPD usually grow slowly, and the disease status can remain unchanged for up to 10 years or more in some cases [4].

Because of the rarity of this disease, which accounts for only approximately 1% of vulvar malignancies, the actual incidence and prevalence of vulvar EMPD are still unknown [4-6]. However, it is known to affect individuals between the ages of 50 and 80 years, with the highest incidence at age 65 years [3,7]. It is more often diagnosed in postmenopausal Caucasian women, while few cases have been reported in Asian individuals [8,9]. There were no significant differences between Asians and Caucasians in clinical features such as age at onset and clinical manifestations although the incidence of internal malignancies in Asian patients with EMPD seemed to be lower than that of Caucasian patients [10]. The relatively lower prevalence in Asians of malignancies that are related with EMPD, such as rectal cancer, breast cancer, genitourinary adenocarcinoma, could explain the lower incidence of the secondary EMPD in Asians [10].

Currently available treatments for vulvar EMPD include surgical excision, laser ablation, photodynamic therapy, radiation therapy, or topical imiquimod administration [1,6]. Although no consensus has been attained regarding the optimal chemotherapy regimen for metastatic EMPD, chemotherapy including 5-fluorouracil (FU), 5-FU plus cisplatin, or docetaxel was described in previous case reports or case series [11]. Individualized treatment depending on the clinical presentation, medical history, and patient preference is recommended. However, cure rates may be superior with surgical approaches compared to other types of treatment [9]. According to recent practice guidelines, the primary treatment of EMPD is complete surgical excision with clear surgical margins while preserving function to the greatest extent possible [9]. In addition, surgical re-excision is preferred even for recurrent lesions in EMPD patients [8,9].

Several surgical methods have been attempted in the treatment of EMPD, including local excision, wide local excision, Mohs micrographic surgery, and radical resection. This variety of surgical approaches is a by-product of the fact that EMPD is treated by a variety of specialists, including gynecologists, dermatologists, and colorectal surgeons [12]. However, the mainstay of treatment by gynecologists is wide local excision of gross disease [8]. Wide local excision involves an incision to a depth of 4–6-mm to encapsulate the pilosebaceous unit and skin adnexal structures [4]. The surgical defect can generally be closed primarily, but sometimes a skin graft or other plastic reconstructive procedure is required to cover an extensive defect [4,8]. If an underlying invasive carcinoma is present in EMPD patients, these lesions should be treated in the same manner as a squamous vulvar cancer [8]. Consequently, radical vulvectomy with ipsilateral inguinofemoral lymphadenectomy may be performed, as necessary [8].

Due to its low incidence, most prior studies on EMPD have analyzed mixed cases of EMPD occurring in different locations, including the scrotum, penis, and vulva, and the majority

were conducted on the Caucasian population [1,3,7,9,12-15]. Thus, studies of vulvar EMPD alone are still lacking, particularly in Asian women. Moreover, studies investigating the prognostic factors in EMPD showed inconsistent results because the treatment received by the study subjects was not uniform, due to the various specialties of the treating doctors [6,12,13,15-18]. Therefore, a study on Asian patients with vulvar EMPD receiving standardized treatment is needed.

In the present study, we aimed to identify the clinical features of patients with vulvar EMPD in Korea, and to evaluate the risk factors of recurrence and postoperative complications in EMPD patients surgically treated by board certified gynecologic oncologists at a tertiary hospital.

MATERIALS AND METHODS

After obtaining approval from the Institutional Review Board (IRB) (IRB number: 2020-1174), we conducted a single center retrospective study of patients with biopsy-proven EMPD of the vulva who underwent surgical treatment in Asan Medical Center from 2005 to 2020. The patients who had underlying adjacent adenocarcinoma in rectum, bladder, or upper genital tract, and did not undergo surgical treatment were excluded. The clinical data were collected from medical records, including the age at diagnosis, clinical presentation, the interval from the onset of symptoms to diagnosis, history of secondary malignancy, the type of surgery, complications following surgery, postoperative treatment, recurrence, and the treatment of recurrence. Histopathologic disease features, such as invasiveness, adnexal involvement, lymph node status, and surgical margin status were also retrieved. Tumors were assessed by traditional section with hematoxylin and eosin until the early 2000s, and cytokeratin immunostaining was introduced around 2010.

