



Research Article

Vulvar Paget Disease: a series of cases in southern Brazil

Marcella B. Persiano¹, Elisa T. Rosin¹, Giovana A. Cabrera¹, Fernanda Uratani¹, Leticia V. Pires², Felipe Luzzatto³, Kathleen M. Schmeler⁴ , Mila P. Salcedo⁵ 

¹ Gynecology and Obstetrics Service, Irmandade Santa Casa de Misericórdia Hospital of Porto Alegre, Porto Alegre, Brazil, ² The Obstetrics and Gynecology Department, Irmandade Santa Casa de Misericórdia Hospital of Porto Alegre, Porto Alegre, Brazil, ³ Pathology and Cytology Service, Irmandade Santa Casa de Misericórdia Hospital of Porto Alegre, Porto Alegre, Brazil, ⁴ The Department of Gynecologic Oncology & Reproductive Medicine, The University of Texas MD Anderson Cancer Center, Houston, Texas, United States of America, ⁵ The Department of Gynecologic Oncology & Reproductive Medicine, The University of Texas MD Anderson Cancer Center, Houston, Texas, United States of America

Keywords: Vulvar diseases, extramammary Paget disease, vulvar neoplasms, vulvar cancers

<https://doi.org/10.29392/001c.77616>

Journal of Global Health Reports

Vol. 7, 2023

Background

Vulvar Paget's disease is rare and manifests clinically as erythematous itchy skin lesion with areas of hyperkeratosis. The current report describes the diagnosis, management and outcomes data from a case series of women diagnosed with vulvar Paget's disease in a tertiary hospital in southern Brazil.

Methods

A retrospective review of medical records of women with vulvar Paget's disease at a single institution in the period 2000-2020 was carried out. Fisher's exact test was used to compare recurrence in relation to the status of surgical margins after primary treatment and in relation to the surgical modality. Quantitative variables were described using mean and categorical variables using absolute and relative frequencies.

Results

Ten patients were identified with the diagnosis of vulvar Paget's disease and two of them were excluded due to lack of information in medical records, therefore eight patients are described. The majority of the patients self-identified as white (87.5%, 7/8) and the median age at diagnosis was 65 years (range 45-81). The most common clinical symptoms were vulvar pruritus (62.5%, 5/8) and burning (37.5%, 3/8). It was not possible to identify the type of initial surgery in three patients, as they started follow-up at the institution after undergoing primary treatment at other institutions. The remaining five patients underwent surgery as their primary treatment – simple vulvectomy (60%, 3/5) and radical vulvectomy (40%, 2/5). In total, 75% (6/8) of patients had disease recurrence. Radiotherapy and imiquimod were used at the time of recurrence in three patients (50%, 3/6), but surgery remained the most common treatment for recurrence (83%, 5/6). The margin status of surgical specimens from patients starting treatment at the institution was negative in four (80%, 4/5) and positive in one woman (20%, 1/5). There was no significant difference in recurrence rates in patients with negative or positive margins, nor in relation to the surgical modality of the primary treatment. There were two deaths (25%, 2/8), one of them due to complications from Paget's disease and the other one due to metastatic urothelial adenocarcinoma.

Conclusions

Vulvar Paget's disease has a significant morbidity and limited data are available, especially in Brazil. Due to the rarity of the disease, no randomized clinical trials are available in the literature and therefore it is difficult to compare the results of surgical treatment and other therapeutic modalities. There is an opportunity to explore best options for adequate Paget's disease treatment.

