Morbidity of Inguinofemoral Lymphadenectomy in Vulvar Cancer and Evolution of Operative Treatment

Amr A. Soliman*, Basel Refky† and Eduard Malik*

1 Epidemiology

Vulvar cancer is the fourth most common gynecologic malignancy, accounting for 5 to 8% of all female genital tract malignancies (Stehman, 2007). It affects 4850 new patients annually in the United States (Siegel, Ma, Zou, & Jemal, 2014) and 3190 new patients in Germany (Kaatsch et al., 2013), with an annual estimated death rate of 1030 and 750, respectively, in the two countries (Kaatsch et al., 2013; Siegel et al., 2014). The incidence of the disease is on the rise, and has almost doubled in the last 10 years (Kaatsch et al., 2013), with a bimodal age distribution of a first peak at 45 to 50 years of age and a second peak at 70 to 75 years of age (Jones, Baranyai, & Stables, 1997).

The main risk factor for developing vulvar cancer is human papilloma virus (HPV) infection, whereas 40 to 60% of vulval cancers and 90% of vulvar intraepithelial neoplasia (VIN) are related to HPV infection (Hampf, Deckers-Figiel, Hampf, Rein, & Bender, 2008). HPV subtypes 6, 16, 18, 31, and 33 are most related to the development of vulvar cancer, especially type 16, which has the largest share, approaching 50% of all the affected cases (Insinga, Liaw, Johnson, & Madeleine, 2008). The role of high risk HPV infections was thoroughly studied in cervical dysplasia as a precancerous lesion (Saccardi et al., 2014) that makes us convinced that there is much to be explored in the field of vulvar cancer. The role of HPV vaccination is well established in cervical cancer and its precancerous lesions (Gizzo, Noventa, & Nardelli, 2013) but still needs to be further explored in vulvar cancer. Moreover, the role of antiretroviral medications was explored in precancerous lesions of cervical cancer (Patrelli et al., 2013) while its role in the field of vulvar cancer is still unclear. Other possible risk factors of vulvar cancer are smoking and immune deficiency, whether inherited or acquired.

The mainstay of treatment has always been operative, unless the tumor has already reached beyond local clearance so that palliative radiation therapy or combined radio-chemotherapy remains the only possible option. Figure 1 shows a locally advanced vulvar cancer before (a) and after (b) a radical vulvectomy with bilateral inguinofemoral lymphadenectomy using a triple incision and abdominal wall flap to cover the resulting defect.

2 En Bloc Resection of the Vulva and Inguinofemoral Lymph Nodes as a Primary Operative Treatment

* University Women's Hospital of Oldenburg, University of Oldenburg, Germany
† Department of Surgical Oncology, Oncology Center, University of Mansoura, Egypt
Operative therapy has been the primary treatment of choice for vulvar cancer for decades, providing complete resection of the primary tumor and removal of the draining locoregional lymph node groups, namely the inguinofemoral lymph nodes. Primary radio(chemo)therapy is reserved for locally advanced tumors, where a complete resection of the tumor does not seem achievable or for multi-morbid patients whose general condition does not allow such a radical procedure to be performed without grave consequences.

2.1 The Operative Technique

Since its introduction by Taussig in the 1940s (Taussig, 1940) and up to the 1990s, en bloc radical vulvectomy with bilateral inguinofemoral lymphadenectomy, the ‘butterfly resection’, has been the standard therapy for vulvar cancer. The aim of radical en bloc resection is to remove all tissue possibly involved in vulvar cancer, including the skin bridge between the vulva and the groins (Magrina et al., 1998; Taussig, 1940). However, the severe morbidity of this mutilating procedure as well as the consecutive psychosexual impairment are a very high price for the treatment.

In butterfly incision, a single incision is made, starting from 2 cm medial and about 2 cm caudal to the anterior superior iliac spine, curving downwards, above the superior border of the inguinal ligament, to the inguinal ring including the mons pubis, and extends to meet the same starting point on the contralateral side. Through this incision, bilateral inguinofemoral lymphadenectomy can be performed. The same incisions are continued at their lateral edge, across the groin skin, downwards along the labiocrural folds on each side and across the perineum, where they meet. Through this part of the incision, the radical vulvectomy is performed. A medial mucosal incision is made along the introitus, extending through the
anterior vestibule and around the urethral meatus. Attempts are made to attain at least a 2 cm margin of normal specimen, as a safety margin. The removed specimen then includes the tumor, the surrounding vulvar tissues till the fascia in the depth, the clitoris, the labia minora and possibly majora, according to the tumor location and size, and variable areas from the vaginal mucosa according to the location of the primary tumor. The wound is then copiously irrigated, hemostasis is secured, and groin wounds are closed in layers. Drains are inserted through separate incisions bilaterally. The vulvar wound is closed with delayed absorbable sutures (Byron RL, 1962; Lin, Dubeshter, Angel, & Dvoretsky, 1992). One step towards further radicality was introduced by (Way, 1978), who reported an improvement in survival in vulvar cancer patients by integrating pelvic lymphadenectomy into the procedure, which was advocated to be the standard operative therapy for some time (Way, 1978). A study from MD Anderson Hospital showed that of 191 patients, only nine (4.7%) had positive deep pelvic nodes, and all nine patients also had metastatic disease in the groin nodes (Curry, Wharton, & Rutledge, 1980). This study has demonstrated that the pelvic lymph nodes are only involved when the inguinal lymph nodes are already involved, an observation that suggests pelvic lymphadenectomy should be reserved for patients with involved inguinal lymph nodes (Stehman, 2007).