In our institution, surgical procedure and adjuvant radiotherapy was determined by the physician's discretion. The patients were recommended to be followed up every 3 to 6 months for 5 years after surgery. Physical examination and history taking were performed in all patients, and imaging studies such as computed tomography scan or magnetic resonance imaging (MRI) were performed at the physician's discretion. Vulvar biopsy was conducted if the patients had relevant symptoms, or the clinicians found suspicious lesions on physical examination during routine surveillance. Recurrence was defined as pathologically confirmed EMPD after primary treatment. Patients without recurrence were censored at the date of the last follow-up. Recurrence free survival (RFS) was defined as the period between the date of the surgery and the date of the first documented evidence of recurrent disease or the time of latest follow-up.

We used chi-square and Fisher's exact tests to compare the clinical and histopathologic factors of patients in each group, as appropriate. Multivariable logistic regression was performed to identified independent risk factors. Survival curves were calculated using the Kaplan-Meier method, and the differences between the groups were determined using the log-rank test. All calculated p-values were two-sided, and p-values<0.05 were considered statistically significant. Statistical analyses were conducted using SPSS 20.0 software (IBM Corp., Armonk, NY, USA).

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RESULTS

A total of 47 patients with vulvar EMPD were treated with wide local excision or radical vulvectomy in Asan Medical Center in the study period. **Fig. 1** shows preoperative pictures of vulvar EMPD lesion. Characteristics of the patients are shown in **Table 1**. The most common symptom was pruritis, and the median duration from the onset of symptoms to diagnosis was 12 months (range 1–120 months). Six patients had a history of cancer, including three with breast cancer, two with stomach cancer, and one with thyroid cancer. Of this cohort, 29 patients underwent MRI at initial diagnosis, and lesions were observed on MRI in 9 of them. Overall, 68% of patients underwent flap surgery concurrently with wide local excision or radical vulvectomy (**Fig. 2**). Frozen sections for margin status were recorded in 45 patients, among whom five (11%) showed discrepancies between frozen and permanent pathologic results for margin involvement.

The patients with vulvar lesions larger than 40 mm at initial physical examination had an increased risk of invasive disease (odds ratio [OR]=5.71; 95% confidence interval [CI]=1.53–21.31; p=0.007). Age above 65 years, duration of symptoms over one year, and underlying cancer were not found to be significantly associated with the presence of invasion (p=0.391, 0.526, and 0.372, respectively). The most common complication after surgery was wound dehiscence (**Fig. 3**), observed in 7 patients, followed by wound stricture requiring further

