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Review article

Surgical management of squamous cell vulvar cancer without clitoris, urethra or anus involvement

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ABSTRACT

Vulvar cancers, which constitute 5% of all gynecologic cancers, are the fourth most common female genital cancers, preceded by uterine, ovarian and cervical cancers. The treatment methods employed for vulvar cancers have changed over the years, with previously applied radical surgical approaches, such as en bloc resection, being gradually suspended in favor of treatment approaches that require dissection of less tissue. While the removal of less tissue, which today's approaches have focused on, prevents morbidity, this method seems to result in higher risks of recurrence. It is therefore important that the balance between preventing the recurrence of the disease and forefending against postoperative complications and vulvar deformity be properly understood. As a working assumption, if patients with vulvar cancer are diagnosed at an early stage, properly evaluated and administered appropriate treatment, the most positive results can be obtained. This paper aims to highlight this assumption and demonstrate, through the provision of actual data, how to plan the treatment approach for patients who are diagnosed early. Statements extracted from the National Comprehensive Cancer Network (NCCN) Guidelines Version 1.2016 Sub-Committees on vulvar squamous cell carcinoma and articles by the European Society of Gynaecological Oncology (ESGO) regarding Vulvar Cancer Recommendations were used to obtain updated information.

Contents

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1. Introduction

Vulvar cancers, which constitute 5% of all gynecologic cancers, are the fourth most common female genital cancers, preceded by uterine, ovarian and cervical cancers (Siegel et al., 2014). Although the histological types of vulvar cancers, such as malignant melanoma, basal cell carcinoma, Bartholin gland adenocarcinoma, Paget's disease and sarcoma, are rare, 90% of vulvar cancers have squamous cell carcinoma histology features (Gunther et al., 2012). In more than half of the patients, the disease is localized, while in 5%, distant metastatic disease occurs (SEER Cancer Stat Facts: Vulvar Cancer, 2017). Recent data shows that when the disease is diagnosed at the localized stage, the survival rate is 86.1% (SEER Cancer Stat Facts: Vulvar Cancer, 2017).

The treatment methods employed for vulvar cancers have changed over the years, with previously applied radical surgical approaches, such as en bloc resection, being gradually suspended in favor of treatment approaches that require dissection of less tissue. These changes in treatment approaches aim to prevent postoperative morbidity and to reduce vulvar deformity and sexual dissatisfaction, which especially occur in younger patients following treatment.

Recurrence is a particularly problematic feature of vulvar cancer cases. Relapses can generally be attributed to the disease's nature (multi-focused), delayed diagnosis and inadequate treatment (Rouzier et al., 2002). Studies have found that en bloc resections yield better results in terms of recurrence (de Hullu et al., 2002; Van der et al., 2004; Leminen et al., 2000; Magrina et al., 1998). While the removal of less tissue, as today's approaches have focused on, prevents morbidity, this method seems to result in higher risks of recurrence. It is therefore important that the balance between preventing the recurrence of the disease and forefending against postoperative complications and vulvar deformity be properly understood.

As a working assumption, if patients with vulvar cancer are diagnosed at an early stage, properly evaluated and administered appropriate treatment, the most positive results can be obtained. This paper aims to highlight this assumption and demonstrate, through the provision of actual data, how to plan the treatment approach for patients diagnosed early. Statements extracted from the National Comprehensive Cancer Network (NCCN) Guidelines Version 1.2016 Sub-Committees on vulvar squamous cell carcinoma and articles by the European Society of Gynaecological Oncology (ESGO) regarding Vulvar Cancer Recommendations were used to obtain updated information.

1.1. Vulvar anatomy

The vulva consists of the labium majus and minus, the clitoris, the vestibule, the vaginal introitus and the urethral meatus. Additionally, the Bartholin gland complex (gland and ductus) is a component of the vulva. Bartholin gland malignancies are recognized to be a function of vulvar cancers. A build-up of blood mainly originates from the internal pudendal artery, with a far greater amount generated from the external pudendal artery. The anterior and posterior parts are innervated by branches of the ilioinguinal nerve, as well as the pudendal nerve and the posterior cutaneous nerve. Lymphatic drainage affects the superior inguinal nodes, whereas the deep inguinal and external iliac nodes may be directly subjected to drainage from the front parts of the clitoris and labium minus.