Vulvar Paget's disease is a rare neoplasm, representing less than 1% of all vulvar tumors, most commonly identified in postmenopausal Caucasian women.¹⁻¹⁰ According to

GLOBOCAN 2020, 45,240 new cases of vulvar cancer were estimated for 2020 worldwide. Fu et al. have described the average cost of treatment in the first year for new cases of

vulvar cancer in the United States in 2015 was of US\$37,657 per patient.^{11,12}

Clinically, vulvar Paget's disease manifests as an irregular, elevated, slow-growing, erythematous skin lesion with islands of hyperkeratosis and/or erosion. The most common symptom is vulvar pruritus, which may be associated with pain/discomfort, irritation/burning, serous exudation, bleeding, visible lesion and palpable mass, but up to 10% of patients may be asymptomatic.^{2,4,6,8-10,13-17} According to the Wilkinson and Brown classification, vulvar Paget's disease is divided into primary and secondary. Primary, also called type 1, is the most common. It originates from the epidermal basal cells, commonly with adnexal involvement and eventually with dermal invasion or with underlying primary adenocarcinoma of a skin appendage or a subcutaneous vulvar gland. Secondary, also called type 2, arises from an underlying non-cutaneous adenocarcinoma, most often of the anal, rectal, or urothelial region, and is detected synchronously or metachronically.^{4,7,8,15,18-20} Type 1 can be subdivided into 1A – non-invasive primary intraepithelial disease, 1B – invasive disease, and 1C – intraepithelial disease with underlying adenocarcinoma. Type 2 can be subdivided into 2 subtypes – the disease originates from a rectal or anal adenocarcinoma and 3 – associated with bladder cancer.² There are reports describing the association between vulvar Paget's disease and other types of synchronous or metachronous tumors in about 20-25% of cases, such as breast cancer, colorectal or cervical adenocarcinoma, and transitional cell carcinoma from the renal pelvis to the urethra.^{5,6,8,9,13,16}

Among the differential diagnoses, melanoma and vulvar intraepithelial neoplasia should be considered. Definitive diagnosis of Paget's disease can be challenging and take up to 20 months on average. This occurs because the appearance of the disease can simulate eczematous dermatitis or superficial fungal infections, and multiple topical therapies are initially prescribed.^{8,14,15,21}

The gold standard treatment for the disease remains uncertain, but the most commonly used initial approach is surgery, which may involve local or radical excision or vulvectomy with or without lymphadenectomy. Other interventions include local application of imiquimod, 5% cream applied by the patient to the affected region, chemotherapy, photodynamic therapy or carbon dioxide laser.^{1,3-6,8-10,13-16,21} Paget's disease tends to be multifocal and the lesion margins often extend beyond the clinically normal area, so its complete eradication is not guaranteed.^{1,4,13,15,21} Recurrence is common, occurring in about 30-60% of cases, and some studies claim that it is independent of surgical modality or margin status.^{1,2,4-6,10,13-15,21} Surgical treatment can cause significant vulvar mutilation, as in many cases it involves radical excisions or re-approaches, contributing to the high morbidity inherent to the pathology.^{1,3-6,8-10,13-16,21} Women who have undergone surgical treatment for vulvar cancer are more likely to experience psychological distress, sexual dysfunction and dissatisfaction with relationships with partners.²² There are limited data available to guide the treatment of Paget's disease, particularly in Brazil. The aim of this report is to describe a

series of cases of vulvar Paget's disease evaluated at a Tertiary Hospital in southern Brazil.

METHODS

A retrospective chart review of patients evaluated for vulvar Paget's disease between 2000 and 2020 at Irmandade Santa Casa de Misericórdia Hospital of Porto Alegre (ISCMPA) was performed after Institutional Review Board (IRB) approval. Eligible women were identified through the lists of vulvar surgeries of the surgical unit of the hospital, registered in the pathology service, and/or evaluated in the Gynecology and Obstetrics department during this time period. All women who have Paget's disease of the vulva confirmed by anatomopathological examination at ISCMPA were included. Cases without enough detailed clinical information were excluded. The study was approved by ISCMPA's IRB, with a waiver of informed consent.

Study data were collected and managed using the electronic data capture tool Research Eletronic Data Capture (REDCap) which is a secure application developed to support data capture for research studies, hosted at ISCMPA.²³ Fisher's exact test was used to compare recurrence in relation to the status of surgical margins after primary treatment and in relation to the surgical modality. The quantitative variables were described using mean and the categorical variables (such as race, symptoms, pathological findings) were described using absolute and relative frequencies.