2.2 Morbidity of en Bloc Butterfly Resection

Although the en bloc resection resulted in reported cure rates of 80 to 90% for patients with stage I disease and exceeding 90% in cases without lymph node involvement (Hacker, Berek, Lagasse, Leuchter, & Moore, 1983; Podratz, Symmonds, Taylor, & Williams, 1983), the technique had high reported morbidity rates. The reported morbidities after en bloc resection included wound breakdown and/or infection (18 to 91%), chronic leg edema (8 to 70%), lymphocyst formation (0 to 31%), genital prolapse (0 to 14%), stress incontinence (0 to 12%), thrombophlebitis (0 to 9%), grafting skin flaps (0 to 24%), inguinal or femoral hernia (0 to 5%), pulmonary embolism (0 to 3%), ruptured femoral artery (0 to 5%), and hospital deaths (0 to 12%) (C. Morrow & Townsend, 1987), with the overall morbidity of 85% in the treated patients (Sultana & Naz, 2007).

3 The Triple Incision Technique as a Primary Operative Treatment

As a result of the aggressive nature of en bloc butterfly resection of the vulva and the inguino-femoral lymph nodes, with the very high reported primary morbidity rates, a modification of the technique was suggested (DiSaia, Creasman, & Rich, 1979). The aim of this modification is to remove the primary tumor, and as radically as is required, to remove the inguinal lymph nodes superficial to the cibriiform fascia through a separate incision, preserving vulval and inguinal tissues as much as possible. If the superficial lymph nodes are involved, the group of lymph nodes deeper than the cibriiform fascia are then removed. The outcome and survival, as reported, are comparable to the more radical en bloc resection (DiSaia et al., 1979; Helm et al., 1992). Hence, the triple incision technique offers a less radical approach without sacrificing outcome, with less reported morbidity.
3.1 The Operative Technique

As originally described, the operative technique comprises three incisions, one for each groin and a separate incision for the radical vulvectomy. The superficial group of inguinal lymph nodes is removed first and sent for frozen section examination. If it is not involved, the procedure then comes to an end. If the superficial group of lymph nodes is involved, the deep group of lymph nodes along the femoral vessels should also be removed. No intentional attempts are made to preserve the great saphenous vein even if the cribiform fascia is not opened or removed (Berman, Soper, Creasman, Olt, & Disaia, 1989; DiSaia et al., 1979; Hacker, Leuchter, Berek, Castaldo, & Lagasse, 1981). Some authors reported, however, a complete inguinofemoral lymphadenectomy, removing both the superficial and the deep group of lymph nodes, as a part of the standard technique, not employing the superficial group of lymph nodes as a sentinel for the deep group (Gaarenstroom et al., 2003; Soliman, Heubner, Kimmig, & Wimberger, 2012). Figure 2 shows the boundaries of the superficial inguinofemoral lymphadenectomy as presented by (Stehman, 2007).

Figure 2: A diagram showing the boundaries of superficial inguinofemoral lymphadenectomy (Stehman, 2007).

Inguinofemoral lymphadenectomy is performed through a skin incision between the anterior superior iliac spine and the pubic tubercle, parallel to the inguinal ligament and with a length of 8 to 10 cm. The superficial part of the lymphadenectomy involves removal of the superficial inguinal lymph nodes that lie within the superficial fascial compartment of the groin and surround the branches of the saphenous vein. The anatomic boundaries of the su-
perficial lymphatic dissection are the inguinal ligament superiorly, the border of the sartorius muscle laterally, the border of the adductor longus muscle medially, and the superficial subcutaneous fascia anteriorly. The deep femoral nodes are approached by opening the cribiform fascia along the sartorius muscle and mobilizing the fascia medially as a part of the specimen or by splitting the fascia lata longitudinally over the proximal femoral vessels. Once the femoral vein is identified and dissected free, the deep nodes that lie mainly medial to the femoral vein beneath the cribiform fascia are removed. These tissues are removed along with the cribiform fascia just below the inguinal ligament till about 2 cm proximal to the beginning of Hunter’s canal when the femoral vessels are crossed by the Sartorius muscle. At the conclusion of the groin dissection, a suction drain is left in situ and the wound is closed in two layers (Soliman et al., 2012).

