

Initial surgical management of squamous carcinoma of the vulva

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Abstract

Vulvar cancer accounts for approximately 4% of gynecological malignancies. At the Instituto Nacional de Cancerología in Mexico it occupies the fourth place. The purpose of this study is to assess the management of squamous carcinoma of the vulva with initial surgical treatment. It is a descriptive retrospective, observational study, from January 1, 2002 to December 31, 2012. Twenty-seven patients, clinical stages I, II, or III, initial surgical management, with at least one year of follow-up were included. In 51.85% a partial vulvectomy was performed and in 40.74% a wide excision; 66.66% underwent inguinofemoral dissection. Recurrence occurred in 25.91% of cases and the overall survival at 10 years was 63%. It is concluded that with invasion of up to 1 mm of lymph node, affection is 0%; with invasion of 1 mm and up to 5 mm this increases to 25%; an invasion of more than 5 mm implies up to 45%. Recurrence in our study was primarily distant, necessitating long-term monitoring with emphasis on symptoms to request imaging studies when suspected. Adjuvant therapy should be offered to patients with positive nodes, close or positive margins, and tumors larger than 4 cm. (Gac Med Mex. 2016;152:266-72)

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Introduction

Vulvar cancer is a rare entity that accounts for approximately 4% of all gynecological neoplasms, with peak incidence ranging from 65 to 75 years of age. However, in the past few years, a marked increase, associated with human papillomavirus infection, as well as with a history of smoking, has been observed in younger patients¹⁻⁵.

In Mexico, 162 vulvar cancer cases were reported in 2006, accounting for 0.15% of genital tract tumors

in both genders⁶. At the National Institute of Cancer Research (INCan – Instituto Nacional de Cancerología) in Mexico, 16 cases of vulvar cancer were reported in 2013, placing this pathology at fourth place among all gynecological cancers.

The most common histological type is squamous cell carcinoma^{3,4,7-21}, with a frequency of 86.2%, followed by melanoma with 4.8% and sarcoma with 2.2%. Clinical presentation is characterized by long periods of itching associated with a vulvar tumor in 50% of patients with invasive cancer; pain, bleeding, ulceration and dysuria are also likely to occur. About 70% of

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lesions are located in the labia majore. Their main route of dissemination is lymphatic⁴.

Vulvar cancer staging is surgical^{3,4}. The last revision was made in 2008, where the main changes were:

- Creation of the clinical stage IB for tumors larger than 2 cm in diameter.
- Clinical stage II includes those patients with lower third of the vagina, urethra and/or anal canal involvement regardless of the size of the tumor.
- Clinical stage III is subdivided according to the number and size of lymph nodes involved, as well as to the presence of extracapsular invasion¹¹.

For treatment selection, the patient's age and the conditions of the vulvar tissue have to be considered, in addition to other factors such as: size and location of the tumor, as well as depth of invasion. Lymph node status is the most important prognostic factor, with an impact on both local and distant recurrence⁹.

Radical local excision is more appropriate for posterior or lateral vulvar lesions, where preservation of the clitoris is possible. Radical vulvectomy is the ideal procedure in multifocal lesions or tumor size larger than 4 cm. With this procedures, the survival percentage is close to 96.4%^{12,13}.

An important factor in radical or wide vulvar excision is the margin, which should be at least 1 cm macroscopically to reduce the probability of recurrence. A retrospective study reported that recurrence rate increases from 0% for margins > 8 mm to 50% for margins of less than 8 mm¹⁴. The contraction of nearly 20% sustained by tissues when fixed with formalin should be taken into account. For patients with clinical stage IA, only excision of the lesion is necessary, which, after its definitive histopathological examination, will enable to assess if lymph node staging is required or not. At clinical stage IB, inguinal region evaluation is necessary, whereas at clinical stage II, if adequate margins are obtained, wide local excision and lymph node staging will be sufficient management.

