

RESEARCH ARTICLE

Early and Late Complications after Inguinofemoral Lymphadenectomy for Vulvar Cancer

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Abstract

Background: We aimed to determine the frequency of early and late complications following groin surgery for vulvar cancer and analyze possible risk factors. **Materials and Methods:** This retrospective cohort study included 99 women who underwent for vulvar cancer. The early (≤ 1 month) complications were wound infection, breakdown and lymphocyst and late (> 1 month) complications were lower limb lymphedema, incontinence and erysipelas. The risk factors for developing each of the complications were analyzed with regression analysis. **Results:** In the entire cohort, 29 (29.3%) women experienced early and 12 (12.1%) had late complications. Wound complications including infection and breakdown were the leading early complications (23.2%). In the multivariate analysis, both obesity (body mass index ≥ 30 kg/m²) and advanced age (≥ 65 years) were found as independent predictive factors for early complications. Obese women of advanced age had 6.32 times more risk of experiencing any of the early complications, when compared to non-obese and young women (55.6% vs 8.7%). The most common late complication was lower limb lymphedema (10.1%) that was more frequently seen in young women. However, neither age nor lymph node count were significantly associated with the occurrence of lower limb lymphedema. **Conclusions:** More than 40% of the women suffered from postoperative complications after inguinofemoral lymphadenectomy in the current study. While advanced age and obesity were the significant predictors for any of the early complications, there was no identified risk factor for lower limb lymphedema.

Keywords: Vulvar cancer - complication - inguinofemoral lymphadenectomy

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Introduction

Vulvar cancer is the fourth most common genital tract cancer that accounts for approximately 5% of all female gynecological cancers (Siegel et al., 2014). Quality of life scores especially, emotional and social function scores in vulvar cancer were also the lowest among all gynecologic cancer (Goker et al., 2011). Recent population based studies showed that all HPV-related cancers including vulvar cancer continued to increase in incidence over the last three decades (Shack et al., 2014). Fortunately, vulvar cancer is usually diagnosed in its earlier stages and is usually treated only with surgery with adjuvant therapy added when necessary. Standard surgical treatment of vulvar cancer consists of vulvar tumor resection and inguinofemoral lymphadenectomy (IFLND) (Levenback et al., 1996; De Hullu et al., 2004). In the late 1980s, surgical complications after IFLND had been occurring with up to 85% incidence with en bloc resection and had a significant effect on the life quality of women (Podratz et al., 1983; Gaarenstroom et al., 2003).

Promisingly, introduction of the triple incision technique significantly decreased the complication rates. However, 17-49% of women still suffer from various early and late complications after lymphadenectomy (Gould et al., 2001; Angela et al., 2013) Sentinel node procedure was recently introduced as an alternative to IFLND for decreasing the complication rate. And using sentinel node procedure instead of standard IFLND significantly reduced the postoperative complications (Van der Zee et al., 2008). However, the efficacy of the sentinel node procedure has only been illustrated for unifocal tumors less than 4 cm and the other 50% of women with vulvar cancer still need IFLND (Hinten et al., 2011).

Many oncology centers still perform IFLND as a standard procedure for groin lymph node assessment and the post-operative complications not only threaten women's health but also bring additional economic burdens to the country. Therefore, we determined early and late complications that develop after IFLND for vulvar cancer and risk factors related to patient, tumor and surgical characteristics.

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Materials and Methods

Patients' characteristics

Data of 136 women who underwent lymphadenectomy for vulvar cancer between February 1991 and May 2013 in the Gynecologic Oncology Department of our institution were reviewed. Thirty-seven women who did not undergo IFLND due to having stage IA disease (n=7), refusal of surgery (n=6), having pulmonary disease that did not permit general anesthesia (n=1), having first had surgery in another center (n=1) and having primary chemoradiotherapy for advanced stage disease (n=22) were excluded from the study. The remaining 99 women were included for further analysis in the study. The recruited data were the women's age, body mass index (BMI), tumor size, depth of tumor invasion, the type of vulvar surgery, presence of uni-bilateral lymphadenectomy, the number of total and metastatic lymph nodes and the presence of adjuvant therapy.