Radical vulvectomy in the triple incision technique commences on the mons and extends posteriorly along the labial crural folds to the perineum. The medial incision extends around the vaginal mucosa at the introitus and anterior to the urethra. The vulva is resected to the level of the fascia overlying the urogenital diaphragm (total deep vulvectomy) (Siller et al., 1995). Table 1 shows a scheme of the operative management of vulvar cancer according to its stage.

<table>
<thead>
<tr>
<th>Vulvar cancer stage</th>
<th>Management</th>
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<tbody>
<tr>
<td>T1a</td>
<td>Wide local excision</td>
</tr>
<tr>
<td>T1b</td>
<td>Vulvectomy, Lymph node dissection Ipsilateral, contralateral if &lt; 1 cm from midline (triple incision). Sentinel lymph node procedure could be offered.</td>
</tr>
<tr>
<td>Locally advanced</td>
<td>Patient tailored according to the infiltrated organ</td>
</tr>
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</table>

Table 1: Operative management of vulvar cancer according to stage.

Modification of the vulvar dissection to radical local excision or heimvulvectomy, according to the size and site of the presenting tumor, reduces local morbidity, with no increase in local recurrence (Burrell, Franklin, Campion, Crozier, & Stacy, 1988; Leminen, Forss, & Paavonen, 2000; Lin et al., 1992). From the 1990s and till now, modified radical vulvectomy and bilateral inguinosfemoral lymphadenectomy using separate incisions is the most appropriate form of surgical management for the majority of patients presenting with early stage vulvar cancer (Griffiths, Silverstone, Tobias, & Benjamin, 1997). Regardless of which surgical procedure is adopted for the vulvar lesion, i.e., radical vulvectomy or wide local excision, a minimal intraoperative macroscopic safety margin of 10 mm should be achieved, in order to ensure that the 8 mm margins required for the pathological examination to assign the specimen margins as tumor-free are still reachable even after artifacts from shrinkage during specimen fixation (Heaps, Fu, Montz, Hacker, & Berek, 1990).

In a Cochrane review comparing en bloc radical resection to the triple incision technique, the authors concluded that radical local excision, ipsilateral lymph node dissection for lateral tumors, and the triple incision technique with bilateral lymph node dissection for midline tumors are safe treatment options for early vulvar cancer (Ansink & van der Velden, 2000). However, superficial groin node dissection resulted in an excess of groin recurrences compared with a full inguinosfemoral lymphadenectomy.
3.2 Morbidity of the Triple Incision Technique

Despite modifications of the technique, the triple incision technique still has high morbidity rates. The morbidity rates are much lower than those reported after en bloc resection, but they are high enough to affect the quality of life of the patients in the long term. The morbidity rates of this technique and the possible factors affecting their development have been reported by many groups. In a report concerning the complications of inguinofemoral lymphadenectomy and the predictors of their development, the authors demonstrated a variety of postoperative problems but could not highlight a single factor as a predictor of occurrence of complications (Gould et al., 2001). In this retrospective cohort of 67 vulvar cancer patients who received triple incision as primary operative treatment, early postoperative cellulitis developed in 35.4% while late cellulitis developed in 22.2%. Early wound breakdown occurred in 19.4%, late wound breakdown developed in 3.2%, early lymphedema occurred in 4.8%, and 29.5% developed late lymphedema. A total of 13.1% of patients developed early lymphocysts while 5% developed late lymphocysts. Patients who developed early cellulitis were more likely to have early wound breakdown (p < 0.001) or early lymphocyst formation (p < 0.02). The type of procedure, postoperative prophylactic antibiotic use, need for adjuvant therapy, and duration of suction drainage did not significantly influence the incidence of early cellulitis. Late cellulitis was unaffected by early cellulitis, early wound breakdown, type of procedure, use of prophylactic antibiotics, duration of suction drainage, and need for adjuvant therapy (Gould et al., 2001). These results are summarized in Table 2.

<table>
<thead>
<tr>
<th>Wound cellulitis</th>
<th>35.4%</th>
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<tr>
<td>Wound breakdown</td>
<td>19.4%</td>
</tr>
<tr>
<td>Wound seroma</td>
<td>13.1%</td>
</tr>
<tr>
<td>Early lower limb lymphedema formation</td>
<td>4.8%</td>
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</table>

Table 2: Frequency of complications after inguinofemoral lymphadenectomy (Gould et al., 2001).