RESULTS

Ten patients eligible for the study were identified. Two of them were excluded due to lack of enough detailed information in their medical records, therefore eight patients are included in this case series. Seven patients self-identified as white (87.5%, 7/8) and one brown (12.5%, 1/8). The median age at diagnosis was 65 years (range 45 to 81). The most commonly reported clinical symptoms were: vulvar pruritus (62.5%, 5/8) and burning sensation (37.5%, 3/8). Vulvar lesions were described as regions of hyperemia, associated or not with a whitish lesion. The average time elapsed from symptoms to definitive diagnosis was 13 months.

Four (50%, 4/8) patients had an immunohistochemical panel performed on their pathologic specimen. The markers used were: C-erb-B2, GCDFP15, CK7, Hmb45, S100, CK 20, p16, p63, GATA-3, AR441, EMA, CEA, Melan-A and MUC 1. The presence of cytokeratin 7 (75%, 3/4) and the absence of cytokeratin 20 (50%, 2/4) were the most common results. Immunohistochemical analysis associated with histopathological findings confirmed Paget's disease in all these patients. The only patient who had a positive C-erb-B2 marker died from complications associated with Paget's disease.

Of the eight patients, seven (87.5%) were classified as having primary Paget's Disease or type 1. Five (71.4%) were classified in subgroup IA, one (14.2%) in subgroup IB, and

one (14.2%) in subgroup IC. One (12.5%) patient was classified as secondary or type 2, subgroup 3.

Three patients (37.5%, 3/8) had a history of associated metachronic neoplasms: urothelial neoplasm, periampullar adenocarcinoma and non-small cell undifferentiated liver carcinoma. The remaining patients had no clinical history of associated neoplasms.

All patients underwent surgery as the primary treatment – simple vulvectomy (60%, 3/5) and radical vulvectomy (40%, 2/5). It was not possible to identify the type of initial surgery in three patients, as they underwent primary treatment at other institutions, and there was no information regarding the details of the previous surgeries in their medical records. In total, 75% (6/8) of patients had disease recurrence. Surgery was performed in 5 of the 6 patients (83%). Two patients underwent margin expansion (40%, 2/5), two had amplified vulvectomy (40%, 2/5) and one did amplify vulvectomy plus lymphadenectomy (20%, 1/5). Radiotherapy was used in the recurrence of two patients (33%, 2/6) and both of them also had surgery. Topical treatment with imiquimod was used in two patients (33%, 2/6), and both of them also had surgery. The surgical margin status was described in the five patients who underwent surgery for recurrence disease at ISCMPA, and was negative in four (80%, 4/5) and positive in one (20%, 1/5). The surgical margin status at the time of primary treatment with surgery was unknown in three women (37.5%, 3/8), negative in four women (50%, 4/8) and positive in one woman (12.5%, 1/8). No patients underwent chemotherapy, photodynamic therapy or carbon dioxide laser treatment.

There was no significant difference regarding recurrence rates in patients with negative or positive margins ($P=1$) and no significant difference regarding surgical modality (simple vs. radical vulvectomy) as the primary treatment ($P=0.1$).

Of the eight women in this series, there were two deaths (25%, 2/8), one of them due to complications from invasive Paget's disease and the other one due to complications associated with metastatic urothelial adenocarcinoma. Three patients (37.5%, 3/8) in this series were kept under follow-up, with a follow-up ranging from three to nine years. There were three (37.5%, 3/8) that were lost to follow-up after one to two years after diagnosis.

DISCUSSION

In this case series, the majority of the cases (87.5%) were primary Paget's Disease or type 1. All patients underwent surgery as primary treatment, with simple vulvectomy being the most preferred type of surgery (60%). When the patients presented recurrence, surgical treatment was the most common treatment (83%).