Inguinal-femoral region assessment can be made using a sentinel lymph node (SLN), with the purpose to decrease complete lymphadenectomy-associated morbidity without affecting survival¹⁵. At clinical stage IA, evaluation of this region is not necessary, since the rate of involvement is 0%. However, the risk of lymph node involvement is directly related to the depth of invasion in such a way that if it ranges from 1.1 to 3 mm, involvement is 8%, and if invasion is > 3 mm, lymph node involvement increases to 26-34%^{16,17}. Currently, therapeutic lymphadenectomy is only considered if there is corroborated lymph node disease present, or if during

SLN dissection it turns out being positive in the intra-operative examination. When inguinal region positive adenopathies are found, the behavior to this day is to perform the contralateral dissection, since contralateral groin recurrence rate after unilateral dissection is close to 2.6 vs. 0.4% in women with negative lymph nodes¹². The requirements for the SLN approach in vulvar cancer include unifocal lesions, size smaller than 4 cm and clinically non-palpable lymph node¹⁵.

The purpose of this work is to assess the management of patients with squamous cell carcinoma of the vulva who have initially received surgical treatment at the INCan of Mexico.

Material and methods

A retrospective, observational, descriptive study was conducted in the period encompassed from January 1, 2002 to December 31, 2102. Both electronic and physical clinical records of all vulvar cancer patients who were admitted to the INCan within said period (n = 104) were reviewed, with those diagnosed with squamous cell cancer at clinical stage I, II or III, initially managed with surgery, with no sequential or concomitant chemotherapy (CT) or radiotherapy (RT) and with at least 1-year follow-up at the INCan being selected. In all cases, the vulvar squamous cell cancer diagnosis was confirmed by histopathological analysis. Variables such as age, number of pregnancies, history of hormone replacement therapy, time of evolution, clinical and pathological tumor size, multifocality, clinically and surgically positive lymph nodes, type of diagnostic biopsy, type of surgical procedure of the primary tumor, inguinal region surgical treatment, margins, depth of invasion, lymphovascular invasion (LVI), complications, SLN, adjuvance, recurrence, treatment of recurrences, disease-free period and overall survival were analyzed.

The data were analyzed using descriptive statistics, whereas the survival analysis was carried out with the Kaplan-Meier method, with the use of the statistical package Stata, version 12.0.

Results

Twenty-seven vulvar squamous cell cancer-diagnosed patients, who met the selected inclusion criteria, with ages ranging from 67 to 78 years (average, 72.41 ± 13.85 years) were included in this study. With regard to parity, average pregnancies were 4.93 (range, 3.36 to 6.49). The presence of human papillomavirus infection (HPVI) or a history thereof was observed only in

18.52% (n = 5). The most common symptom was itching, which occurred in 88.89% of patients. In 51.85% of these, itching was accompanied by a tumor, whereas in 18.52%, it was accompanied by a tumor, bleeding and pain. Average evolution time was 11.22 months, ranging from 1 to 36 months. The vulvar squamous cell carcinoma diagnosis was made by incisional biopsy in 88.8% of the patients, while in the rest it was made by excisional biopsy. In 66.67% of the cases, tumors were moderately differentiated, 22.2% were well differentiated, and only 3 cases were considered to be undifferentiated (Table 1).

With regard to staging (Fig. 1), which was made based on FIGO's last revision (2009)¹¹, 77.77% (n = 21) of the patients were initially at clinical stage I, with this percentage being reduced to 51.85% (n = 14) at post-surgical staging. On the other hand, 18.5% (n = 5) of the patients were initially at clinical stage III, which increased to 29.6% (n = 8) at post-surgical procedure staging. The location of the primary tumor in all 27 patients had the following distribution: 8 at the right labia majora, one at the right labia minora, 4 at the left labia majora, 4 at the left labia minora, 3 at the clitoris, 6 at the fourchette and one at the perineum. One patient was considered to be multifocal. Based on physical exam, 81.48% (n = 22) had negative lymph nodes at diagnosis, and the remaining 5 patients (18.5%) had clinically palpable lymph nodes, 2 of them with cytological confirmation. Average clinical tumor size was 29.74 mm, whereas average pathologic tumor size was 30.22 mm.