In a retrospective cohort of 194 patients, another report concluded that preservation of the fascia lata and saphenous vein in inguinofemoral lymphadenectomy was associated with a decreased risk of postoperative morbidity, without jeopardizing outcomes (Rouzier, Haddad, Dubernard, Dubois, & Paniel, 2003). Table 3 shows the frequency of distribution of cellulitis, wound breakdown, and lymphedema in this cohort and the correlation with possible factors affecting their development.

A recent retrospective cohort of 67 operated groins showed an incidence of wound cellulitis of 24.2%, while 9.7% developed wound breakdown, 12.5% developed wound seroma, and 3.2% developed wound infection; 4.8% developed early limb lymphoedema while on long-term follow-up and 21.4% showed lower limb lymphedema (Soliman et al., 2012). Table 4 shows the frequency of occurrence of simultaneous complications in the same groin (Soliman et al., 2012).

Another report studying the same issue reported retrospectively from a cohort of 101 patients that as many as 66% of the patients suffered one or more complications following groin dissection (Gaarenstroom et al., 2003). Wound breakdown of the groin, lymphocyst formation, infection, and lymphedema were noted in 17%, 40%, 39%, and 28% of the patients,
respectively. Regarding the rate of complications per groin, the incidence was 11%, 27%, 27%, and 21%, respectively. The study also reported that the occurrence of early complications after groin dissection such as wound breakdown, lymphocyst formation, and infection was significantly related to the occurrence of late lymphedema (p = 0.002). Of the 187 complete inguinofemoral lymph node dissections reported in this study, the great saphenous vein was ligated in 150 groins, preserved in 19 groins, and the status was unknown in 18 groins. The overall complication rate of the groin dissection was not significantly related to removal of the saphenous vein. In particular, the development of lymphedema showed no relationship with ligation or removal of the vein. Table 5 shows a comparison of the three relatively recent case series reporting on the incidence of wound complications of the triple incision technique for vulvar cancer.

The above-mentioned reports studied, in addition to the rates of development of morbidities after inguinofemoral lymphadenectomies, factors that may lead to the development of inguinal wound and lower limb morbidities. Unfortunately, no single factor was found to be directly related to the development of complications; thus, the practice cannot be selectively changed in order to avoid the development of wound morbidity. The studied factors were cardiovascular disorders, diabetes, amount of intraoperative blood loss, number of infiltrated lymph nodes, saphenous vein ligation, number of removed lymph nodes, duration of suction drainage, and amount of exudate accumulated in the drains (Gaarenstroom et al., 2003;
Table 5: Comparison of the incidence of wound complications in the published case series of the triple incision technique for vulvar cancer (Gaarenstroom et al., 2003; Gould et al., 2001; Soliman et al., 2012).

<table>
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<tbody>
<tr>
<td>Wound cellulitis</td>
<td>24.2% (n = 15)</td>
<td>Not studied</td>
<td>35.4%</td>
</tr>
<tr>
<td>Wound breakdown</td>
<td>9.7% (n = 6)</td>
<td>11% (n = 21)</td>
<td>19.4%</td>
</tr>
<tr>
<td>Wound seroma</td>
<td>12.5% (n = 8)</td>
<td>27% (n = 50)</td>
<td>13.1%</td>
</tr>
<tr>
<td>Wound infection</td>
<td>3.2% (n = 2)</td>
<td>27% (n = 51)</td>
<td>Not studied</td>
</tr>
<tr>
<td>Early lower limb lymphedema formation</td>
<td>4.8% (n = 3)</td>
<td>21% (n = 40)</td>
<td>4.8%</td>
</tr>
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</table>

Soliman et al., 2012). However, development of early lower limb edema was related to development of long-term lower limb edema (Gaarenstroom et al., 2003; Gould et al., 2001; Soliman et al., 2012).

3.3 Modifications of the Triple Incision Technique Aimed at Decreasing Morbidity

Modifications have been introduced in an attempt to decrease the morbidity of the triple incision. One of these modifications is preservation of the great saphenous vein during the groin operation. In a prospective study on 64 patients, 31 of them received a vein-sparing groin operation while in 33 patients, the vein was ligated or excised. The key process of the saphenous vein-sparing technique is to dissect the saphenous vein trunk in its way to the sapheno-femoral junction during superficial inguinal lymphovascular fat tissue removal and then to spare it. When the saphenous vein affects exposure of the operative area during deep inguinal node excision, it should be pulled aside using a vein retractor rather than being severed or excised (Zhang et al., 2007). The reported complications from this study are summarized in Table 6.

Table 6: Comparing the incidence of complications in the saphenous vein-sparing and saphenous vein excision groups. *p < 0.05 is statistically significant (Zhang et al., 2007).