Black et. al.⁴ demonstrated that there was no correlation between microscopically positive margins and disease recurrence. Onaiwu et. al.¹⁵ described the main finding in their study was that the majority of patients with vulvar Paget's disease develop multiple recurrences regardless of therapeutic modality or margin status. The gold standard treatment of Paget's disease remains uncertain, although

the initial approach usually involves surgery.^{1,3-6,8-10,13-16, 21} Hendi et. al.²¹ reviewed twenty-five cases of vulvar Paget's disease treated surgically with Mohs micrographic surgery technique. A recurrence rate of 16% was observed in patients who underwent Mohs micrographic surgery in the primary treatment versus 50% recurrence in those who underwent non-surgical modalities or without this technique. Edey et. al.⁸ published a Cochrane review of interventions for the treatment of vulvar Paget's disease. Few studies were included due to the low quality and high risk of bias in the majority of the studies analyzed. However, they conducted a review of twenty-four studies on the effects of interventions and 581 women were included. The most common surgical modalities were wide local excision (202/581, 35%) and radical vulvectomy (157/581 – 27%). Nevertheless, there was no evidence to support the use of surgery over any other treatment modality. Most studies in this review described that the margins status did not imply differences in the chance of recurrence. These results are similar to the current study, in which there was no significant difference regarding recurrence rates in patients with negative or positive margins and no significant difference regarding surgical modality of the primary treatment.

Sendagorta et. al.³ published a therapeutic schedule proposal for the use of imiquimod in patients with vulvar Paget's disease. Remission was seen in all patients after completion of treatment with Imiquimod and there was no recurrence during a 20-month follow-up period. Cowan et. al.¹ evaluated the use of imiquimod in vulvar Paget's disease recurrence. Complete remission was observed in 75% (6/8) of patients after topical application of the medication, but with a new recurrence in 67% (4/6) of them during the median follow-up period of 35 months. In our study, there were two patients (25%, 2/8) who underwent treatment with imiquimod, both of them after multiple surgeries. They are currently under outpatient follow-up at ISCMPA.

In 2000, Parker et. al.⁹ determined prognostic and risk factors for relapse of vulvar Paget's disease. They analyzed 76 mostly white woman with a mean age of 67.5 years. Patients who received chemotherapy had a worse prognosis, but this was a group with a worse histological prognosis. Son et. al.¹⁰ reviewed three cases of patients who underwent radiotherapy (primary, adjuvant or in relapse treatment after recurrence). In their study, the patient who underwent primary treatment with radiotherapy had no recurrence. The patient who received radiation as adjuvant therapy had previously undergone wide local excision with bilateral lymphadenectomy and had no recurrence during an eight-year follow-up. And one patient was treated with radiotherapy for recurrence. Niikura H. et. al.²⁰ evaluated treatments of patients diagnosed with vulvar Paget's disease. Of the 22 recruited patients in their study, two received postoperative adjuvant chemotherapy with etoposide due to positive surgical margins (no relapse after treatment), one received cisplatin and 5-fluoracil (with partial response) and another one, also with positive margins, received associated mitomycin, etoposide and cisplatin (the patient died from complications of Paget's dis-

Table 1. Summary of treatments administered to patients

Patient	1	2	3	4	5	6	7	8
Primary treatment	*	Simple vulvectomy + sentinel lymphnode	**	Radical vulvectomy	*	Simple vulvectomy	Radical vulvectomy	Simple vulvectomy
Margins	Unknow	Negative	Unknow	Negative	Unknow	Positive	Negative	Negative
Recurrence time	Yes	Yes, after 1 year and 7 months	Yes	No	Yes	Yes	Unknow	Yes, after 11 months
First reintervention	Margin expansion	Amplified vulvectomy	Amplified vulectomy + lymphadenectomy	Not applicable	Amplified vulvectomy	Margin expansion	Unknow	Unknow
Margins	Positive	Negative	Positive	Not applicable	Positive	Positive	Unknow	Unknow
Number of reinterventions	2	1	2	Not applicable	Unknow	6	Unknow	Unknow
Non-surgical treatment	Radiotherapy	None	Radiotherapy and imiquimod	Not applicable	Unknow	Imiquimod	Unknow	Unknow
Ending	Death unrelated to the disease	Death from the disease	Follow-up	Follow-up	Lost to follow-up	Follow-up	Lost to follow-up	Lost to follow-up

*Surgery as the primary treatment, but it is not known which technique was used.