Hundred percent of the patients received vulvar surgery, with most common being hemivulvectomy (51.85%) and wide excision (40.74%). On the other hand, 66.66% of the patients were practiced inguinal surgery: unilateral inguino-femoral dissection in 4 patients (14.81%) and bilateral in 14 cases (51.85%). Surgical complications occurred in 48.1% (n = 13) of the patients who underwent vulvar surgery, and in 22.22% (n = 4) of those who had inguinal surgery, with surgical wound dehiscence being the most common complication (Fig. 2).

The SLN procedure was performed in 8 patients, with location being unilateral. The technique failed in 2 patients and, in the remaining 6 patients, 4 negative and 2 positive results were obtained in the intraoperative examination. Average lymph nodes obtained including SLN and inguino-femoral dissection was 10.14 lymph nodes. Fifty percent sensitivity, 75% specificity and 50% positive predictive value (PPV), with 16% false negatives, were calculated for SLN.

Table 1. Clinical characteristics

Age	72.4 years (66.9-77.8)
FIGO stage	
I	14 (51.8%)
II	1 (3.7%)
III	8 (29.6%)
IV	0
*	4 (14.8%)
Tumor location	(%)
Right labia majora	8 (29.63)
Left labia majora	4 (14.8)
Right labia minora	1 (3.7)
Left labia minora	4 (14.8)
Clitoris	3 (11.1)
Fourchette	6 (22.22)
Perineum	1 (3.7)
Main symptom	(%)
Itching plus tumor	14 (51.85)
Itching	5 (18.52)
Tumor	1 (3.7)
Pain	1 (3.7)
Bleeding	1 (3.7)
All	5 (18.52)
Tumor size (average)	Average (mm)
Clinical	29.74
Pathologic	30.22
Stromal invasion	5.74 (1-13 mm)
Histologic grade	(%)
Well differentiated	6 (22.2)
Moderately differentiated	18 (66.67)
Undifferentiated	3 (11.13)

*Clinical stage could not be identified.

When positive lymph nodes [LN (+)] and disease recurrence were correlated, no statistical significance was obtained (Fig. 3); however, the percentage of patients with LN (+) who recurred was 50 vs. 17.7% of those with negative lymph nodes. On the other hand, when tumor location and LN (+) were correlated, the patients with tumors at the left or right labia majora or the fourchette had higher percentage of positivity, although with no statistical significance. With regard to centrality and LN (+), 3 out of 15 (20%) patients had the lesion at more than 1 cm and LN (+), in contrast with 5 patients out of 12 (41.6%) in whom the lesion was located at a less-than-or-equal-to 1-cm distance, also with no statistical significance.

LVI was detected in 22.22% (n = 6). Fifty percent of the patients with LVI had LN (+), in contrast with 40%

