Original Articles

Frequency and risk factors of lower limb lymphedema following lymphadenectomy in patients with gynecological malignancies

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Summary

Objective: Lower limb lymphedema (LLL) is a major cause of morbidity in patients with gynecological malignancies after surgical treatment involving lymph node (LN) dissection. The aim of this study was to estimate the prevalence of LLL in such patients and detect risk factors for its occurrence. *Materials and Methods:* A retrospective analysis of all patients undergoing lymphadenectomy in newly-diagnosed gynecological malignancies at the University Hospital of Zurich between 2000 and 2007 was performed. Data from 313 patients were collected. Twenty patients with pre-existing edema or missing information were excluded before analysis. Time-to-LLL was estimated using the Kaplan-Meier estimate and potential risk factors were evaluated by a Cox regression model. *Results:* Estimated prevalence of LLL one year after surgery was 32%, increasing to 58% eight years after surgery. Median time to diagnosis of LLL was 5.2 years. The number of removed lymph nodes was significantly associated with time-to-LLL. Diagnosis of postoperative lymphocysts and local infections were accompanied by a significantly elevated risk for the development of LLL. Furthermore, time-to-LLL decreased with a higher body mass index (BMI) of the patient. In contrast, chemo- and radiotherapy, age, positive LNs, site of lymphadenectomy, and type of cancer were not observed to be associated with the occurrence of LLL. *Conclusions:* LLL is a frequent postoperative complication in patients undergoing lymphadenectomy for gynecological malignancies. It is thus imperative to sufficiently educate patients about the risk and symptoms of LLL prior to surgery. The data clearly show an association between time-to-LLL and number of dissected LNs, stressing the need to prospectively analyze the prevalence of LLL and carefully plan LN sampling as increasing knowledge is gained regarding the therapeutic benefit of sentinel and systemic lymphadenectomy in patients with different stages of gynecological malignancies.

Key words: Lymphedema; Gynecological malignancies; Risk factors.

Introduction

Secondary lymphedema is a major complication and source of morbidity after dissection of lymph nodes (LNs) in patients with gynecological malignancies. Diagnosis of lower limb lymphedema (LLL) is difficult and lymphedema is frequently overlooked by the physician if it is not reported by the patient [1-3]. Lymphedema initially presents with changes in appearance or sensation of the affected region, including swelling, visible lumps, puffiness and reddened areas, as well as pain, heaviness, hardness, heat, tenderness, and sensation of pins and needles [1]. Symptoms are often noticed within the first 12 months after surgery [3, 4]. With chronicity frequently due to delayed diagnosis or treatment and accompanied by tissue remodelling, the involved structures develop the characteristic features of induration and fibrosis [5]. The consequences are a deterioration of the quality of the patient's life with important health, as well as financial implications, leading to a considerable economic burden to healthcare systems [1, 3, 6-8].

Reported prevalence of LLL following surgery for gynecological malignancies ranges from 2.1% to 44% [3, 4, 6, 7, 9-15]. Lymphadenectomy is employed for staging and improvement of prognosis in nodal positive patients. A large number of LNs is frequently removed to obtain a reliable nodal status; however, this in turn may impair lymphatic drainage.

The number of removed LNs has repeatedly shown to have a significant impact on the development of LLL [4, 9, 10]. Other potential risk factors include radiotherapy [2, 4, 11], postoperative infection [16], and removal of LNs in the groin region [4]. Various authors previously excluded chemotherapy [4, 11], body mass index (BMI) [4, 9], positive LNs [2, 12], and age [4, 9, 12] as contributing factors. However, the pathophysiology of LLL is still not fully understood and to date, there are no reliable guidelines available permitting the clinician to identify patients at high-risk to develop LLL.

The present study determined the occurrence of LLL in patients undergoing lymphadenectomy in newly diagnosed gynecological malignancies and identified associated risk factors.