<table>
<thead>
<tr>
<th>Complication</th>
<th>Sparing</th>
<th>Acute cellulitis</th>
<th>Seroma</th>
<th>Acute low extremity phlebitis</th>
<th>Lymphocele</th>
<th>Acute lymphedema</th>
</tr>
</thead>
<tbody>
<tr>
<td>Postoperative fever</td>
<td>96.8%</td>
<td>67.7%</td>
<td>30.6%</td>
<td>11.3%</td>
<td>25.8%</td>
<td>43.5%</td>
</tr>
<tr>
<td>Acute cellulitis</td>
<td>96.8%</td>
<td>67.7%</td>
<td>30.6%</td>
<td>11.3%</td>
<td>25.8%</td>
<td>43.5%</td>
</tr>
<tr>
<td>Seroma</td>
<td>93.9%</td>
<td>72.7%</td>
<td>37.9%</td>
<td>25.8%</td>
<td>31.8%</td>
<td>66.7%</td>
</tr>
<tr>
<td>Acute low extremity phlebitis</td>
<td>&gt;0.05</td>
<td>&gt;0.05</td>
<td>&gt;0.05</td>
<td>&lt;0.05*</td>
<td>&gt;0.05</td>
<td>&lt;0.01*</td>
</tr>
<tr>
<td>Lymphocele</td>
<td>93.9%</td>
<td>72.7%</td>
<td>37.9%</td>
<td>25.8%</td>
<td>31.8%</td>
<td>66.7%</td>
</tr>
<tr>
<td>Acute lymphedema</td>
<td>93.9%</td>
<td>72.7%</td>
<td>37.9%</td>
<td>25.8%</td>
<td>31.8%</td>
<td>66.7%</td>
</tr>
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</table>

The findings of this report, however, contradict the findings of two reports that studied retrospectively the morbidity of inguinofemoral lymphadenectomy and the factors that might affect its development and found no correlation between saphenous vein ligation/preservation and the development of any type of groin complications (Gaarenstroom et al., 2003; Soliman et al., 2012). Another operative modification aimed at decreasing groin wound complications was addressed through a randomized controlled trial that assessed whether different cutaneous skin flap dissection above or below the inguinal ligament would reduce groin wound complications (Manci et al., 2009). This prospective randomized clinical trial of 62 consecutive patients affected by vulvar carcinoma requiring inguinial lymphadenec-
tomy compared skin inguinal incision carried out 3 to 4 cm above the inguinal ligament (group A) and that carried out below it (group B). Inguinal dehiscence was present in 32.1% of patients in group B and in 16.7% of patients in group A (p = 0.10). Lymphocele was observed in 18.9% of lymphadenectomies in group B and in 5.6% of dissections in group A (p = 0.07). Upper incision allows more precise identification of the Camper’s fascia, is less painful, and gives better cosmetic results. Moreover, there may be other advantages, albeit not statistically significant, regarding wound dehiscence rate and speed of wound healing. The study concluded that there was no difference in chronic leg edema, number of nodes removed, or hospital stay when adopting the new incision site.

In an attempt to decrease morbidity, Bell et al. (2000) performed the lymphadenectomy with preservation of the fascia lata and cribriform fascia superficial to the femoral vessels. The main aim was to assess the recurrence rates after this procedure. They reported low incidence rates of lymphedema (13%) and lymphocyst (15%) in their retrospective cohort of 60 patients. The groin recurrence rate was, however, 7.6% in patients with fewer than three involved lymph nodes. The study concluded that the zero groin recurrence rate in patients with negative nodes and the low rate of recurrence in patients with positive nodes indicated that groin lymphadenectomy with preservation of the fascia lata was complete, therapeutic, and comparable to radical techniques of lymphadenectomy involving skeletonization of femoral vessels, resection of the fascia lata, and muscle transposition.

Another modification to the operative technique was studied in a randomized controlled prospective trial in 61 patients and 99 operated groins, comparing transposition of the sartorius muscle versus non-transposition in an attempt to decrease postoperative groin morbidity (Judson et al., 2004). The results revealed, however, that there were no statistically significant differences in the incidence of wound cellulitis, wound breakdown, lymphedema, or re-hospitalization. The incidence of lymphocyst formation was increased in the sartorius transposition group. After adjusting for age, however, the groups appeared similar. The study concluded that sartorius transposition after inguinofemoral lymphadenectomy did not reduce postoperative wound morbidity.