2. Pre-treatment evaluation

During the evaluation of a patient suspected of having vulvar cancer, the first step is to conduct a biopsy of the vulva section under question. Only a hemogram is necessary before performing the biopsy (if anamnesis shows there to be no risk of bleeding diathesis), which can be done under local anesthesia. At this stage, it is important to avoid making a broad excisional biopsy, as this could possibly complicate the surgical plans related to a vulvectomy that may be required later. Instead, the dissection should be conducted in punch biopsy form. Furthermore, the dissected tissue should also contain some dermis and connective tissues in order to determine the invasion depth. In cases of multiple lesions, all lesions should be subjected to biopsy and analyzed. The histological type and depth of invasion need to be specified in the pathology report. If invasive squamous cell carcinoma (SCC) is diagnosed as a result of the biopsy, the stage of the disease should be noted. Vulvar cancers are staged according to the surgical staging system of the American Joint Committee on Cancer (AJCC) and the International Federation of Gynecology and Obstetrics (FIGO) (Table 1).

Table 1
Surgical staging of vulvar cancer cases.

IA	Lesions ≤ 2 cm in size, confined to the vulva or perineum and stromal invasion ≤ 1.0 mm
IB	Lesions > 2 cm in size or any size with stromal invasion > 1.0 mm, confined to the vulva or perineum
II	Tumor of any size, with extension to adjacent perineal structures (lower/distal 1/3 urethra, lower/distal 1/3 vagina, or anal involvement)
III	Tumor of any size, with or without extension to adjacent perineal structures (lower/distal 1/3 urethra, lower/distal 1/3 vagina, or anal involvement) and with positive inguino-femoral lymph nodes
IVA	Tumor of any size, with extension to any of the following: upper/proximal 2/3 of urethra, upper/proximal 2/3 vagina, bladder mucosa, rectal mucosa, or fixed to pelvic bone
IVB	Any distant metastases involving pelvic lymph nodes

In patients diagnosed with invasive cancer, imaging techniques, such as magnetic resonance imaging (MRI), computed tomography scan (CT) and positron emission tomography (PET), can be used to determine the limits of the tumor and any possible metastases. Here, it is important to note that CTs and MRIs should be performed in such a manner as to show contrast. However, in the event that a thorax CT is performed, the showing of contrast is not required. If invasion is suspected in the urethra, bladder or anal channel during the imaging examination, a cystoscopy or proctoscopy may help to clearly identify this. Moreover, patients should be evaluated through the performance of a papanicolaou smear in addition to a cervical and vaginal colposcopy (Berek and Hacker, 2015) to determine whether other simultaneous malignancies in the lower genital tract exist. Should all these examinations reveal that the diameter of the tumor does not exceed 4 cm and that there is no vaginal, anal, or urethral involvement, the patient can then be diagnosed with early stage vulvar cancer.

In general, treatment approaches may differ according to the following four management criteria (Fig. 3):

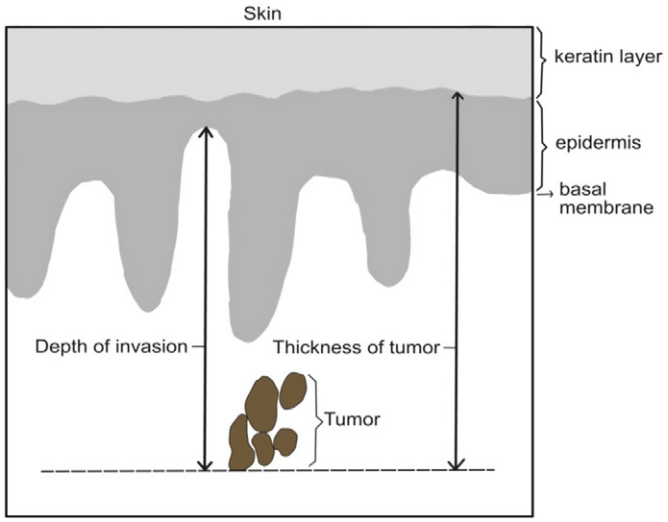

Fig. 1. Measurement of tumor invasion depth.