Materials and Methods

Patients

A retrospective analysis of all patients undergoing lymphadenectomy in newly diagnosed gynecological malignancies at the University Hospital of Zurich between 2000 and 2007

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was performed. Of the 313 patients for whom data were collected, two patients with incomplete records and 18 patients with pre-existing edema were excluded from further analysis. According to the type of cancer, a distinction was drawn between cervical (74 patients), uterine (104 patients), ovarian (71, including five patients with cancer of the tube), vulvar and vaginal (31 and four patients, respectively), and dual primary cancers (eight patients with uterine and ovarian cancer, one patient with uterine and cervical cancer). In respect to the site of lymphadenectomy, pelvic only, para-aortic, and inguinofemoral LN dissections were differentiated. Most patients with para-aortic lymphadenectomy also underwent pelvic lymphadenectomy. Positive LNs were documented for each patient. Depending on the type and stage of cancer, patients underwent standard local surgery with or without adjuvant therapy. Patients undergoing radiotherapy received either intravaginal brachytherapy of 20-25 Gy, external beam radiotherapy of 20-95 Gy, or a combination of both with cumulative doses of 50-122 Gy. Standard chemotherapy in patients with uterine or ovarian cancer consisted mainly of paclitaxel and carboplatin. Cisplatin was predominantly administered to patients with vulvar/vaginal or cervical cancer (Table 1).

Clinical information including age and BMI at diagnosis, type of cancer, number and site of dissected LNs, occurrence of postoperative infection and lymphocyst formation, radiotherapy, and chemotherapy were abstracted from patients' medical records. All patients included in this study underwent a postoperative physical examination performed by a gynecological oncologist. Postoperative infection was defined as documented erythema or inflammation surrounding the wound and requiring antibiotic therapy, abscess formation, infected lymphocyst or infected hematoma. Lymphocyst formation was verified by ultrasound and/or computed axial tomography. Patients with LLL were identified through a review of all available medical records, as documented by the physician and/or self-reported by the patient. Patients with cases of edema exclusively attributable to other causes such as renal, cardiovascular, or thrombotic disease, were considered non-lymphedema patients. Symptomatic lymphedema were subdivided into mild (lymphedema of the mons pubis, discrete LLL), moderate (LLL requiring therapy such as compression stockings or manual lymph drainage), and severe (therapy resistant LLL or causing serious complications e.g. erysipelas). Median patient follow-up period after initial surgery was 24 months (CI [16, 30]). A total of 293 patients entered the analysis for evaluation of potential risk factors associated with the occurrence of LLL.

Statistical analysis

Descriptive statistics include frequencies and percentages for categorical and median (range) for continuous data. The main endpoint was time-to-LLL, defined as the time between surgery and diagnosis of LLL. If a patient was seen without LLL, she was censored at the last follow-up date. Time to mild, moderate, and severe edema was handled in a similar manner; the authors censored all patients not seen with the edema type of interest for a given endpoint. Survival functions were estimated using the Kaplan-Meier estimate to report the probabilities of LLL. Time-to-LLL was estimated using the inverted Kaplan-Meier estimate. To obtain confidence intervals for a survival curve after a given follow-up time, Peto's variance estimate was used. A Cox regression model was generated to associate potential risk factors to time-to-LLL. To obtain a reduced model, stepwise variable selection was performed according to the Bayesian Information Criterion (BIC).

The authors did not perform a correction for multiple testing in these exploratory analyses. All tests were performed at a significance level of $p = 0.05$ and confidence intervals were computed at a confidence level of 95%.

Statistical analysis was conducted using R software [17]. Kaplan-Meier estimates and Cox regression were performed with the R-package survival [18]. Stepwise variable selection via BIC was performed employing the function stepAIC from the R library MASS [19].