Modifications to the triple incision technique were not only limited to the operative steps. A randomized gynecologic oncology group (GOG) trial used a fibrin sealant in order to decrease the incidence of lower extremity edema following inguinofemoral lymphadenectomy (Carlson et al., 2008). A total of 150 patients were enrolled into the study and randomized to receive standard closure (SC) of the wound using sutures or the VH fibrin sealant (FS) (Tisseel®, Baxter Healthcare Corporation, Glendale, CA, USA) followed by suture closure. The incidence of grade 2 and 3 lymphedema was 67% in the SC arm and 60% in the FS arm (p = 0.478). At the 6-week assessment, 48% of the patients demonstrated grade 2 or worse lymphedema. The frequency of grade 2 or 3 lymphedema increased to 57% at 3 months and 63.5% at 6 months. Among those patients who developed a grade 2 or 3 lymphedema, 75.9% had done so by 6-week follow-up and 90.8% by the 3-month follow-up. The overall complication rate was 59% for patients in the SC arm and 61% for those in the FS arm. The overall incidence of inguinal infections was 35% in the SC arm and 36% in the FS arm. The incidence of inguinal wound breakdown was 13% in both treatment arms. The number of patients who had either a grade 3 or grade 4 inguinal infection was also similar between the SC (n = 8) and FS (n = 7) arms. The incidence of either a grade 3 or grade 4 vulvar infection was the same (n = 3) in both arms. The study concluded that postoperative lymphedema at 6 months was not affected by utilization of a fibrin sealant in the inguinal wound.
Madhuri et al. used a Plasmajet® hand piece to seal the groin lymphatics after inguino-femoral lymphadenectomy with saphenous vein preservation, and suggested this method could promise decreasing the rate of postoperative wound complications (Madhuri, Tailor, & Butler-Manuel, 2011).

Moreover, the laparoscopic approach to inguino-femoral lymphadenectomy, which is reported for managing penile carcinoma, may provide an acceptable treatment modality with lower complications rate (Pompeo et al., 2013; Tobias-Machado et al., 2007; Yuan et al., 2014). The data as regard this technique is however not yet mature to consider it a standard procedure.

As demonstrated above, many modifications have been introduced to the technique of triple incision. However, they have failed to improve the morbidity rates. Nevertheless, the technique remains, to date, the recommended standard operative therapy. Despite these failed attempts to decrease the morbidity, further trials were conducted to find a better therapeutic option for patients suffering early vulvar cancer. These trials and new modalities are discussed in the next section.

4 The Sentinel Lymph Node Technique in Vulvar Cancer: Lower Morbidity without Compromising the Oncological Outcome

The triple incision technique as introduced by (DiSaia et al., 1979) considered the superficial inguinal group of lymph nodes as a 'sentinel' group of nodes for the whole groin. When this group is involved, a full inguino-femoral clearance is necessary. The aim of introducing this surgical technique was less radicality, with consequently less morbidity without sacrificing oncological outcome. Based on the reports about the sentinel lymph node technique in cutaneous melanoma, (Levenback et al., 1994) published the results of their pilot study examining the feasibility of sentinel lymph node examination for vulvar cancer patients. They recruited nine patients in whom 12 groins were examined. They used blue dye and succeeded in identifying seven of 12 sentinel lymph nodes. Moreover, one positive non-sentinel lymph node was identified in a sentinel-negative patient. They concluded that intraoperative lymphatic mapping was technically feasible in patients with vulvar cancer, particularly those with unilateral disease. They recommended further studies be designed to gain more experience with this technique. Since then, the technique has been applied in breast cancer with high accuracy (Mansel et al., 2006) and improved quality of life of patients (Lucci et al., 2007; Purushotham et al., 2005). Many study groups are interested in examining the sentinel technique in vulvar cancer in order to improve the morbidity rates after a formal inguino-femoral lymphadenectomy and hence the quality of life of the patients. The motive for these studies, besides the high rate of postoperative complications for a systematic inguino-femoral lymphadenectomy, is that only 25 to 35% of patients with early stage disease will have lymph node metastases, and the remaining 65 to 75% of patients are unlikely to benefit from elective inguino-femoral lymphadenectomy but will be at risk for its significant morbidity (Bell, Lea, & Reid, 2000; Hacker et al., 1981).

Although some early reports about this new technique were very promising, with a 100% success rate in detecting sentinel lymph nodes and 0% false negative rates (De Cicco et
al., 2000), some authors were skeptical about it. In a prospective trial of the GOG in 121 patients with early stage vulvar cancer (Stehman, Bundy, Dvoretsky, & Creasman, 1992), the authors questioned the benefit of the sentinel procedure concerning recurrence in the groins that did not receive a formal inguinofemoral lymphadenectomy based on a negative sentinel lymph node procedure, as originally described by (DiSaia et al., 1979). The groin recurrence in this report was almost always fatal; five of the seven patients with groin recurrence passed away.