**Surgery and Radiotherapy were the primary treatment, but it is not known which technique was used.

ease). Hata M. et. al.¹⁶ reviewed treatment with radiotherapy alone, adjuvant and after surgery. The authors reported that all macroscopic tumors disappeared after 2-9 months, with an initial complete response rate of 100%, but there was a 59% recurrence rate between three and 43 months after radiotherapy. In our study, one patient underwent radiotherapy for recurrence and another one with radiotherapy and imiquimod. The first patient died from complications unrelated to the disease. The second patient has been followed up for 12 months with no evidence of recurrence.

Tebes et. al.⁶ identified that 26% of women had underlying adenocarcinoma. Onaiwu et. al.¹³ described that 46.1% (41/89) of patients in their study were diagnosed with synchronous or metachronic neoplasms. The high rate of associated malignancies identified in our study (37,5%) is aligned with data reported by Onaiwu and colleagues.

Cai Y. et. al.¹⁵ described the pathophysiological features of vulvar Paget's disease and identified a mean interval of 36 months from symptom onset to histological diagnosis. In their report, 61.9% had a retardment in starting treatment. This delay was due to the initial treatment with corticosteroids and topical antifungal agents, confirming that the appearance of the disease may simulate eczematous dermatitis or superficial fungal infections. In our study, the mean interval from symptom onset to histological diagnosis was 13 months.

Kumar et. al.²⁴ conducted a review study of case records from a prospectively maintained database of 20 patients with vulvar cancer treated at a hospital in India and found that social stigma, low to middle socioeconomic status, low literature rate, logistic issues, poor screening program, and insufficient awareness about the disease are the reasons why the majority of the patients present in the advanced stage in developing countries. There is no current evidence for a specific screening of vulvar cancer, however self-examination in women with lichen sclerosis and public awareness of warning symptoms of vulvar malignancy may help in early detection and cure. Also, any patients with suspicious signs (e.g., pigmented lesions, irregular ulcers) or symptoms (e.g., chronic vulvar pruritus) should be early evaluated with skin biopsy.

The high incidence of recurrence highlights the importance of continuous postoperative surveillance.^{2-4,6,7,13,19} Tebes et. al.⁶ concluded the same in their evaluation of twenty-three women with vulvar Paget's disease. In our study, three patients (37,5%, 3/8) were kept under follow-up, ranging from three to nine years. The other three patients (37,5%, 3/8) were lost follow up and two patients died (25%, 2/8).

CONCLUSIONS

Our study is limited by a high rate of lost to follow-up or a very short period of follow-up, retrospective data collec-

tion, group of patients from a single institution, small sample size and lack of detailed information on primary treatment of some patients. The reasons for loss to follow-up may be due to the need for adherence for a long period of follow-up, treatment costs and/or poor patient adherence, as most patients were of low or modest socioeconomic status and had no education. The strengths of our study include that the retrospective review was carried out at a referral center in a developing country and over a long period of time. Also, all cases were confirmed by experienced pathologists. The disease is rare and data are limited, especially in Brazil. There are no randomized clinical trials found in the literature and therefore it is difficult to compare surgical treatment results and other therapeutic modalities. Per our knowledge, only one Brazilian review article on the subject was identified. Therefore, there is an opportunity to study and explore non-surgical options for the treatment of Paget's disease, with the intention of promoting better care for these women with a diagnosis of vulvar Paget's disease in low-middle income countries.