Table 1. — *Treatment characteristics according to the type of gynecological cancer.*

	Type of gynecological cancer n (%)				
	Cervical	Uterine	Ovarian	Vulvar/ Vaginal	Dual cancer
All	74 (25.3)	104 (35.5)	71 (24.2)	35 (11.9)	9 (3.1)
Radiotherapy Yes	44 (59.5)	66 (63.5)	1 (1.4)	13 (37.1)	5 (55.6)
Chemotherapy Yes	37 (50.0)	13 (12.5)	55 (77.5)	6 (17.1)	7 (77.8)
Site of lymphadenectomy					
Pelvic only	53 (71.6)	65 (62.5)	18 (25.4)	2 (5.7)	2 (22.2)
Para-aortic	21 (28.4)	39 (37.5)	53 (74.7)	1 (2.9)	7 (77.8)
Inguinofemoral	1 (1.4)	1 (1.0)	0 (0.0)	32 (91.4)	0 (0.0)
Positive lymph nodes	23 (31.1)	23 (22.1)	22 (31.0)	14 (40.0)	0 (0.0)

Table 2. — *Clinical characteristics and estimated probabilities of LLL.*

Characteristics	n (%) of patients	Rates of LLL 1 year after surgery in % [95% CI]	Rates of LLL 8 years after surgery in % [95% CI]
All	293 (100)	32 [26; 38]	58 [47; 67]
Mild LLL	40 (13.7)	14 [9; 19]	29 [18; 38]
Moderate LLL	45 (15.4)	15 [10; 20]	34 [22; 45]
Severe LLL	16 (5.5)	8 [4; 11]	11 [4; 17]
Type of gynecological cancer			
Cervical	74 (25.3)	28 [15; 39]	45 [20; 62]
Uterine	104 (35.5)	31 [20; 41]	67 [44; 80]
Ovarian	71 (24.2)	26 [14; 37]	52 [30; 67]
Vulvar/Vaginal	35 (11.9)	60 [32; 77]	70 [35; 86]
Double primary cancer	9 (3.1)	35 [0; 61]	68 [3; 89]
Site of lymphadenectomy			
Pelvic only	90 (30.7)	22 [14; 30]	52 [36; 65]
Para-aortic	121 (41.3)	37 [27; 46]	59 [41; 71]
Inguinofemoral	34 (11.6)	62 [33; 79]	75 [32; 91]
Radiotherapy			
Yes	129 (44.0)	28 [19; 36]	52 [36; 64]
No	164 (56.0)	36 [27; 45]	63 [46; 75]
Chemotherapy			
Yes	118 (40.3)	27 [18;35]	54 [38; 65]
No	175 (59.7)	36 [27;44]	60 [44; 72]
Postoperative infection			
Yes	42 (14.3)	50 [30; 64]	73 [33; 89]
No	251 (85.7)	29 [22; 35]	55 [43; 64]
Postoperative lymphocyst			
Yes	61 (20.8)	53 [37; 64]	75 [49; 88]
No	232 (79.2)	27 [20; 33]	53 [40; 63]

LLL: Lower Limb Lymphedema; CI: Confidence Interval.

Table 3. — *Patient characteristics (continuous variables).*

	Minimum	Median	Maximum	IQR
Number of removed LNs	1	27.00	97	21.00
BMI	15.4	24.70	50.00	7.10
Age	24.00	57.00	89.00	20.00

LN: Lymph Node, SD: Standard Deviation, IQR: Interquartile Range.

Results

Estimated prevalence of LLL one year after surgery was 32%, increasing to 58% at eight years. Thus, 55% of

Table 4. — *Risk factor analysis by Cox regression*.

	Estimate	Hazard ratio (HR)	*p* value	95% CI for HR
Age	0.01	1.01	0.19	[0.99, 1.03]
BMI	-0.04	0.96	0.03	[0.92, 0.99]
Type of cancer				
Cervical	0.19	1.21	0.73	[0.40, 3.66]
Uterine	0.43	1.54	0.43	[0.52, 4.66]
Ovarian	-0.30	0.74	0.59	[0.25, 2.18]
Vulvar/Vaginal	1.11	3.04	0.33	[0.32, 28.48]
Site of lymphadenectomy				
Pelvic only	1.26	3.52	0.42	[0.16, 76.17]
Para-aortic	1.59	4.88	0.31	[0.23, 104.28]
Inguinofemoral	1.17	3.23	0.29	[0.38, 27.64]
No. of removed lymph nodes	0.02	1.02	0.01	[1.00, 1.03]
Positive lymph nodes	-0.04	0.96	0.86	[0.59, 1.56]
Radiotherapy	-0.43	0.65	0.12	[0.38, 1.11]
Chemotherapy	-0.01	0.99	0.99	[0.55, 1.78]
Postoperative infection	0.53	1.70	0.05	[0.99, 2.89]
Postoperative lymphocyst	0.70	2.01	0.0031	[1.27, 3.18]

Table 5. — *Risk factor selection by BIC*.