In their study in 37 patients with a total of 55 operated groins, (De Cicco et al., 2000) aimed to verify the predictive value of the sentinel lymph node status in a larger series of patients. They used technetium-99m-labeled colloid human albumin administered perilesionally 1 day before surgery to perform lymphoscintigraphy of the groin, and used a gamma-detecting probe intraoperatively to find sentinel lymph nodes. An inguinofemoral lymphadenectomy was performed regardless of the results of the sentinel mapping. As mentioned above, they reported a 100% detection rate of sentinel lymph nodes and a 0% false negative rate. They concluded that this technique was an easy and reliable method for the detection of sentinel nodes in early vulvar cancer. This technique may represent a true advance in the direction of less aggressive treatments in patients with vulvar cancer. The high accuracy and negative predictive value are attributed to using lymphoscintigraphy, applying strict quality control steps while performing the sentinel procedure, and using step section and immunohistochemistry in the examination of the sentinel lymph nodes by the pathologist.

In 51 patients in which blue dye was used to identify sentinel lymph nodes, (Ansink et al., 1999) reported a very low detection rate of only 56%, with a relatively high false negative rate (two false negative sentinels), rendering the technique unreliable. There is no consensus on which technique is better to use. Some authors advocate the use of blue dye alone (M. Morrow et al., 1999), while others advocate the use of radioactive isotope alone (Levenback et al., 2001) or a combination of both (de Hullu et al., 2004).

The detection rate and false negative rate of the sentinel procedure remain controversial. In a multicenter prospective study, Hampl et al. recruited 127 patients suffering T1 to T3 vulvar cancers, performed a sentinel lymph node biopsy uni- or bilaterally, according to the tumor location from the midline, then performed a formal inguinofemoral lymphadenectomy to examine the detection rate of the sentinel node procedure with consecutive standard inguinofemoral lymphadenectomy, to determine the sensitivity and specificity of the method to predict the final lymph node status. The study evaluated the negative predictive value of the procedure and investigated a potential correlation between tumor location and accuracy of the procedure. Patients harboring negative sentinel lymph nodes received a step-sectioning and additional immunohistochemical staining by the pathologist to increase the detection rate of micrometastasis. The authors used both lymphoscintigraphy and blue dye to detect sentinel lymph nodes. The overall detection rate of sentinel lymph nodes was 99.1% and the detection rate was 98.3% for solely technetium-labeled sentinels. The reported sensitivity was 92.3% and false negative rate was 7.7%. Based on their results, the authors issued some recommendations, which agreed with the recommendations of the 6th Biennial International Sentinel Node Society Meeting in Australia, February 2008 (personal communication), that gynecologic oncologists should perform at least 10 groin dissections with successful identification of sentinel lymph nodes and no false negative sentinel lymph nodes before performing lymph node biopsy on their own. They also recommended performing the sentinel lymph
node identification only in patients with tumors smaller than 4 cm. In case of a midline tumor, sentinel lymph nodes should be identified in both groins. If sentinel lymph nodes are not identified or any doubt exists regarding the correlation between a preoperative lymphoscintigram and the operative findings, the sentinel procedure should be abandoned and a formal inguinofermal lymphadenectomy should be performed. A suspicious non-sentinel node should always be resected. They finally recommended ultrastaging for all removed sentinel lymph nodes (Hampl et al., 2008b).

The ultimate goal of oncologic surgery is to reach complete cure, represented by high overall survival and progression-free survival rates. Johann and coworkers compared retrospectively long-term outcomes of the sentinel lymph node procedure to those of a formal inguinofermal lymphadenectomy. In this study, they analyzed data from 114 operated groins, with a sentinel detection rate of 95%, and a false negative rate of 2.2%. The median follow-up for patients who received a sentinel lymph node procedure and for those who received a formal inguinofermal lymphadenectomy was 24 months and 111 months, respectively. Figure 3 shows the rate of development of local morbidity in the group that received a sentinel lymph node procedure and the group that received a lymphadenectomy (Johann et al., 2008). Figure 4 shows the recurrence rate in both groups.

![Figure 3: Percentage of development of lower limb complications after the sentinel procedure (white bar) and inguinofermal lymphadenectomy (gray bar) (Johann, Klaeser, Krause, & Mueller, 2008).](image1)

![Figure 4: Rate of recurrence after the sentinel procedure (white bar) and inguinofermal lymphadenectomy (gray bar) (Johann et al., 2008).](image2)
Based on these results, the authors concluded that sentinel lymphadenectomy could be considered a feasible, accurate, and reliable method in a clinical routine setting for identifying nodal negative patients in vulvar cancer who will not benefit from a complete inguinofemoral lymphadenectomy (Johann et al., 2008). They also concluded that the risk of groin relapse was not elevated after the sentinel procedure. Moreover, their results demonstrated that the risk of leg edema as a treatment-related morbidity after the sentinel lymph node procedure was considerably lower than that after inguinofemoral lymphadenectomy.

