

## Selection of surgical strategies for vulvar Paget's disease

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Extramammary Paget disease (EMPD) is an uncommon intraepithelial adenocarcinoma that tends to occur in regions with an abundance of apocrine glands. EMPD typically affects older individuals aged 50 to 80 years. The most commonly affected area of EMPD is the vulva; it accounts for 1% to 2% of vulvar malignancies.<sup>[1]</sup> The most common symptoms are chronic itching, vulvar pain, and erythema. However, symptoms can vary, and patients can remain asymptomatic for years. The typical feature of vulvar Paget's disease (VPD) is an "icing cake effect" on the skin.<sup>[2]</sup> This disease is often misdiagnosed as eczema. Treatment delay is usually more than 2 years, and treatment can sometimes result in failure with a high recurrence rate.<sup>[3]</sup>

Complete surgical removal in the localized stage is the treatment of choice for VPD. However, VPD is characterized by the fact that its margin is often unclear and can be accompanied by satellite lesions, usually with no apparent symptoms in the early stages. The tumor can also expand unexpectedly beyond the clinical tumor boundaries, making it difficult to determine the appropriate resection line.<sup>[4]</sup> Current studies indicate that Morse microsurgery appears to be superior to extensive local excision in terms of tissue retention and disease recurrence.<sup>[5]</sup> However, some studies have shown that even negative margins after surgical resection does not significantly reduce the recurrence rate of the disease.<sup>[6]</sup> Therefore, we aimed to discuss the specific effects of and patient indications for these various operations.

Real-world research differs from a traditional randomized controlled trial in that the former is non-interventional and does not artificially restrict patients' enrollment conditions, age, medication regimen, and other factors. The results obtained are more consistent with the clinical reality, or the real world. The results have important guiding significance for clinical practice.<sup>[7]</sup> Because of the current situation of elderly patients with VPD, they may have some other

chronic diseases while suffering from this disease. We cannot only screen out some patients with this disease for investigation, or the conclusion drawn in this way cannot be widely applied to all elderly patients. Therefore, this study adopted the method of real-world research to better fit the actual clinical situation. The study was approved by the Ethical Committee of West China Hospital of Sichuan University (No. 957-2020). We followed up 54 patients with VPD from January 2010 to September 2018. VPD was diagnosed by pathological examination. In fact, during this period, a total of 75 VPD patients were treated in our department; however, 21 of them refused to participate in this study or were lost to follow-up. Of the remaining 54 patients, 25 patients were treated by extended resection. Among these patients, 8 experienced unilateral or bilateral inguinal lymph node metastasis and underwent inguinal lymph node dissection. A total of 29 patients were treated with palliative resection. No distant metastases occurred in any of the patients during their initial visit.

The inclusion and exclusion criteria were as follows: For the extended resection group: 1) The resection line was >2 cm from the edge of the tumor<sup>[8]</sup>; 2) The tumor resection was accompanied by unilateral or bilateral inguinal lymph node dissection; and 3) The frozen pathological results were negative at the margin of resection. For the palliative resection group: 1) The resection line was ≤2 cm from the edge of the tumor; 2) Only one-time tumor was resected, and no frozen pathological examination was performed during the operation; and 3) The tumor resection was extended several times, but the frozen pathological margin was still positive. There was no statistical difference in the average age, course of disease, and lesion area between the two groups in each age group.