FUNDING

This research was supported in part by the Raby/Dunaway Family Fund.

AUTHORSHIP CONTRIBUTIONS

Conception and design: MBP, MPS, KMS. Drafting the work: GAC, FU, LVP, FL, ETR. Final approval of manuscript: All authors. Accountable for all aspects of the work: All authors.

DISCLOSURE OF INTEREST

The authors completed the ICMJE Disclosure of Interest Form (available upon request from the corresponding author) and disclose no relevant interests.

CORRESPONDENCE TO:

Mila Pontremoli Salcedo
Department of Gynecological Oncology and Reproductive Medicine, University of Texas MD Anderson Cancer Center, Houston, Texas, United States of America
Address: Unit 1362 PO Box 301429, CEP 77.230-1429, Houston - Texas, United States of America
Email: mpsalcado@mdanderson.org

Submitted: November 14, 2022 GMT, Accepted: May 02, 2023 GMT



This is an open-access article distributed under the terms of the Creative Commons Attribution 4.0 International License (CCBY-4.0). View this license's legal deed at <http://creativecommons.org/licenses/by/4.0> and legal code at <http://creativecommons.org/licenses/by/4.0/legalcode> for more information.

REFERENCES

1. Cowan RA, Black DR, Hoang LN, et al. A pilot study of topical imiquimod therapy for the treatment of recurrent extramammary Paget's disease. *Gynecologic Oncology*. 2016;142(1):139-143. doi:10.1016/j.ygyno.2016.04.028
2. Mendivil AA, Abaid L, Epstein HD, et al. Paget's disease of the vulva: a clinicopathologic institutional review. *Int J Clin Oncol*. 2011;17(6):569-574. doi:10.1007/s10147-011-0325-0
3. Sendagorta E, Herranz P, Feito M, et al. Successful treatment of three cases of primary extramammary Paget's disease of the vulva with Imiquimod - proposal of a therapeutic schedule. *Journal of the European Academy of Dermatology and Venereology*. 2010;24(4):490-492. doi:10.1111/j.1468-3083.2009.03451.x
4. Black D, Tornos C, Soslow RA, Awtrey CS, Barakat RR, Chi DS. The outcomes of patients with positive margins after excision for intraepithelial Paget's disease of the vulva. *Gynecologic Oncology*. 2007;104(3):547-550. doi:10.1016/j.ygyno.2006.09.017
5. Brummer O, Stegner HE, Böhmer G, Kühnle H, Petry KU. HER-2/neu expression in Paget disease of the vulva and the female breast. *Gynecologic Oncology*. 2004;95(2):336-340. doi:10.1016/j.ygyno.2004.07.043
6. Tebes S, Cardosi R, Hoffman M. Paget's disease of the vulva. *American Journal of Obstetrics & Gynecology*. 2002;187(2):281-284. doi:10.1067/mob.2002.125700
7. Fanning J, Lambert HCL, Hale TM, Morris PC, Schuerch C. Paget's disease of the vulva: prevalence of associated vulvar adenocarcinoma, invasive Paget's disease, and recurrence after surgical excision. *American Journal of Obstetrics & Gynecology*. 1999;180(1):24-27. doi:10.1016/s0002-9378(99)70143-2
8. Edey KA, Allan E, Murdoch JB, Cooper S, Bryant A. Interventions for the treatment of Paget's disease of the vulva. *Cochrane Database of Systematic Reviews*. 2019;2019(6). doi:10.1002/14651858.cd009245.pub3
9. Parker LP, Parker JR, Bodurka-Beyers D, et al. Paget's disease of the vulva: pathology, pattern of involvement, and prognosis. *Gynecologic Oncology*. 2000;77(1):183-189. doi:10.1006/gyno.2000.5741
10. Son SH, Lee JS, Kim YS, et al. The role of radiation therapy for the extramammary paget's disease of the vulva; experience of 3 cases. *Cancer Res Treat*. 2005;37(6):365-369. doi:10.4143/crt.2005.37.6.365
11. Fu S, Lairson DR, Chan W, Wu CF, Ramondetta L. Mean medical costs associated with vaginal and vulvar cancers for commercially insured patients in the United States and Texas. *Gynecologic Oncology*. 2018;148(2):342-348. doi:10.1016/j.ygyno.2017.12.019
12. Ferlay J, Ervik M, Lam F, et al. Global Cancer Observatory: Cancer Today. International Agency for Research on Cancer. Accessed November 11, 2022. <https://gco.iarc.fr/today>
13. Onaiwu CO, Salcedo MP, Pessini SA, et al. Paget's disease of the vulva: A review of 89 cases. *Gynecologic Oncology Reports*. 2017;19:46-49. doi:10.1016/j.gore.2016.12.010
14. Hatch KD, Davis JR. Complete resolution of Paget disease of the vulva with imiquimod cream. *Journal of Lower Genital Tract Disease*. 2008;12(2):90-94. doi:10.1097/igt.0b013e31815a58a5
15. Cai Y, Sheng W, Xiang L, Wu X, Yang H. Primary extramammary Paget's disease of the vulva: the clinicopathological features and treatment outcomes in a series of 43 patients. *Gynecologic Oncology*. 2013;129(2):412-416. doi:10.1016/j.ygyno.2013.02.029
16. Hata M, Omura M, Koike I, et al. Role of radiotherapy as curative treatment of extramammary Paget's disease. *International Journal of Radiation Oncology, Biology, Physics*. 2011;80(1):47-54. doi:10.1016/j.ijrobp.2010.01.073
17. Dubreuilh W. Paget's disease of the Vulva. *British Journal of Dermatology*. 1901;13(11):407-413. doi:10.1111/j.1365-2133.1901.tb16346.x
18. Wilkinson EJ, Brown HM. Vulvar Paget disease of urothelial origin: a report of three cases and a proposed classification of vulvar Paget disease. *Human Pathology*. 2002;33(5):549-554. doi:10.1053/hupa.2002.124788
19. Jones ISC, Crandon A, Sanday K. Paget's disease of the vulva: Diagnosis and follow-up key to management; a retrospective study of 50 cases from Queensland. *Gynecologic Oncology*. 2011;122(1):42-44. doi:10.1016/j.ygyno.2011.03.033