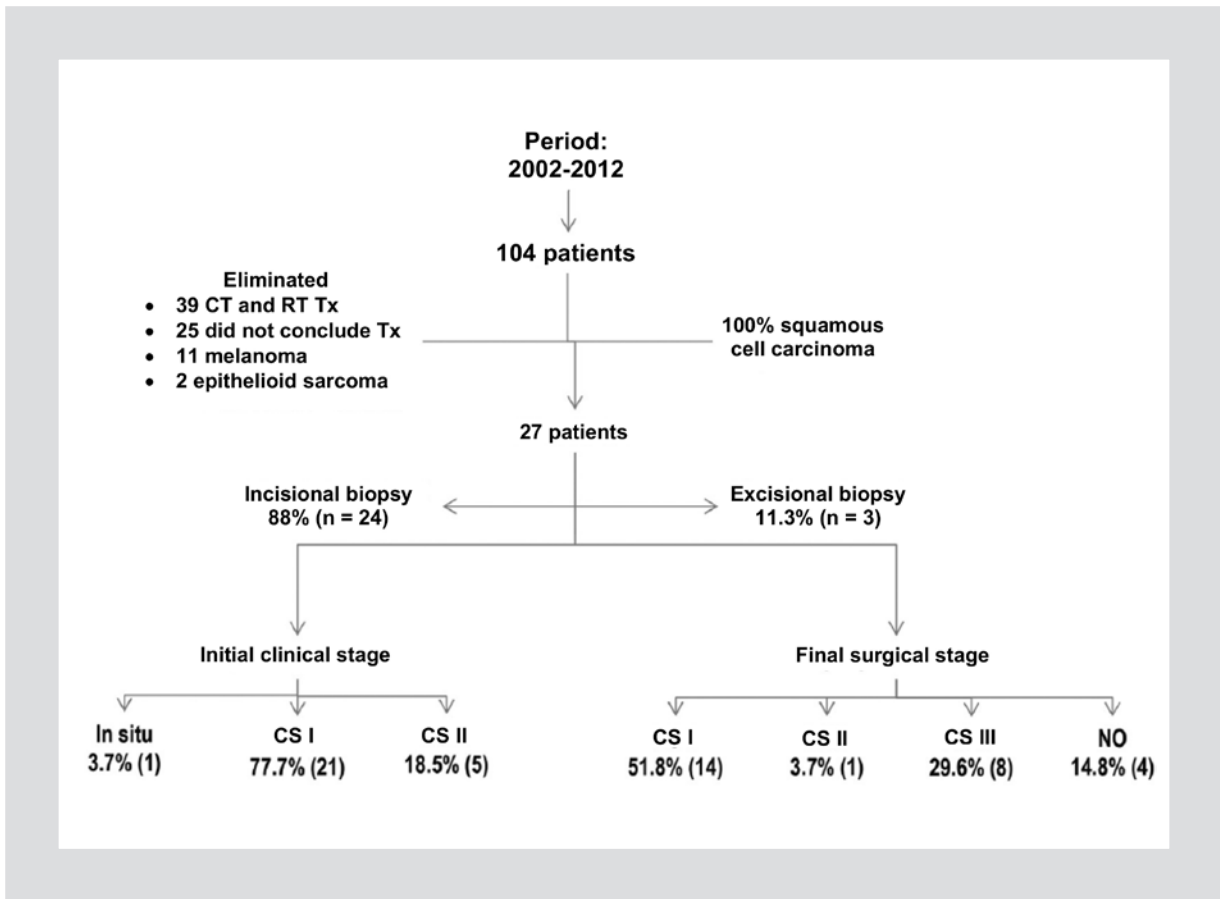


Figure 1. Study group selection flow chart.