1. Depth of invasion
2. Tumor within surgical limits
3. Proximity to midline
4. Involvement of inguino-femoral lymph node

2.1. Management of the primary lesion

The primary criterion to be used for evaluation of the primary lesion is the depth of invasion of the preoperative biopsy material. Determination of depth of invasion is made by taking a measurement from the epithelium-stroma border of the most superficial dermal papilla to the bottommost point of the tumor (Fig. 1) (Wilkinson et al., 1986). In recent years, alternative measurement methods for depth of invasion have been suggested (Van den Einden et al., 2015).

If the depth of invasion of preoperative biopsy material is <1 mm, the tumor can be excised through broad local resection, and in cases where the analysis of the tumoral tissue shows that the invasion area does not exceed 1 mm, current treatment measures can proceed along with follow-up care of the patient, as it can be safely assumed that no metastasis of the lymph node has occurred (Hacker et al., 1981; Hampl et al., 2009). However, if it is found that the depth of stromal invasion in excised tumoral tissue exceeds 1 mm or, in other words, that the excised tumoral tissue is different from the preoperative biopsy material, then the performance of a broad local resection surgical procedure will not be able to sufficiently address this matter. Studies have shown that metastasis of the groin lymph node increases in direct proportion to the depth of invasion (7–8% for 1.1–3.0 mm invasion and 26–34% for >3 mm invasion) (Homesley et al., 1993). In these cases, the proximity of the tumor to the midline will determine the supplementary surgical intervention to be performed. If the distance between the lesion and the midline is <2 cm, it is designated a midline tumor, while if the distance is >2 cm, it is designated a lateral tumor.

2.1.1. Midline tumor

The distance between the lesion and midline is <2.0 cm. In this case, the recommended surgical procedure is either radical local resection or modified radical vulvectomy. In addition, the inguino-femoral lymphadenectomy (IFL) should be bilateral.

2.1.2. Lateral tumor

The distance between the lesion and midline is >2.0 cm. Accordingly, the tumor should be dissected through radical local resection or modified radical vulvectomy. Unlike in cases of midline tumors, an ipsilateral IFL is sufficient at the first stage. The morbidity rate associated with the performance of an ipsilateral IFL is lower than that of a bilateral IFL. As this may be advantageous for patients with lateral tumors, ipsilateral IFL is recommended for use (Stehman et al., 1992). In terms of recurrence, results from studies conducted on the reliability of an ipsilateral IFL in cases of lateral tumors are promising. If the ipsilateral lymph node is found to be negative, it can be assumed that the lymph nodes will be negative. Even in cases where they are positive, the recurrence rate of the opposite lymph node is lower than 3% (Andrews et al., 1994; Farias-Eisner et al., 1994; Stehman et al., 1992).

Many studies have indicated there to be no difference regarding early stage recurrence between modified radical vulvectomy and radical local resection (Rouzier et al., 2005; Ansink and van der Velden, 2000; DeSimone et al., 2007; Burke et al., 1995). The resection depths of both techniques are similar and restricted to the urogenital diaphragm. At minimum, a 1–2 cm tumor-free section should be dissected clinically. Outlining the borders of the tumor with a pen helps to make the performance of the surgery far more convenient.

2.2. Lymphadenectomy

The lymphatic spread from vulvar carcinomas initially occurs to the superficial inguinal and deep femoral lymph nodes. The superficial inguinal nodes are usually the first nodes involved, but this does not always appear to be the case (DiSaia et al., 1979; Chu et al., 1981). It is not very clear whether groin lymph node dissections should be complete or limited in patients with vulvar cancer or how many lymph nodes should be dissected (Stehman et al., 2009; van Beekhuizen et al., 2014).