Treatment protocol

According to our clinical protocols, women were given dual intravenous antibiotic prophylaxis (plus low dose heparin in high-risk patients) for at least five days starting from the operation day. Excision of the vulvar tumor was performed via wide local excision, hemivulvectomy and radical vulvectomy. Wide local excision was performed on women who had resectable tumors with 2 cm tumor-free margin. Other women underwent hemivulvectomy

or radical vulvectomy according to the location, size and histologic type of tumor. The triple incision technique was the method of choice for all participants. The IFLND procedure consists of the removal of both superficial and deep inguinal lymph nodes. All subcutaneous tissue was also removed until the fascia lata in this procedure. Saphenous vein was preserved when possible. The adipose tissue medial to the femoral vessels was also resected during the femoral lymphadenectomy procedure. One vacuum drain was subcutaneously placed in each inguinal region after lymphadenectomy and daily drainage was monitored.

The incisions were closed without tension, ice was applied to wounds in the recovery room, and this ice application was continued up to 72 hours after operation. Later, cleaning the wounds with showerhead and immediate drying with blow dryer was performed. These procedures were done to keep the groin warm, clean and dry, repeated three times a day and continued until the wound healed. An additional compression dressing was kept on the groins for up to 48 hours to prevent lymphocyst formation. The women's drains were removed when the drainage fell below 50cc. On the day of the operation, women were provided with an elastic stocking, which they continued to use until the day of discharge. After discharge, patients were told about the danger signs for early and late complications and called for a control visit one month later. Other routine follow-up visits were done every three months in the first two years, every six months for five years and then annually. The early complications that occurred within one month of the operation were wound infection, wound breakdown and lymphocyst. And the late complications that occurred after one month but within one year following the surgery were lower limb lymphedema, erysipelas and urinary incontinence.

Table 1. Early and Late Post-operative Complications after Inguinofemoral Lymphadenectomy for Vulvar Cancer (n=99)

Complications	n	%
Early (< 1 month)		
Wound infection	9	22.0
Wound breakdown	15	36.6
Lymphocyst	6	14.6
Late (> 1 month)		
Lower limb lymphedema	9	22.0
Incontinence	1	2.4
Erysipelas	1	2.4
Total	41	100

Table 3. Multivariate Analysis of the Variables Associated With Early Complications of Vulvar Cancer

Variables	P value	OR	95% CI
Age (<65 years vs ≥65 years)	0.037	3.02	1.07- 8.51
Obesity (BMI<30 kg/m ² vs ≥30 kg/m ²)	0.009	3.63	1.38- 9.54

Table 2. The Impact of Patients and Tumor Characteristics, Surgery and Adjuvant Therapy on Early Postoperative Complications: an Univariate Analysis

Parameters		Wound complication		Early complications	
		OR (%95 CI) ¹	n	OR (%95 CI)	n
Age	<65 years	1.0 (Ref)	39	1.0 (Ref)	39
	≥65years	2.91 (0.98-8.66)	60	2.65 (1.0-6.99)*	60
Body mass index	<30 kg/m ²	1.0 (Ref)	62	1.0 (Ref)	62
	≥30 kg/m ²	2.29 (0.87-6.04)	31	3.21 (1.28-8.08)*	31
Tumor location	Midline	1.0 (Ref)	46	1.0 (Ref)	46
	Lateral	0.68 (0.26-1.75)	53	0.61 (0.25-1.48)	53
Removed LN ² count	<22	1.0 (Ref)	52	1.0 (Ref)	52
	≥22	0.16 (0.19-1.33)	47	0.58 (0.24-1.40)	47
LN involvement	Negative	1.0 (Ref)	57	1.0 (Ref)	57
	Positive	0.72 (0.32-2.17)	42	0.77 (0.32-1.87)	42
Adjuvant therapy	No	1.0 (Ref)	54	1.0 (Ref)	54
	Yes	1.13 (0.45-2.88)	45	1.17 (0.49-2.80)	45

¹Odds ratio (confidence interval); ²Lymph node; *p value <0.05

Table 4. The Impact of Patients and Tumor Characteristics, Surgery and Adjuvant Therapy on Late Postoperative Complications: An Univariate Analysis

Parameters		Lower Limb Lymphedema		Late complications	
		OR (%95 CI) ¹	n	OR (%95 CI)	n
Age	<65 years	1.0 (Ref)	39	1.0 (Ref)	39
	≥65 years	0.29 (0.07-1.24)	60	0.42 (0.12-1.42)	60
Body mass index	<30 kg/m ²	1.0 (Ref)	62	1.0 (Ref)	62
	≥30 kg/m ²	3.82 (0.45-32.52)	31	2.46 (0.49-12.10)	31
Tumor location	Midline	1.0 (Ref)	46	1.0 (Ref)	46
	Lateral	2.50 (0.59-10.63)	53	1.72 (0.51-5.85)	53
Removed LN ² count	<22	1.0 (Ref)	52	1.0 (Ref)	52
	≥22	1.43 (0.36-5.67)	47	1.12 (0.34-3.75)	47
LN involvement	Negative	1.0 (Ref)	57	1.0 (Ref)	57
	Positive	3.00 (0.71-12.77)	42	1.42 (0.42-4.75)	42
Adjuvant therapy	No	1.0 (Ref)	54	1.0 (Ref)	54
	Yes	1.56 (0.39-6.20)	45	1.19 (0.35-4.05)	45