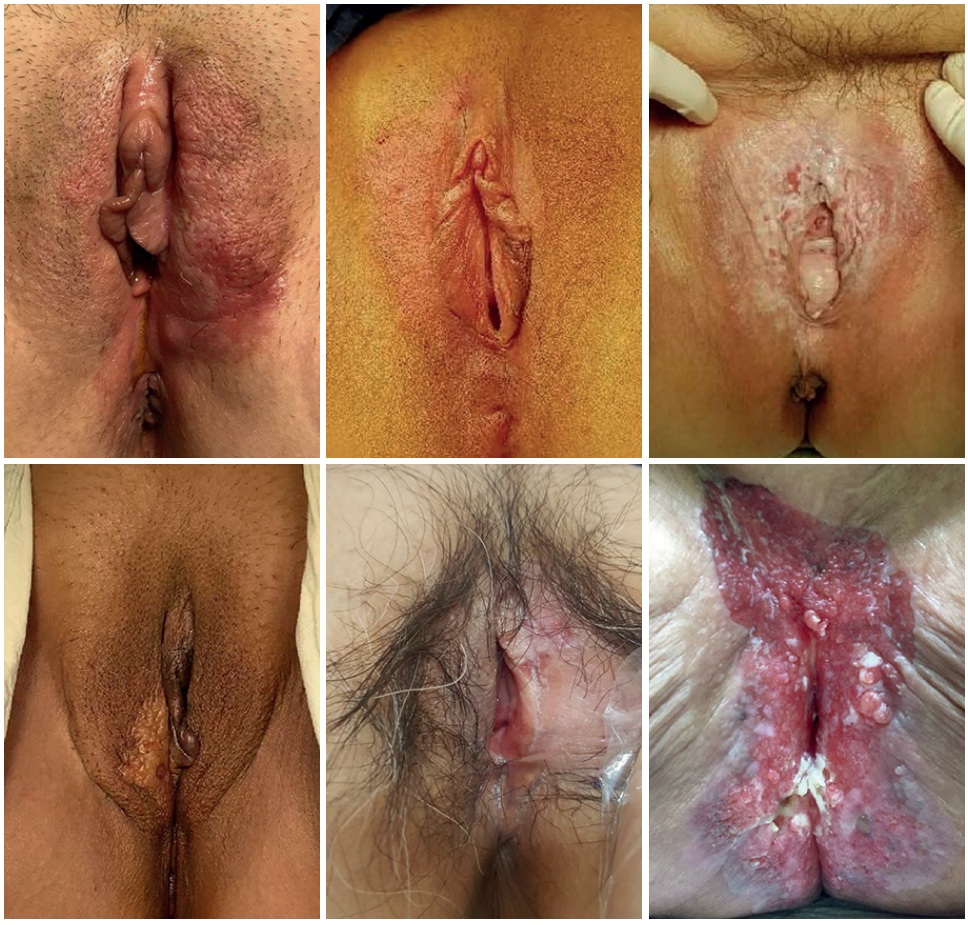

Fig. 1. Preoperative pictures of vulvar extramammary Paget's disease lesion.

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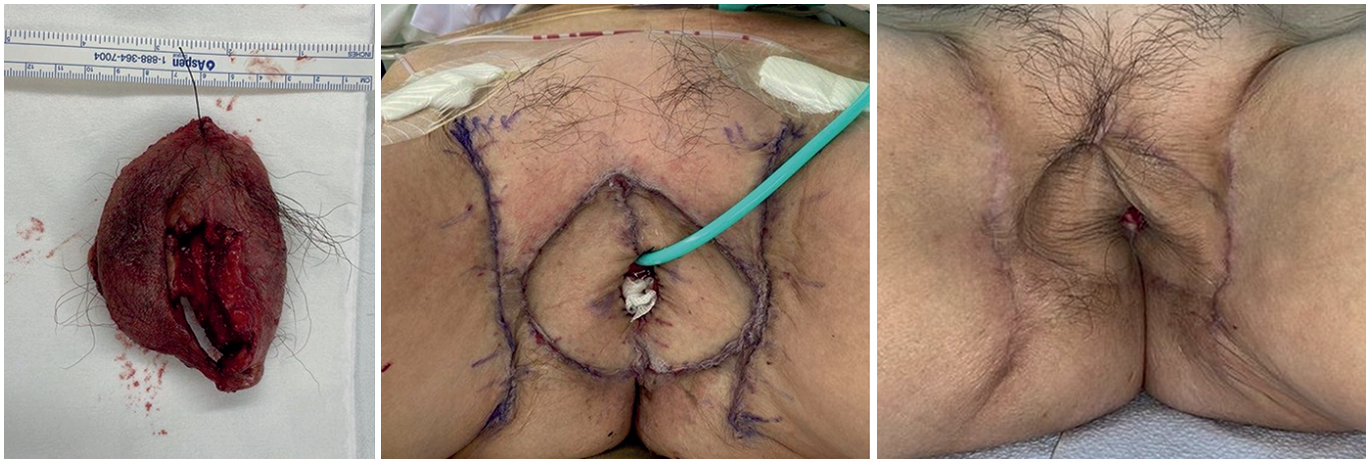

Fig. 2. A case of wide local excision and gull wing flap.