2.2.1. Superficial inguinal lymphadenectomy

Fascia incision and skeletonization of femoral veins are not required for superficial inguinal lymphadenectomy. The borders of this area are below the inguinal ligament, medial to the sartorius and lateral to the adductor longus. The process includes dissection of the fatty tissues. Because the femoral lymph nodes are not dissected, the morbidity rate for this procedure is lower; however, recurrence rates have been shown to be higher. In a prospective GOG study conducted in 1992, 121 patients with early stage vulvar cancer were subjected to a superficial inguinal lymphadenectomy, and no metastasis into the femoral lymph nodes was found. Nonetheless, inguino-femoral recurrences were observed in 6 patients. It is unclear whether such recurrence originated from the femoral lymph nodes, but the authors have suggested that groin dissection should be a complete IFL since superficial inguinal lymphadenectomy was associated with higher rates of recurrence (Stehman et al., 1992; Ansink and van der Velden, 2000).

2.2.2. Complete inguino-femoral lymphadenectomy

The inguino-femoral dissection routinely includes removal of the lymph nodes superficial to the inguinal ligament, nodes within the proximal femoral triangle (borders formed by the sartorius muscle and the adductor longus muscle) and lymph nodes that extend deep into the cribriform fascia. The superficial fascia is accessible by making an 8–10 cm incision between the anterior superior iliac spine and the pubic tubercle (1 cm above inguinal crease). The superficial circumflex iliac vessels located laterally, the pubic tubercle located medially, the external oblique aponeurosis located superiorly and the inguinal ligament located inferiorly constitutes the borders of this area. The caudal end of the dissection should reach the femoral triangle. Here, the great saphenous vein crosses the medial border of the femoral triangle. The superior point should be the start position for dissection. After fatty tissue is removed from the external oblique aponeurosis and lymph nodes around the inguinal ligament are excised, the incision should be deepened to the external oblique aponeurosis.

At this point, different ideas govern whether or not the great saphenous vein should be preserved. Although it has been stated that preservation may reduce certain complications, such as lymphedema and cellulitis, several authors disagree (Zhang et al., 2007; Dardarian et al., 2006). Suction drains are placed in the inguinal area following the completion of the dissection.

2.3. Evaluation of the patient based on pathologic findings

If the pathologic evaluation of a patient whose surgery has been completed reveals that at least 8 mm (surgical borders) of healthy tissue exists in the excised primary tumor mass and that no metastasis of the lymph nodes has occurred, follow-up care can begin on the patient.

2.3.1. Cases of surgical border positivity

The presence of a tumor within the surgical border is regarded as an important factor in SCC cases of recurrence. It is suggested that a healthy tissue border be preserved during the course of primary surgery (Heaps et al., 1990; de Hullu et al., 2002). In terms of what exactly is considered to be an adequate surgical border, differences involving 1 cm–2 cm are open to argument. Since the tissue will contract and shrink after excision and fixation, at least 15 cm of clearance seems to be acceptable as a disease-free border for fresh surgical preparations (Gotlieb, 2003).

If there is a tumor on the surgical border or if the distance between the tumor and surgical border is shorter than 8 mm, reevaluation of the patient is suggested.

In the event that a resection is performed in this case, a re-excision can be planned for the purpose of leaving an adequate surgical border. As an alternative to re-excision, local adjuvant radiotherapy can be considered at this stage (Faul et al., 1997). It is important to note here that re-excision should not be performed in cases where metastasis of the lymph node has occurred, as in these cases, re-excision will not be useful. Instead, the patient should be directed to undergo adjuvant radiotherapy. Moreover, if surgical border positivity is detected in the re-excision material, adjuvant radiotherapy should be considered. On the other hand, if the surgical borders of the excision material are negative, adjuvant therapy can be planned based on the presence of other risk factors, such as lymphovascular invasion, a negative surgical border of approximately 8 mm, tumor size, invasion depth and invasion pattern (spray or diffuse). The existence of lymphovascular invasion can be regarded as a strong indicator for lymph node involvement. In such cases, adjuvant radiotherapy to the inguino-femoral area is necessary.