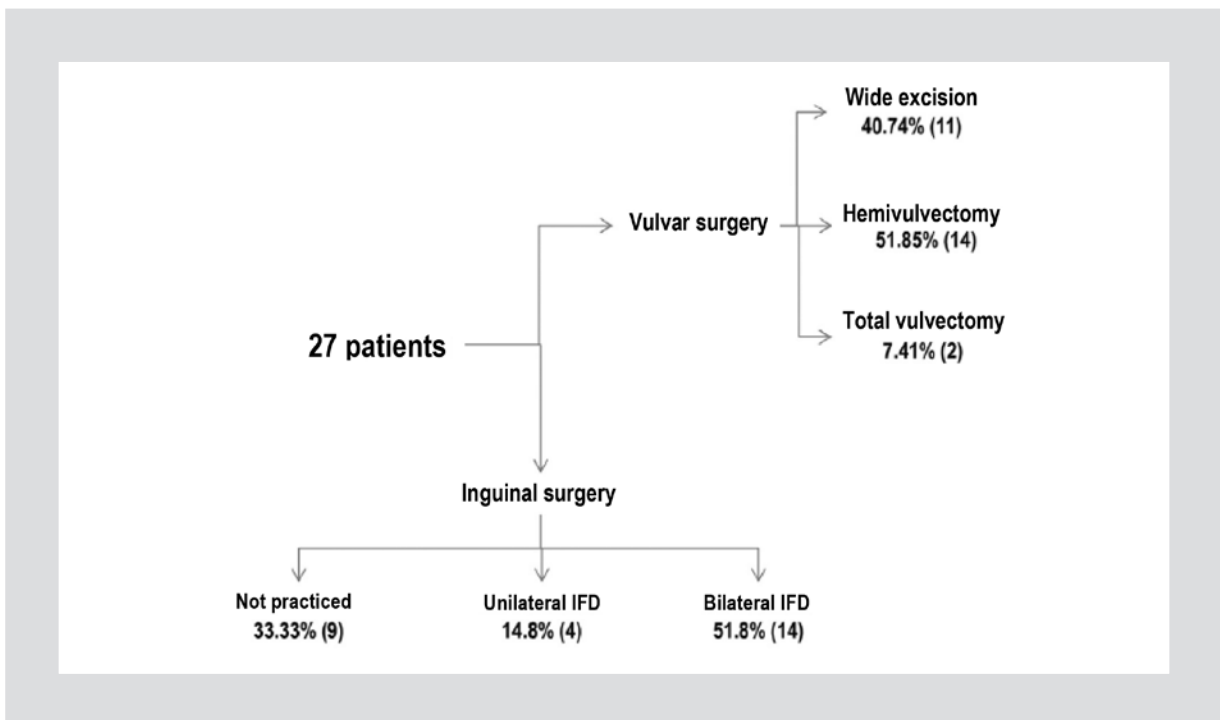


Figure 2. Surgical procedure practiced.

of those without LVI, with a tendency towards significance being present ($p = 0.051$).

Adjuvant therapy was decided based upon tumor-free margins, LN (+), tumor size and LVI. In 4 patients, total pelvic RT was administered with a mean of 46.9 Gy, boost RT was administered in 2 patients to the vulvar region and in 4 to the inguinal region at a mean dose of 11.83 Gy. In CT adjuvance, the following agents were used: carboplatin ($n = 1$) or cisplatin ($n = 2$) monotherapy, and cisplatin plus 5-fluorouracyl combination regimen ($n = 1$). When administered together with RT, the dosing period was concomitant. The decision to administer the CT regimen was mainly based on the presence or absence of lymph node disease.

Recurrence occurred in 25.91% ($n = 7$) of cases, with bone recurrence being the most common (42.8%). The treatment of bone recurrence was with RT administration; main sites were the femur, sacrum, ilium, bony thorax, lumbosacral region. One patient recurred at the groin (she had no history of previous inguinal region surgery), and underwent resection, which was complemented with RT; she remains alive, free of disease. One patient had recurrence in the vulva, had surgery with positive margins, was considered inoperable for margins re-excision and was treated with complementary RT; however, she died of cor pulmonale.

With regard to survival and the surgical procedure used, no statistically significant difference was found between hemivulvectomy and wide excision ($p = 0.9$). Overall survival at 123 months of follow-up in our patients was 63%.

Discussion

The theory that the greater the depth the greater the lymph node involvement was corroborated in this work. In patients with up to 1 mm invasion, the percentage of lymph node involvement was 0%, in contrast with those where the invasion was of 1 mm and up to 5 mm, in whom lymph node involvement was increased to 25%; on the other hand, an invasion larger than 5 mm implied a percentage of lymph node involvement of 45% (5/11 patients). The predominant detection site was the right labia majora. Itching associated with the presence of tumor occurred in 58% of our cases, which is similar to observations reported in most studies^{4,18}.