*¹Odds ratio (confidence interval); ²Lymph node

Statistics

Variables of the study were analyzed by using the SPSS (version 15.0 for windows, Chicago, IL, USA). Because the vast majority of the women underwent bilateral lymphadenectomy, all complications were calculated per patient. The relationship between complications and patients' characteristics, tumor characteristics and the surgical factors were analyzed by using univariate logistic regression model. The odds ratios were presented with 95% confidence interval. Multivariate logistic regression was used with forward selection method to identify the independent predictors of early and late complications of lymphadenectomy. Odds ratios were presented again with this method and cut-off value for statistical significance was accepted as 0.05.

Results

Clinical and pathological data

Median age of all participants was 61.2 years ranging from 30 to 84 years. Median BMI was 28.6 kg/m² and 33 women were obese (BMI ≥30). Tumor was located midline in 46 women, median tumor size was 20 mm (range: 2-80 mm) and median depth of tumor was 3 mm (range: 1-25 mm). The most commonly encountered histology was squamous cell carcinoma (n=91). Eight other women had non-squamous cell histology and the most frequent was malign melanoma (n=5). In the entire cohort, 82 women (82.8%) underwent radical vulvectomy, 12 had wide local excision and five had hemivulvectomy. Except one, all patients underwent bilateral IFLND and 57 (57.5%) had lymph node positivity. Median number of lymph nodes was 22 ranging from four to 66. Forty-five women had adjuvant therapy following surgery.

Postoperative complications

A total of 41 women suffered from postoperative complications after lymphadenectomy for vulvar cancer. Details of the complications are shown in Table 1. Twenty-nine women experienced early complications such as wound infection, breakdown and lymphocyst. The main early complication was wound complications including infection and breakdown, encountered in 23.2 % of the

entire cohort. In the univariate analysis, advanced age (≥65 years) and obesity (BMI ≥30 kg/m²) were identified as the significant predictors of any of the early complications (p=0.046 and p=0.011, respectively). Elderly women had 2.65 times more risk to experience any of the early complications and obese women had 3.21 times more risk in terms of early complications. Women who had both risk factors (advanced age and obesity) were detected to have 6.32 times more risk to experience any of the early complications, when compared to non-obese women aged less than 65 years (55.6% vs 8.7%). Advanced age was also a borderline predictor when only wound complications were considered (p=0.054). Obese women also had higher incidence of wound complication compared to non-obese women but it did not reach statistical significance (p=0.089). Univariate analysis of the risk factors for early lymphadenectomy complications are shown in Table 2. In the multivariate analysis, both advanced age and obesity were also confirmed as the independent predictors of early complications. Elderly women (≥65 years) had 3.02 times more risk to have any of the early complications after lymphadenectomy for vulvar cancer and obese women also had 3.63 times more risk in terms of any of the early complications (Table 3).

In the entire cohort, twelve (12.1%) women experienced any of the late complications. Lower limb lymphedema was the most common late complication of the women treated with lymphadenectomy for vulvar cancer. When the probable risk factors were analyzed, no significant risk factor was found for any of the late complications and only lower limb lymphedema in the univariate analysis. Although it was not significant, lower limb lymphedema was more commonly encountered in young women (<65 years) compared to older ones (p=0.079). Removing more lymph nodes also did not decrease the incidence of lower limb lymphedema (p=0.78). The risk factors for late complications are analyzed in Table 4.

Discussion

This is the one of the largest studies (n=99) conducted in a single center, examining the postoperative complications after groin dissections for this rare cancer. This study

was conducted in a tertiary referral center that provides health service to the whole country. All cases were operated on by a small number of gynecological oncologists (4-5) experienced in vulvar surgery. Despite the use of prophylactic antibiotics, the triple incision technique and adequate surgical wound care, significant numbers of women (41.1%) still experienced early or late complications after lymphadenectomy for vulvar cancer in the current study. Limited data in the literature identified the frequently encountered lymphadenectomy complications such as wound infection, wound breakdown, lower limb lymphedema and lymphocyst formation (Hacker et al., 1983; Gould et al., 2001; Gaarenstroom et al., 2003). Therefore, we analyzed the risk factors for these complications in the present study separately.