(Van der Zee et al., 2008) conducted the largest prospective multicenter trial on the sentinel lymph node procedure, examining the accuracy, safety, local recurrence, and long-term outcome. A multicenter observational study on sentinel node detection using radioactive tracer and blue dye was performed in patients with T1/2 (< or = 4 cm) squamous cell cancer of the vulva. When the sentinel node was found to be negative at pathologic ultrastaging, inguinofemoral lymphadenectomy was omitted, and the patient was observed with a follow-up of 2 years every 2 months. Stopping rules were defined for the occurrence of groin recurrences. The sentinel node procedure was performed in 623 groins of 403 assessable patients. In 259 patients with unifocal vulvar disease and a negative sentinel node (median follow-up time, 35 months), six groin recurrences were diagnosed (2.3%), and 3-year survival rate was 97%. Short-term morbidity was decreased in patients after sentinel node dissection compared with patients with a positive sentinel node who underwent a subsequent inguinofemoral lymphadenectomy (wound breakdown in groin: 11.7% vs. 34.0%, respectively, p < 0.0001; and cellulitis: 4.5% vs. 21.3%, respectively, p < 0.0001). Long-term morbidity was also less frequently observed after removal of only the sentinel node compared with sentinel node removal and inguinofemoral lymphadenectomy (recurrent erysipelas: 0.4% vs. 16.2%, respectively, p < 0.0001; and lymphedema of the legs: 1.9% vs. 25.2%, respectively, p < 0.0001). This data is summarized in table 7.

<table>
<thead>
<tr>
<th></th>
<th>Sentinel</th>
<th>Inguinofemoral systematic lymphadenectomy</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wound breakdown</td>
<td>11.7%</td>
<td>34%</td>
<td>p &lt; 0.0001</td>
</tr>
<tr>
<td>Cellulitis</td>
<td>4.5%</td>
<td>21.3%</td>
<td>p &lt; 0.0001</td>
</tr>
<tr>
<td>Recurrent erysipelas</td>
<td>0.4%</td>
<td>16.2%</td>
<td>p &lt; 0.0001</td>
</tr>
<tr>
<td>Lymphedema</td>
<td>1.9%</td>
<td>25.2%</td>
<td>p &lt; 0.0001</td>
</tr>
</tbody>
</table>

Table 7: Rate of complications compared between sentinel and systematic inguinofemoral lymphadenectomy. p < 0.05 is statistically significant(Van der Zee et al., 2008).

Based on these results, the authors concluded that in early stage vulvar cancer patients with a negative sentinel node, the groin recurrence rate was low, survival was excellent, and treatment-related morbidity was minimal. They even suggested that sentinel node dissection, performed by a quality-controlled multidisciplinary team, should be part of the standard treatment in selected patients with early stage vulvar cancer. In a subsequent analysis of a subset of the patients recruited to the study by (Van der Zee et al., 2008), (Oonk et al., 2009) performed a questionnaire on the quality of life after a sentinel procedure in comparison with that after a sentinel procedure followed by inguinofemoral lymphadenectomy due to positive lymph nodes. They found that patients who underwent a sentinel procedure alone reported
less treatment-related morbidity compared with patients who underwent inguinofemoral lymphadenectomy, but this did not influence the overall quality of life. Patients who underwent the sentinel procedure without inguinofemoral lymphadenectomy were more content with the procedure they underwent and were more likely to recommend this new treatment option to relatives, probably because they themselves experienced the benefits of the new procedure. On the other hand, the patients who received an inguinofemoral lymphadenectomy after a sentinel procedure due to a positive lymph node were probably not going to recommend the new procedure to their relatives, for fear of false negative results.

Although pathological ultrastaging of the retrieved inguinofemoral lymph nodes using the sentinel technique is recommended from some authors (Sutton et al., 2013; Van der Zee et al., 2008), the role of HPV genetic material testing during frozen section and its role in adding more accuracy in detecting metastasis in inguinofemoral lymph nodes can be investigated as it proved useful in the field of cervical cancer as reported by some authors (Noventa, Ancona, Cosmi, et al., 2014; Noventa, Ancona, Saccardi, et al., 2014)

As discussed in this text, the treatment of vulvar cancer has evolved from a more radical procedure to a less radical one through the years, aimed at decreasing morbidity without compromising survival outcomes. It seems that the sentinel lymph node procedure, with its remarkable accuracy, low morbidity, and survival outcomes that are comparable to those of the triple incision technique, may slowly become the standard surgical option in early stage vulvar cancer and replace the current standard of the triple incision technique. This can be achieved after gaining enough experience with the technique, accurately detecting sentinel lymph nodes, accurately ultrastaging them pathologically, and minimizing the false negative rate to almost nil.

References