To establish patient treatment it is important to determine the relationship of the tumor with the midline, as shown by the GOG study, where only 2.5% of 272 patients with tumors located outside the midline had contralateral metastases in the absence of ipsilateral

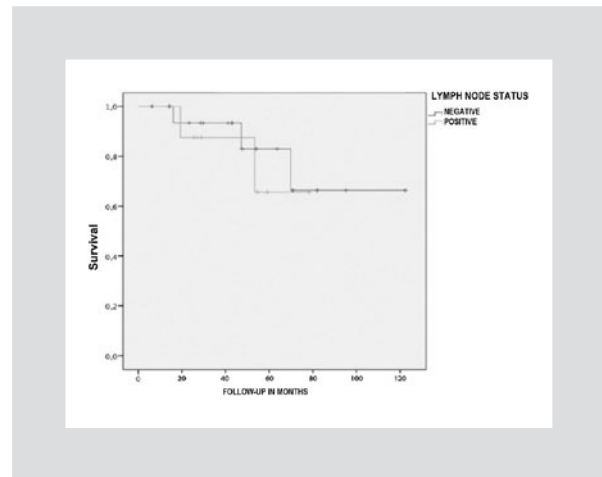


Figure 3. Survival according to lymph node status.

involvement. In the study population of the present work, 44.4% ($n = 12$) had central lesions; however, during the analyzed period, it can be observed that this modified the behavior until the year 2009, when the location of the lesion was considered in order to perform or not a bilateral dissection.

The history of local control goes from radical vulvectomy to the current wide excision, both procedures with a follow-up mean of 84 months, with a survival percentage close to 96.4%, depending on the margins¹⁰. In a retrospective study where 135 cases were analyzed, patients with margins larger than 8 mm did not have locoregional recurrence compared with those with margins < 8 mm, where it was increased to 50%¹⁴.

De Simeone et al., in 2007, assessed the treatment with T1 ($n = 62$) and T2 ($n = 61$) tumors that underwent hemivulvectomy or radical vulvectomy. Eleven and 31% of the T1 and T2 tumors, respectively, had superficial ipsilateral inguinal involvement. Of the T1, none had deep involvement and the T2 had deep involvement in 11% and, therefore, treatment of these tumors can be accomplished with hemivulvectomy or radical vulvectomy in addition to superficial inguinal dissection, and only deep dissection if lymph node disease is corroborated⁷.

In the course of the history of the INCan, it can be observed that treatments between 2002 and 2006 were more radical, with superficial and deep inguinal lymph node dissection being performed regardless of tumor location or size or if there was lymph node disease present or not; therefore, the most practiced surgery was hemivulvectomy (54%) without showing significant difference when compared with more conservative surgery.

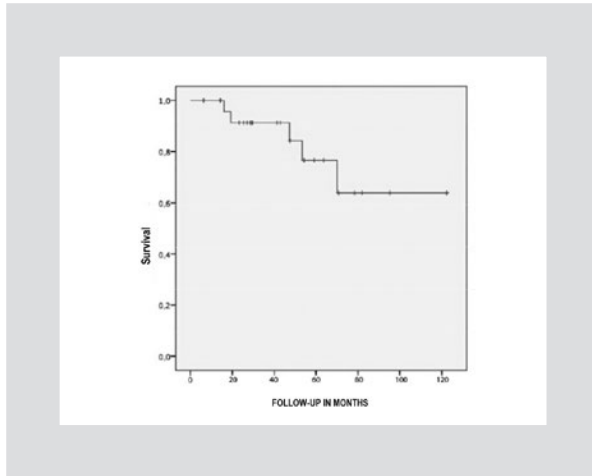


Figure 4. Overall survival.

In the 2011 review of the Cochrane group, local wide excisions are shown to be sufficient treatment with the same recurrence-free period as long as margins are negative¹⁹.

The SLN technique used at the institute was combined using technetium 99 + patent blue dye, with 1 false positive and 1 false negative being obtained. In spite of the number of patients, sensitivity and specificity of this test was calculated, with the following findings: 50% sensitivity, 75% specificity, 50% PPV and 75% negative predictive value (NPV).

The GOG 173 study (GROINSS V) compared SLN (double technique) vs. inguinofemoral lymphadenectomy, with the SLN detection rate with both separate techniques being found to be close to 88%, with 5% false negatives; but if both techniques are used, the detection rate increases to 96.2%²⁰.