The European Organization for Research and Treatment of Cancer quality of life questionnaire (EORTC QLQ)-

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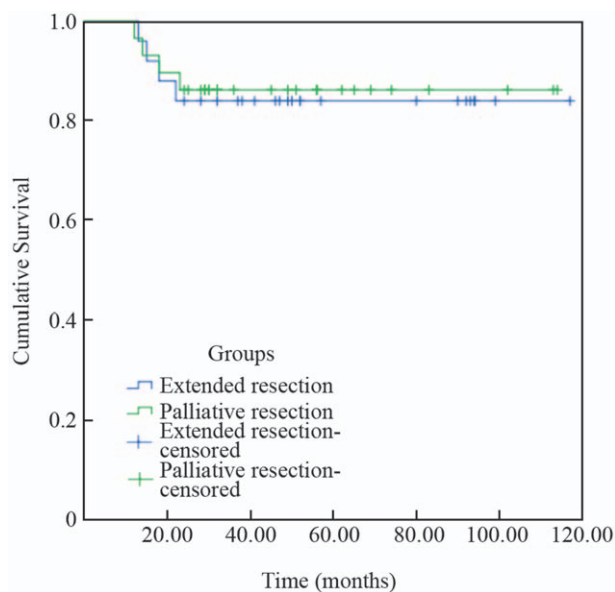
C30 and VPD Prognosis Questionnaires were used to investigate. The EORTC QLQ-C30, version 3.0, is a cancer-specific measure of the health-related quality of life (HRQOL). It consisted of 30 items to assess physical, role, emotional, cognitive, and social functioning, global health status or quality of life (QOL) scales, fatigue, pain, nausea and vomiting, dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties. Respondents were offered four response alternatives: (1) “not at all,” (2) “a little,” (3) “quite a bit,” and (4) “very much.” For the last two questions, the range was 1 to 7 in which 1 was “very poor” and 7 was “excellent.” For the general QOL and functional scale, higher scores indicated a better QOL, whereas higher scores for the symptom scale and single items indicated a lower QOL. All of the scores were linearly transformed to 0–100 scale.

Since there is no currently universally recognized prognostic survey of VPD, we set up seven questions according to the possible postoperative conditions of patients to form a VPD prognosis questionnaire [Supplementary file 1, <http://links.lww.com/CM9/A787>]. It contained questions on pain, itching, clothing, urination, bowel movements, daily activities, and overall QOL. Respondents were offered four response alternatives: (1) “not at all,” (2) “a little,” (3) “quite a bit,” and (4) “very much.” The lower the score of the first six questions and the higher the score of the seventh question, the better the patient’s situation.

The follow-up time was at least 2 years and at most 10 years (except for deaths within 2 years post-surgery), with an average follow-up time of  $4.6 \pm 2.4$  years. The patients were divided into two groups according to the inclusion criteria; each group was divided into two age categories (50–69 years and over 70 years old). The mean age of the participants was  $72 \pm 7$  years. All of the patients’ pathological examination results were Paget’s disease. A total of 46 patients who were still alive were assessed for QOL. The patients who died before the last follow-up were included only in mortality and recurrence rates.

The common surgical methods for VPD patients in our hospital are extended resection and palliative resection. The advantage of extended resection is that the tumor has a wide range of resections, the pathological results of the surgical margin are often negative, and the tumor resection is more complete. Palliative resection, on the other hand, preserves the normal skin tissue of the patient as much as possible based on a relatively clean tumor resection visible to the naked eye. However, because of the possible presence of residual tumor cells at some incisions, the traditional view was that the recurrence rate and mortality might be higher than that of patients with the negative incision. In contrast, in this study, we found that there were, in fact, no statistically significant differences in mortality, survival time, and recurrence rates between the two groups [Figure 1 and Supplementary Table 1, <http://links.lww.com/CM9/A787>].

Since the purpose of extended resection is to completely remove the lesion, it is inevitable to require multiple frozen biopsies to determine whether the incision margin is negative during the operation. Therefore, we counted the



**Figure 1:** Cumulative survival analysis of the extended resection group ( $n=25$ ) and the palliative resection group ( $n=29$ ).