Table 1. Characteristics of the patients

Characteristics	Values (n=47)
Age at initial diagnosis (yr), median (range)	64 (44–80)
BMI (kg/m^2), median (range)	24.0 (18.7–38.9)
Symptoms	
Pruritis	29 (61.7)
Skin color change	14 (29.8)
Ulcer	3 (6.4)
Pain	3 (6.4)
History of cancer	
Yes	6 (12.8)
No	41 (87.2)
Invasiveness	
Yes	17 (36.2)
No	30 (63.8)
Lesion size (mm), median (range)	40 (5–90)
Bilaterality of vulvar lesion	
Yes	22 (46.8)
No	25 (53.2)
Type of surgery	
Wide local excision	41 (87.2)
Radical vulvectomy	6 (12.8)
Margin status	
Positive	22 (46.8)
Negative	25 (53.2)
Adnexal involvement	
Yes	26 (55.3)
No	14 (29.8)
Not assessed	7 (14.9)
Lymph node status	
Positive	2 (4.3)
Negative	3 (6.4)
Not assessed	42 (89.4)
Postoperative complications	
Yes	10 (21.3)
No	37 (78.7)
Radiation following surgery	
Yes	11 (23.4)
No	36 (76.6)

Values are presented as median (range) or number (%).

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Table 2. Univariate analysis for possible risk factors for postoperative complications

Variables	Odds ratio (95% CI)	p-value
Age ≥65 yr	2.20 (0.53–9.15)	0.306
BMI ≥25 kg/m^2	2.86 (0.63–12.92)	0.213
Invasive disease	6.30 (1.36–29.24)	0.023
Lesion size ≥40 mm	7.26 (1.55–34.00)	0.020
Bilateral vulvar lesion	3.42 (0.76–15.39)	0.154
Radical vulvectomy	2.06 (0.32–13.31)	0.594
Positive margin	1.97 (0.48–8.17)	0.480

BMI, body mass index; CI, confidence interval.

Table 3. Possible risk factors for disease recurrence

Variable	Odds ratio (95% CI)	p-value
Age ≥65 yr	0.92 (0.18–4.64)	1.000
BMI ≥25 kg/m^2	1.38 (0.23–8.34)	0.659
History of cancer	0.83 (0.72–0.95)	0.571
Invasive disease	1.39 (0.27–7.12)	0.692
Lesion size ≥40 mm	0.28 (0.30–2.54)	0.396
Bilateral vulvar lesion	0.40 (0.07–2.31)	0.423
Radical vulvectomy	1.17 (0.12–11.81)	1.000
Positive margin	0.83 (0.16–4.19)	1.000
Postoperative complications	0.57 (0.06–5.41)	1.000
Radiation following surgery	1.38 (0.23–8.34)	0.659

BMI, body mass index; CI, confidence interval.

surgery and deep vein thrombosis. The size and invasiveness of vulvar lesion was significantly associated with postoperative complications (**Table 2**). Furthermore, lesion size ≥40 mm was independent risk factor for complications in the multivariable logistic regression model (OR=7.259; 95% CI=1.545–34.100; p=0.012).

The median follow-up time was 38 (range 3–192) months. Seven patients (14.9%) experienced recurrence, and the median interval to recurrence from initial treatment was 69 (range 33–169) months. The univariate analysis of risk factors for recurrence is shown in **Table 3**; there were no statistically significant risk factors for recurrence. The mean recurrent free survival time in the entire study population was 119.0 (95% CI=87.7–150.3) months. Log rank tests for RFS were performed by dividing into two groups according to margin status, and there was no significant RFS difference between the groups (**Fig. 4**; p=0.298).

Among the 22 patients with a positive surgical margin, seven (32%) underwent adjuvant radiation therapy with doses ranging from 45 to 56 Gy delivered in 23 to 31 fractions.