In the present study, obese women also had lower limb lymphedema 3.82 times more frequently compared to non-obese women. In the study of Greene et al. (2012) positive correlations between increasing BMI and lower limb lymphedema were found. In a recent study by Yost et al. (2014) BMI, lymphadenectomy and radiation therapy were found as the significant predictors of lower limb lymphedema in endometrial cancer. However, they stated that lower limb lymphedema risk was not associated with the extent of lymphadenectomy or the number of lymph nodes. The rate of lower limb lymphedema was 1.9% in women having sentinel lymphadenectomy and 25.2% in those having lymphadenectomy in the GROINSS-V study (Oonk et al., 2010). The significant decrease in the lower limb lymphedema incidence with sentinel node procedure might be attributed to the removal of fewer lymph nodes with sentinel lymph node procedure compared to classical lymphadenectomy. However, this theory was refuted by the former studies.

Consistent with the literature, wound complications (breakdown and infection) were also the most frequent complications of IFLND in the present study. The analysis of the possible risk factors for wound complications identified obesity (BMI ≥ 30 kg/m²) and advanced age (≥ 65 years) as the independent risk factors for our study population. In the study of Hinter et al. (2011) advanced age was also found as the independent risk factor for wound breakdown, and additionally diabetes predicted all the early complications. The increased risk was attributed to deterioration of wound healing by both aging and obesity that also leads to glucose intolerance, and a moist environment that is predisposed to wound infections. However, no associations between older age and occurrence of complications were found in a recent trial by Gaarenstroom et al. (2003) conducted on 101 women with vulvar cancer. In a small study of 56 patients, age and body mass index were not associated with wound breakdown (Walker et al., 2011).

The main late complication of lymphadenectomy was lower limb lymphedema in the current study 10.1%. It is a chronic debilitating condition that typically occurs within 12 months of lymphadenectomy with a reported incidence ranging from 4.5% to 48.0% in the other series (Gaarenstroom et al., 2003; Hinten et al., 2011; Soliman et al., 2012). Lower limb lymphedema is caused by an imbalance between capillary filtration of lymph vessels

and lymphatic drainage. However, it is not known whether the production or the drainage of the lymphatic fluid is abnormal (Jensen et al., 2014). Lower limb lymphedema not only leads to long-life physical, and psychosocial morbidity but also significant impairment to the life quality of women (Janda, 2004). In the present study, lower limb lymphedema and other late complications were observed to be more common in young women compared to older ones (15.4% vs 5.0%; $p=0.079$). Young age was also reported as an independent risk factor for developing lower limb lymphedema in a former study (Hinten et al., 2011). The reason why lower limb lymphedema is frequently encountered in young women might be explained by the following hypothesis: Older women with vulvar cancer already had certain movement restrictions due to their chronic disease before operation. However, young women were more active before the operation and suddenly become immobilized afterwards and therefore more frequently developed lower limb lymphedema. In the present study, obese women also had lower limb lymphedema 3.82 times more frequently compared to non-obese women. In the study of Greene et al. (2012) positive correlations between increasing BMI and lower limb lymphedema were found. In a recent study by Yost et al. (2014) BMI, lymphadenectomy and radiation therapy were found as the significant predictors of lower limb lymphedema in endometrial cancer. However, they stated that lower limb lymphedema risk was not associated with the extent of lymphadenectomy or the number of lymph nodes. The rate of lower limb lymphedema was 1.9% in women having sentinel lymphadenectomy and 25.2% in those having lymphadenectomy in the GROINSS-V study (Oonk et al., 2010). The significant decrease in the lower limb lymphedema incidence with sentinel node procedure might be attributed to the removal of fewer lymph nodes with sentinel lymph node procedure compared to classical lymphadenectomy. However, this theory was refuted by the former studies.

In conclusion, a significant number of women still suffer early and late complications after lymphadenectomy for vulvar cancer. Although alternative surgical techniques were introduced to reduce the complications of vulvar cancer surgery, inguinofemoral lymphadenectomy still remains in an important place of lymph node dissection of vulvar cancer (Qiang et al., 2014). Both patients' characteristics and extent of the vulvar surgery were related to early and late complications of inguinofemoral lymphadenectomy. In particular, obese and elderly women should be informed and carefully evaluated for early signs of complications. However, there is no identified pre- and intra-operative risk factor for developing lower limb lymphedema. In order to explain the exact mechanism of these complications and determine the risk factors, it is crucial to make multicenter prospective studies with large numbers of patients undergoing lymphadenectomy for vulvar cancer.

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