2.3.2. Metastasis of the lymph node

Metastasis of the lymph node is known to be the most important prognostic factor in vulvar cancer (Burger et al., 1995; Crosbie et al., 2009). Given the absence of metastasis, the 5-year recovery rate is 90%, while in cases of the present metastasis, the recovery rate is approximately 50% (Ghurani and Penalver, 2001). The number and location of the involved lymph nodes and extracapsular involvement are poor prognostic factors that affect recovery (van der Velden et al., 1995). The factors associated with metastasis of the lymph node are lesion diameter, depth of invasion, degree of differentiation, presence of lymphatic and vascular permeation, perineural invasion and clinical node status (Rowley et al., 1988; Homesley et al., 1991). Metastasis of the lymph node is an indication for adjuvant therapy, which can be administered with concurrent chemotherapy.

The standard method for determining lymph node involvement is to perform an IFL. However, an IFL can lead to complications, such as wound dehiscence, wound infection, lymphocysts, lymphedema and prolonged hospital stay, particularly in the postoperative period (Barton, 2003). In studies conducted on this matter, wound site complications and lymphedema in the legs were reported to be 20–40% and 30–70%, respectively (DiSaia et al., 1979). As a matter of fact, given that metastasis cannot be detected in two-thirds of the patients subjected to lymphadenectomy, these patients are unnecessarily exposed to surgery and complications (de Hullu and van der Zee, 2003). As a result, having the ability to adequately predict metastasis of the lymph node is significant. While numerous prediction methods have been explored, all of them have several distinct disadvantages (Table 2).

In recent years, the performance value of SLN biopsy, as an alternative to inguino-femoral lymphadenectomy, has been extensively investigated. As a diagnostic tool, it is regarded as quite reliable for predicting lymph node positivity. In a GOG study, both SLN biopsy and complete inguino-femoral lymphadenectomy were administered to 403 patients (109 patients with lateral lesion, ipsilateral and 294 patients with midline lesion, bilateral). The study's results showed that nodal metastasis was detected in 120 patients and that the sensitivity of sentinel lymph node (SLN) detection rate and false-negative predictive rate were 88% and <5%, respectively (Levenback et al., 2009).

Table 2
Methods used to predict the metastasis of inguino-femoral lymph node.

✓ Clinical palpation
✓ High frequency ultrasound
✓ Ultrasound-guided fine needle aspiration cytology
✓ Magnetic resonance imaging (MRI)
✓ MR lymphography
✓ Positron emission tomography (PET)
✓ Sentinel lymph nodes

As other subsequent studies have found similar results, SLN biopsies have been shown to be a widely accepted alternative to lymphadenectomy as of today.

2.4. Inguino-femoral SLN biopsy for patients with vulvar cancer

Currently, SLN biopsies are accepted to be applicable and reliable (Kramer et al., 2013; Van der Zee et al., 2008; Levenback et al., 2012).

According to the logic underlying SLN biopsy, this method is particularly applicable for patients with early stage vulvar cancer. In these patients, it is important that the SLN biopsy shows an absence of lymph node metastasis in order to confidently eliminate the need for performing a complicated groin dissection. As this procedure may not be suitable for every patient, the following criteria should be followed when selecting patients to undergo an SLN biopsy (Covens et al., 2015; Levenback et al., 2012).

- Absence of suspicion of lymph node involvement during the examination and imaging
- Primary tumor smaller than 4 cm and unifocal
- No history of vulvar surgery, as this may affect lymphatic flow
- Absence of infection in the tumor

Additionally, an SLN biopsy should be applied on both inguinal areas if the tumor is midline (Fuh and Berek, 2012).

2.4.1. Technique

First, to successfully perform the biopsy, the SLN should be clearly identified. Experience in performing SLN biopsies is directly related to improvement in detectability of the SLN (Levenback et al., 2012a).