number of frozen biopsies and the duration of the operation in the extended resection and palliative resection groups. In the extended resection group, the median of pathological examinations was 2 (inter-quartile range [IQR]: 1, 2) times and the median operation time was 3.0 (IQR: 2.3, 3.5) hours. The median of pathological examinations in the palliative resection group was 1 (IQR: 0, 1) time, and the median operation time was 1.5 (IQR: 1.0, 2.0) hours. All of the data of the palliative resection group were lower than that of the extended resection group. In addition, we compared the surgical costs of the two groups, and the median cost of the palliative resection group was significantly lower. During the operation of Paget’s disease, because of the wide range of excision, the wound cannot be closed simply by suture, and sometimes skin grafting is also required; at the same time, because of a wide range of resection, suture, and skin graft, postoperative scar contracture may occur. Skin transplantation was performed in both groups. The data showed that the rate of skin grafting and postoperative scar contracture in the palliative resection group were significantly lower than that in the extended resection group [Supplementary Table 2, <http://links.lww.com/CM9/A787>]. After statistical analysis, the length of hospitalization of the palliative resection group was significantly decreased.

From the study results, it can be concluded from the perspective of surgically related issues that the palliative resection group had better outcomes than the extended resection group did in all aspects.

In this study, the EORTC QLQ-C30 questionnaire was used to assess the postoperative QOL of the patients. We found differences in fatigue, pain, loss of appetite, and financial status in the 50–69-year age group, with the palliative resection group scoring better than the extended

resection group. Other scores of this age group showed no significant difference between the two groups. This suggests that palliative resection is as effective as extended resection in the 50–69-year age group and is even better than extended resection in some aspects. Meanwhile, nausea and vomiting and the pain score were lower in the extended resection group. In the longitudinal comparison of all of the items in the same group, the differences in physical function, emotional function, cognitive function, social function, and scores of various symptoms were more obvious in the palliative resection group, and the overall status of patients >70 years old was worse than that of patients <70 years old. There was no such difference in the extended resection group. This may mean that patients aged >70 years old may be more suitable for extended resection. However, there was no significant difference between the two groups when using the VPD Prognostic Questionnaire, which made us more inclined to choose palliative resection for patients <70 years of age when choosing surgical strategies.

The incidence of VPD in skin cancer is relatively low, and the prognosis is good. Some studies show that in 24% of cases, patients with VPD have an associated adenocarcinoma that worsens their prognosis with mortality rates of up to 46%. The maximum depth of adnexal invasion has been estimated to be 3.6 mm, which might be of therapeutic importance for topical treatment modalities. In this study, the mortality and recurrence rates were calculated based on the presence or absence of inguinal lymph node metastasis. Because of the specificity of VPD symptoms, it is detectable only when the disease has already invaded many surrounding tissues. It is, therefore, recommended that such patients undergo a biopsy as early as possible to determine the type of disease to provide the timely and correct treatment. At present, surgical resection combined with chemoradiotherapy has become the main treatment method for this disease. In the selection of surgical methods, some surgeons will choose to expand the resection to achieve a better effect of resection. As for other surgical methods, such as palliative resection, in this study, a 1 to 2 cm resection was expanded within the visible range, which reduced the difficulty of surgical repair and the area of skin grafting and thus preserved more tissues and functions.

In this study, we found no significant difference in the prognosis of Paget's disease between the patients who underwent extended resection or palliative resection. The number of intraoperative frozen biopsies and operative time of palliative resection showed a downward trend, and the surgical cost, skin graft rate, length of hospital stay, and postoperative scar contracture rate were significantly

reduced. Because palliative resection does not require multiple intraoperative frozen biopsies, it can shorten the operation time and reduce the intraoperative waiting time and anesthesia time. Since most people retire between the ages of 60 and 65 years, patients who are aged <70 years may need a shorter recovery time to adjust to their own jobs, as well as lower costs to ease their financial burden. Our study found that among patients undergoing palliative resection, patients aged 50 to 69 years had better scores in many items than did patients aged over 70 years. Therefore, we are more inclined to perform palliative resection for patients <70 years old to improve their postoperative QOL in many aspects.

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### Conflicts of interest

None.

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