	Estimate	HR
No. of removed lymph nodes	0.018	1.018
Postoperative lymphocyst	0.724	2.062
Inguinofemoral lymphadenectomy	0.940	2.559

BIC: Bayesian Information Criterion; HR: Hazard Ratio.

documented LLL occurred within the first year after surgery. Median time to diagnosis of LLL was 5.2 years with a 95% confidence interval [3.00, infinite] (Figure 1).

Table 2 shows clinical characteristics and estimated prevalence of LLL one and eight years after surgery. Analysis of time to mild, moderate, and severe LLL revealed that the majority of affected patients suffered from mild or moderate edema. Only 8% and 11% developed severe LLL within one and eight years, respectively. Patients who underwent surgery for vulvar/vaginal cancer showed the highest probabilities of LLL when compared to other types of cancer. Furthermore, patients undergoing inguinofemoral lymphadenectomy developed LLL most frequently when compared to other sites of LN dissection. A total of 14.3% of all patients suffered from postoperative infection, developing LLL in 50% (73% after eight years) of these cases. In addition, patients with documented postoperative lymphocysts were at high-risk for developing LLL, 53% (75% after eight years) of them presented with LLL. Patient characteristics of the continuous variables are analyzed in Table 3. Median number of removed LNs was 27 (1-97), median BMI 24.7 (15.4-50.0), and median age 57 (24-89) years.

Potential risk factors associated with time-to-LLL were examined using Cox regression analysis (Table 4). The hazard for occurrence of LLL increased significantly by a hazard ratio (HR) of 1.02 with each additional LN removed ($p = 0.01$), CI [1.00, 1.03]. Postoperative local infection and lymphocysts significantly increased the hazard for development of LLL by a HR of 1.7 ($p = 0.05$) with a CI [0.99, 2.89] and a HR of 2.01 ($p = 0.0031$) with a CI [1.27, 3.18], respectively. Interestingly, the hazard for LLL decreased significantly by a factor of 0.96 ($p = 0.03$) for each additional BMI point with a CI [0.92, 0.99]. Patients with ovarian cancer, positive LNs, a past medical history of pre- and/or postoperative radiotherapy, or chemotherapy presented with a decreased risk to develop LLL when compared to patients without these characteristics. However, these differences were not statistically significant. Due to the small number of patients with dual primary cancers [9], this cohort was not suitable for a reasonable subgroup analysis.

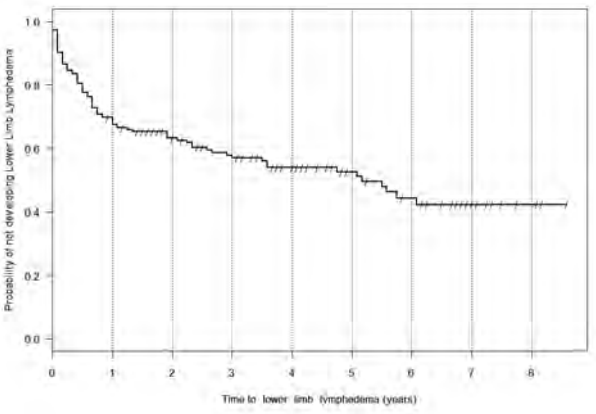

Figure 1. — Kaplan-Meier estimate of time to lower limb lymphedema.

The significant variables in the full model were confirmed by variable selection via BIC, revealing the risk factors with the strongest association to time-to-LLL (Table 5).