Studies have shown that sensitivity is higher when radiocolloid and dye are used together as opposed to the use of dye alone (Van der Zee et al., 2008; Levenback et al., 2012a; Oonk et al., 2010). Today, the most frequently used radiocolloid for vulvar tumors is "Technetium 99 Sulphur Colloid". The colloid substance is injected into the vulvar tumor 2–4 h prior to performing the SLN biopsy. At this stage, a lymphoscintigraphy can be performed to determine the anatomic localization of the SLN. Although various dyes can be used, 1% isosulfan blue is the most common. A 3–4 cc quantity of dye is injected (intradermal) at four different points (hour positions 2, 5, 7 and 10 on a 12-hour clock) around the tumor (peritumoral) 15–30 min before starting the procedure. The biopsy should be performed 20–30 min prior to the vulvectomy in order to prevent the biopsy from influencing the course of injected materials to lymph nodes. At this point, it is possible to detect the location of radiocolloid material in the inguinal area, specifically the location of the SLN, by using a gamma probe that is sensitive to radiocolloid. This process enables the SLN to be reached with a smaller incision.

2.4.2. Evaluation of the SLN biopsy procedure

If SLN was not detected, a complete IFL is recommended. In cases of metastatic SLN, a complete IFL, including the contralateral inguinal area and/or adjuvant radiotherapy to the inguinal area, should be planned (Fig. 2). In cases of negative SLN, the need to perform an IFL can be confidently eliminated. Although an SLN evaluation can be performed by means of frozen sectioning, micrometastases may not be detected. According to ESGO, pathologic evaluations of SLNs that are found to be negative on standard H&E staining should include serial sectioning at intervals of at least every 200 μm and an immunohistochemistry assay should be performed.

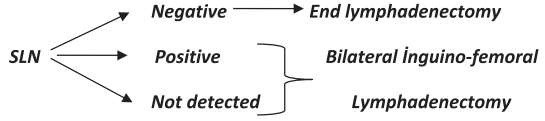

Fig. 2. Evaluation of a sentinel lymph node.