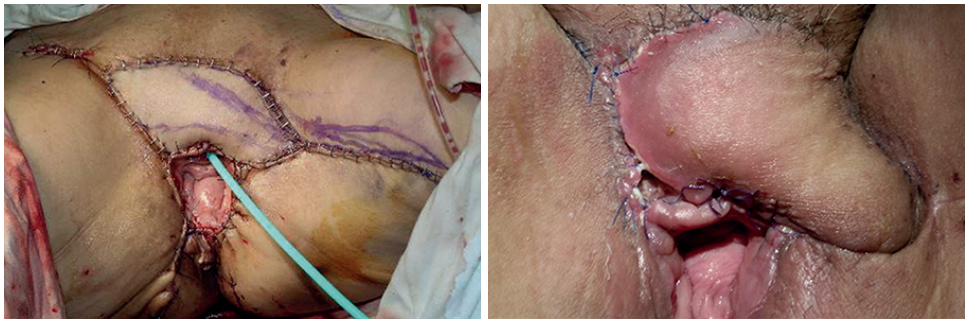

Fig. 3. A case of wound dehiscence.

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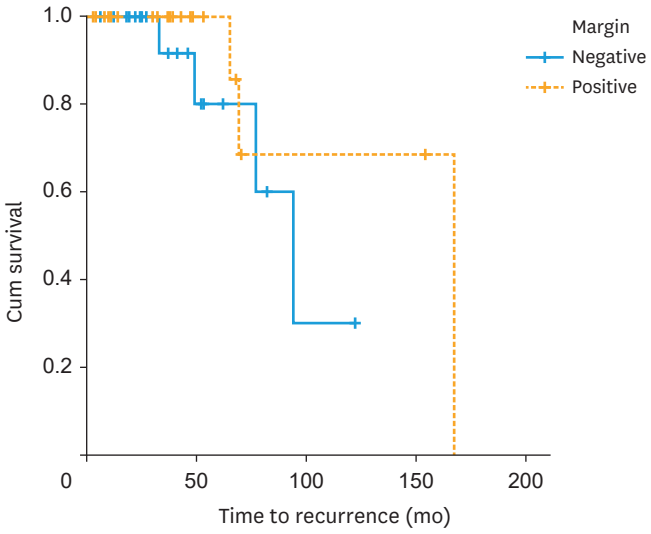

Fig. 4. Kaplan-Meier curves for recurrence free survival according to the margin status.

There was no significant difference in recurrence between patients who received RT and those who did not (OR=1.08; 95% CI=0.08–14.41; p=1.000) in the patients with a positive margin. Recurrent EMPD was predominantly treated with surgery (71%), and two patients experienced a second recurrence. During the study period, there were no cases of death due to EMPD, and only one patient died of other causes.

DISCUSSION

The principal finding of our study is that the margin status was not significantly associated with RFS in patients with vulvar EMPD who underwent surgical treatment. Among the patients with positive surgical margin, postoperative radiation therapy did not reduce the risk of recurrence. We highlight the median interval to recurrence from initial treatment was more than 5 years. In addition, the size of vulvar lesion was a risk factor for invasive disease and postoperative complications.

The median RFS in patients with EMPD who received surgical treatment has been reported to range from 24.3–69.3 months [9,18]. The recurrence rate varies among studies, ranging from 11%–61% with follow-up times of 36–41 months [3,9,16,19]. The mean RFS time in the present study was 119 months, while the recurrence rate was 15%, which is lower than in previous studies.

Many studies have previously investigated the risk factors of recurrence in patients with EMPD. Several of these reported that invasiveness indicates a poor prognosis for recurrence, and that depth of invasion is an important prognostic factor for overall survival [3,13,15]. Some researchers have further argued that deeper invasion or increased thickness is correlated with poorer prognosis [5,20]. Early detection has also been reported to be an important predictor for improving prognosis [13]. In the present study, however, invasiveness of disease and time to diagnosis were not found to be statistically relevant factors for prognosis. We speculate that this may be due to the relatively small number of patients with invasive disease and the low frequency of recurrence in our study.