20. Niikura H, Yoshida H, Ito K, et al. Paget's disease of the vulva: clinicopathologic study of type 1 cases treated at a single institution. *Int J Gynecol Cancer*. 2006;16(3):1212-1215. [doi:10.1111/j.1525-1438.2006.00602.x](https://doi.org/10.1111/j.1525-1438.2006.00602.x)
21. Hendi A, Brodland DG, Zitelli JA. Extramammary Paget's disease: surgical treatment with Mohs micrographic surgery. *Journal of the American Academy of Dermatology*. 2004;51(5):767-773. [doi:10.1016/j.jaad.2004.07.004](https://doi.org/10.1016/j.jaad.2004.07.004)
22. Malandrone F, Bevilacqua F, Merola M, et al. The impact of Vulvar Cancer on Psychosocial and Sexual Functioning: A Literature Review. *Cancers*. 2021;14(1):63. [doi:10.3390/cancers14010063](https://doi.org/10.3390/cancers14010063)
23. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)—A metadata-driven methodology and workflow process for providing translational research informatics support. *Journal of Biomedical Informatics*. 2009;42(2):377-381. [doi:10.1016/j.jbi.2008.08.010](https://doi.org/10.1016/j.jbi.2008.08.010)
24. Kumar N, Ray MD, Sharma DN, et al. Vulvar cancer: surgical management and survival trends in a low resource setting. *J Egypt Natl Canc Inst*. 2020;32(1):32. [doi:10.1186/s43046-019-0015-y](https://doi.org/10.1186/s43046-019-0015-y)