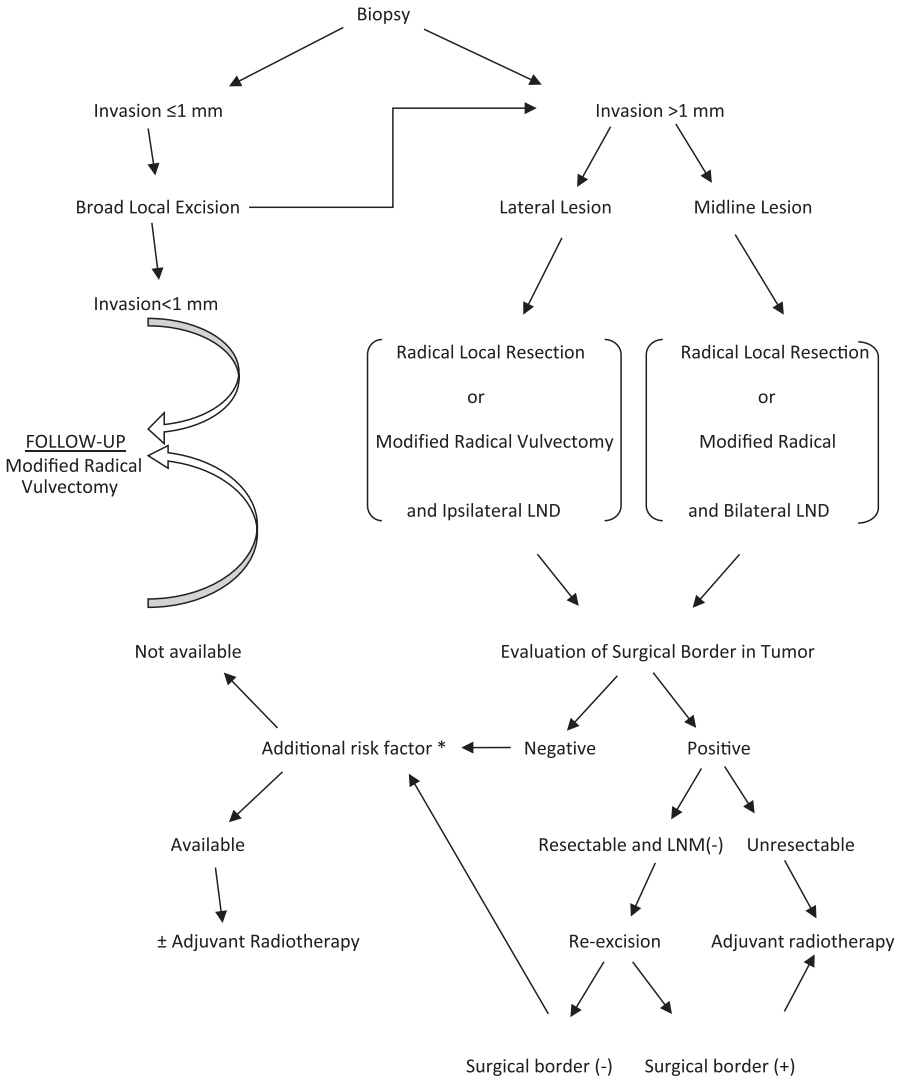

Fig. 3. Treatment diagram. (*): Lymphovascular invasion; negative surgical border, but closer than 8 mm; tumor size; invasion depth; invasion pattern (spray or diffuse).

2.5. Postoperative period

In the post-surgical treatment period, patients may encounter certain morbidities, including those that may become chronic and impair the quality of life of the patients, depending on the treatment.

Particularly, patients subjected to groin node dissection may experience various complications, such as wound infection, lymphocyst formation, prolonged hospital stay, venous thromboembolism and lymphedema (Gould et al., 2001). Risks can be reduced with proper surgical techniques (preservation of the saphenous vein, tension-free wound closure and adequate wound drainage) and suitable perioperative care (prophylactic antibiotics, proper care of wounds by nurses, prompt treatment of wound infection, compression stockings and prophylactic anticoagulation) (Barton, 2003). Drainage has an important role in preventing lymphocyst formation, which has a 10% rate of occurrence. Although the long-term continuance of wound drainage may serve to prevent this problem, the long-term existence of drain material may lead to infection and the development of wounds. The recommended treatment of lymphocyst formation includes drainage, pressure dressings and antibiotic cover (Hoffman et al., 1995).

Lymphedema may develop within a few months following vulvar surgery and radiotherapy. While different figures have been reported, the prevalence rate for the onset of lymphedema has been shown to reach 30% in some cases (Abu-Rustum et al., 2006; Ryan et al., 2003). Although a complete treatment program is still unavailable, specific exercises, massages, skin care and tight socks may serve to prevent the patient from worsening (Hoffman et al., 1995). Potential problems that patients may encounter include micturition and coital difficulties, vulvar asymmetry and psychosexual issues.

2.5.1. Follow up

Research has shown that 80% of recurrence cases occur within two years after primary surgery, whereas 10% of recurrence cases develop 5 years after surgery (Salani et al., 2011; Gonzalez et al., 2005). Although the most common recurrence location is the tumor bed or the remaining vulva, one-third of patients may have a recurrence of the lymph node, remote recurrence or multiple recurrences (Maggino, 2000).

The National Comprehensive Cancer Network (NCCN) recommends that patients with vulvar cancer be examined for recurrence once every three to six months in the first year, and once a year between the second year and the fifth year. In the years following the fifth year, examinations should be made annually. Routine use of the imaging techniques is not recommended, as most of the recurrences can be determined through physical examination. If a recurring mass is suspected, a CT or PET-CT can then be applied. A cervical/vaginal cytology should be analyzed regularly to check for malignancies in the lower genital tract. Regarding recurrence risk, patients should be informed about the symptoms with due importance given to instructing and training

patients on how to conduct self-examinations, in addition to encouraging them to quit smoking, exercise regularly and maintain a healthy diet. When necessary, patients should also be provided support about their sexual health by suggesting the use of a vaginal dilator, vaginal lubricants, or estrogen creams.

Conflict of interest

The authors have no conflicts of interests to disclose.

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