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The relationship between surgical margin status and recurrence in surgically treated EMPD patients was not consistent in previous studies [12]. One systematic review study states that if surgical margin was controlled, the recurrence rate dropped from 37.0% to 18.7% [9]. However, a study of 113 patients with vulvar EMPD in Europe found no significant difference in the RFS between women with clear margins and those with positive margins after initial surgical treatment [18]. Many studies have further supported that there is no correlation between resection margin and recurrence, while enlarging the excision to achieve a clear margin will increase the morbidity of treatment [17,18,21,22]. The results of our study are consistent with these findings, in that we found no association between margin and recurrence.

Although many studies investigated the reliability and usefulness of intraoperative frozen analysis for resection margin in an attempt to decrease the recurrence rate, the results remain controversial. Kodama et al. [23] reported a reduction in local recurrence of up to 50% after surgical resection of vulvar EMPD using frozen section analysis for surgical margin. However, a significant number of false negative results of intraoperative frozen section have been recorded [3,19,24]. Fishman et al. showed that frozen-section analysis was misleading in 37.5% cases, while visual judgment during operation resulted in errors in 35% cases. Moreover, permanent margin status was not associated with disease recurrence [24]. In our study, 11% of cases in which frozen analysis was performed showed discrepancies between frozen and permanent results for margin involvement. Although our frozen analysis results were more reliable than those in previous studies, we still found that the margin status was not associated with recurrence.

According to a previous study, the overall survival rates of patients with EMPD, including those with invasive disease, were similar to those of the general population [14]. The 5-year survival rates of patients with EMPD have been reported to be about 85%–100% in the literature [1,5,9,20]. During our study period, there were no documented deaths due to EMPD, and only one case of death due to other causes. This is consistent with a previous study in which most patients died from a pre-existing condition, and not as a consequence of EMPD [4]. This leads us to cautiously state that EMPD is not a lethal disease, even if there is invasion.

The guidelines for EMPD surveillance recommend history taking and physical examination every 3-6 months for 3 years, then every 6–12 months for 2 years [9]. In our study, however, the median duration from initial therapy to recurrence was 69 months, ranging from 33–169 months. This suggests that a 5-year surveillance period may be too short to detect recurrence of this slow growing tumor. Several studies have shown that some patients can develop recurrences more than 15 years after initial therapy [3,4]. Therefore, long term follow-up is required, although with careful consideration of cost effectiveness.

To our knowledge, there has been only one study about EMPD in the Asian population [25], in which the majority (85%) of the study population was male [25]. The present study is thus the first to report the clinical characteristics and recurrence outcomes of Asian female patients with vulvar EMPD treated surgically. The strengths of the study include its relatively larger sample size compared to those of other studies of vulvar EMPD. Moreover, since the data was collected from a single institute over 15 years, all patients in this study received relatively uniform treatment by board certified gynecologic oncologists.

Although no randomized trial has been conducted to compare wide local excision to radical vulvectomy, the approach to vulvar cancer treatment has evolved from invasive surgery to

more conservative approaches, becoming as personalized as possible [26]. Therefore, the surgical procedure for EMPD often had been determined by the physician's discretion, which was also shown in our study. A major limitation of our study is that the surgical method or postoperative radiation depended on the physician's discretion, not by clear clinical criteria. In addition, it was difficult to collect a sufficient number of cases to increase statistical reliability because EMPD is a very rare disease and recurrence rate is low. Thus, a relatively wide confidence interval of odds in our results may reflect the possibility of a type II error. Retrospective nature of this study may also have introduced selection bias.

In conclusion, margin status was not associated with recurrence in patients with vulvar EMPD who underwent wide local excision or radical vulvectomy. However, patients with vulvar lesions larger than 40 mm at initial physical examination had an increased risk of invasive disease and postoperative complications.

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