The importance of knowing the lymph node status was demonstrated in 1995 by Burger et al., who demonstrated, in patients with T1 and T2, the presence of SLN (+) and 29.4% of early recurrence, whereas with negative lymph nodes, recurrence was only 5%²². Similarly, survival decreases from 70 to 25% in a 120-month period with the fact of having positive lymph nodes. The same was demonstrated in the present work, where patients with LN (+) showed higher cancer-related mortality than those with negative lymph nodes.

The evolution in surgery is associated with decreased morbidity, without losing sight of the cancer control context. In the present study, the rate of complications was 40.7% at the inguinal region and 48.1% at the vulvar region, with the most common being dehiscence.

In our population, 52% received adjuvant treatment, the majority CT with total pelvic RT, with a RT dose similar to that established by the literature (an average of 46.9 Gy); in addition, platinum was used as first-line together with 5-fluorouracil as therapy in one patient.

During the follow-up, 6 patients had recurrences: 2 had distant recurrence, 2 recurred locally and 2 did it regionally, to whom combined treatment was given. A review of 55 patients with cancer of the vulva demonstrated that, at 96 months, most common recurrence was distant, followed by regional and, finally, locoregional. Recurrence was a factor that decreased overall survival when compared with patients who did not experience recurrence²¹.

At early stages I and II, 5-year survival is approximately 90%. In a study carried out from 1980 to 2004 in 373 patients with an average age of 63 years, 76.6% with squamous cell histology, 31.11 and 19.84% at stage I and II, respectively, 5-year survival was 65%⁹; overall survival attained in our study was close to 63%, taking into account that patients included in the study were mostly older than 70 years (Fig. 4).

Vulvar cancer is an entity that can involve diagnostic difficulties, especially owing to the initially occurring symptoms (itching), which makes for patients to be monitored for long periods of time without a definitive diagnosis; however, at the suspicion of neoplasm, the approach is relatively simple by means of colposcopy-guided or direct-vision biopsy.

Owing to its low frequency world-wide, its management has not been able to be standardized, especially at early stages. According to our results, we can determine that individualized treatment should be proposed, with a microscopic margin larger than 8 mm for local control, with probability of recurrence as low as 0%. Staging should be surgical and complete. The SLN technique is an appropriate option for lymph node staging with high sensitivity, specificity and NPV if a combined technique is used; bilateral groin approach includes central lesions or presence of unilateral positive lymph nodes; pelvic dissection does not offer an advantage in overall survival or disease-free period, the rate of complications is high and it is related to the surgical technique or patient education on postoperative care at home.

On the other hand, recurrence in our study was mainly distant and, therefore, imaging studies should be requested if there is suspicion. Adjuvant treatment should be proposed mainly to patients with positive lymph nodes, close or positive margins non amenable to re-excision surgery and tumor size larger than 4 cm.

Throughout time, it can be observed a more radical procedure does not precisely improve survival for these patients, with procedures currently tending to be less radical with similar results in terms of both local and distant recurrence; however, randomized prospective trials assessing the difference in the management of these patients according to the surgical approach are required, since there is not yet a consensus or standardization for the management of this pathology.

References

1. U.S. Cancer Statistics Working Group. United States Cancer Statistics: 1999–2011 Incidence and Mortality Web-based Report. Atlanta (GA): Department of Health and Human Services, Centers for Disease Control and Prevention, and National Cancer Institute; 2014.
2. I.R.C.P. (2012) Gynecologic Cancers Portfolio Analysis: Summary of the burden of gynecologic cancers in the United States and investments in research by the National Center Institute and members of the International Cancer Research Partnership. Recuperado el 21/11/14, de IRCP Partnership sitio web: https://www.icrpartnership.org/Publications/ICRP_GYN_analysis.pdf.
3. Oncoguía Sociedad Española de Ginecología y Obstetricia. Cáncer Escamoso Invasor de Vulva. Guías de práctica clínica en cáncer ginecológico y mamario. Publicaciones S.E.G.O. 2010(3). 978-84-615-5421-8.
4. Schilder JM, Stehman FB. Invasive Cancer of the Vulva. En: Clinical Gynecologic Oncology. DiSaia P, Creasman WT. (editores). 8a ed. Philadelphia, EUA: Saunders, Elsevier Inc.; 2012. p. 220-44.
5. Rodríguez C, González E, Guerra A.I. Cáncer de vulva. Más Dermatología. 2008;4:5-13.
6. SINAI/SINAVE/DGE/SALUD/Perfil Epidemiológico de los Tumores en México. 2011. ISBN 978-607-460-236-4.
7. DeSimone CP, Van Ness JS, Cooper AL, et al. The treatment of lateral T1 and T2 squamous cell carcinomas of the vulva confined to the labium majus or minus. *Gynecol Oncol.* 2007;104(2):390-5.
8. Bromfield ME, Gibson TN, Hanchard B, Waugh N, McNaughton D. A Thirty-year Review of Vulvar Cancer in Jamaica, 1978 to 2007. *West Indian Med J.* 2014;2:138-41.
9. Bosque OJ, Delgado R, Montero JF, Esperón RP, Silveira JM, Aguilar FO. Cáncer de la vulva: cuadro clínico, histopatología y supervivencia (1980 a 2004). *Rev. Cubana Cir.* 2008;47:4.
10. Maggino T, Landoni F, Sartori E, et al. Patterns of recurrence in patients with squamous cell carcinoma of the vulva. A multicenter CTF study. *Cancer.* 2000;89:116.
11. Pecorelli S. Revised FIGO staging for carcinoma of the vulva, cervix, and endometrium. *Int J Gynecol and Obstet.* 2009;105:103-4.
12. Martínez-Palones JM, Pérez-Benavente MA, Gil-Moreno A, et al. Comparison of recurrence after vulvectomy and lymphadenectomy with or without sentinel node biopsy in early stage vulvar cancer. *Gynecol Oncol.* 2006;103:865-70.
13. Messing MJ, Gallup DG. Carcinoma of the vulva in young women. *Obstet Gynecol.* 1995;1:51-4.
14. Heaps JM, Fu YS, Montz FJ, Hacker NF, Berek JS. Surgical-pathologic variables predictive of local recurrence in squamous cell carcinoma of the vulva. *Gynecol Oncol.* 1990;3:309-14.
15. Oonk MH, van der Zee AG. Application of sentinel nodes in gynaecological cancer therapy. *EJC Suppl.* 2013;11:287-8.
16. Barton DP, Berman C, Cavanagh D, et al. Lymphoscintigraphy in vulvar cancer: a pilot study. *Gynecol Oncol.* 1992;3:341-4.
17. Woelber L, Trillsch F, Kock L, et al. Management of patients with vulvar cancer: a perspective review according to tumour stage. *Ther Adv Med Oncol.* 2013;3:183-92.
18. Molero J, Hernández-Aguado JJ, Laila JM. Carcinoma de la vulva. En: *Fundamentos de Ginecología*, Bajo Arenas JM, Laila Vicens JM, Xercavins Montosa J. (editores). 1a ed. Madrid, España: Panamericana Inc.; 2009. p. 347-63.
19. Farias-Eisner R, Cirisano FD, Grouse D, et al. Conservative and individualized surgery for early squamous carcinoma of the vulva: the treatment of choice for stage I and II (T1-2N0-1M0) disease. *Gynecol Oncol.* 1994;1:55-8.
20. van der Zee AG, Oonk MH, De Hullu JA, et al. Sentinel node dissection is safe in the treatment of early-stage vulvar cancer. *J Clin Oncol.* 2008;6:884-9.
21. Bellati F, Angioli R, Mancini N, et al. Single agent cisplatin chemotherapy in surgically resected vulvar cancer patients with multiple inguinal lymph node metastases. *Gynecol Oncol.* 2005;96:227-31.
22. Burger MP, Hollema H, Emanuels AG, Krans M, Pras E, Bouma J. The importance of the groin node status for the survival of T1 and T2 vulval carcinoma patients. *Gynecol Oncol.* 1995;3:327-34.