Discussion

This study estimated the prevalence of symptomatic LLL after lymphadenectomy in patients with newly-diagnosed gynecological malignancies and determined specific risk factors for its occurrence. Among 293 cancer patients undergoing surgical treatment, the authors report an estimated prevalence for LLL of 32% one year after surgery, increasing to 58% eight years after surgery. Thus, the present data clearly demonstrate that LLL is a frequent complication accounting for postoperative morbidity in these patients. Previous retrospective studies reported varying, but mostly lower prevalence of LLL [3, 4, 9-11]. Although patients had different follow-up times, it appears that no survival analytic methods were used to estimate the probability of LLL in these other studies. This lack of analysis, in addition to the absence of a standard definition for LLL, may account for some of the variability in prevalence rates for LLL reported. Furthermore, prevalence of LLL is strongly influenced by the employed detection method. Ryan *et al*. not only extracted data from medical records but also interviewed patients [4]. While 36% of the women reported swelling of their legs, diagnosis of LLL was made in only 18%, indicating that lymphedema is often overlooked if the patient does not complain of it. Two prospective studies, performing circumference measurements and/or volume displacement evaluations, reported incidences of LLL

higher than 40%, despite a shorter follow-up period [7, 13]. However, since patients in both studies self-reported swelling in only approximately 50% of detected cases, it remains unclear how specific these objective findings are. Future studies, implementing serial circumference measurements, and a follow-up period of several years, should reveal whether this method reliably detects early lymphedema or whether variations in leg circumferences are in some cases rather transitory postoperative findings. To date, standardized diagnostics are not available; however, tools such as circumference measurements, volume displacement evaluation methods, and the gynecologic cancer lymphedema questionnaire (GCLQ) [20] may be helpful for future studies.

In the present study, the majority of LLLs were diagnosed within the first year after surgery, which has also been reported by several other researchers [3, 11]. However, according to the Kaplan-Meier plot used in this study, the estimated median time to onset was 5.2 years. Lawenda and colleagues stated that awareness and assessment of signs and symptoms of LLL is essential immediately after surgery in order to initiate timely treatment, if necessary, and avoid chronicity and reduction in quality of life [5]. The results in the present study indicate that raising patient awareness is not only important immediately after surgery, but also during the years of oncological follow-up. Abu-Rustum *et al*. and Füller *et al*. previously documented a positive association between the number of dissected LNs and the prevalence of LLL [9, 10]. These results are consistent with the present findings showing a significantly increased risk for the development of LLL (HR 1.02) with each LN removed. The authors further substantiate their findings with the reduced model, confirming the association between the number of removed LNs and LLL. In this study, only 28% (82/293) of patients undergoing lymphadenectomy presented with a positive LN status post-surgery. Thus, 72% of patients did not directly benefit from lymphadenectomy; nevertheless, they had to face the high morbidity rates associated with this procedure. Further studies are urgently needed to evaluate the benefit of lymphadenectomy at different stages of gynecological malignancies and the value of sentinel node dissection in early cancer stages.

The present analysis clearly identified the postoperative formation of lymphocysts and occurrence of local infections as significant independent risk factors for the development of LLL. To the authors' knowledge, this is the first time that an association between lymphocysts and development of LLL has been shown. However, several authors reported lymphocyst formation as a common finding after pelvic lymphadenectomy, with most of them being asymptomatic [14, 21, 22]. Prospective studies are needed to evaluate whether patients with LLL following lymphadenectomy indeed show an increased incidence of lymphocysts and whether an early intervention is indicated to avoid development and persistence of LLL. Leminen *et al*. previously reported a significantly higher incidence of LLL in patients with wound infections after surgery for vulvar cancer [16]. The present study confirmed these findings, showing that postoperative infection is a significant risk factor for LLL in patients with gynecological malignancies. Whether infection is already a complication facilitated by impaired drainage remains to be investigated.

The reduced statistical model revealed that patients undergoing inguinofemoral lymphadenectomy are at a particularly high-risk for developing LLL, although the saphenous vein has been preserved in most of the patients. Similar to these results, it has been documented that inguinofemoral lymphadenectomy, as part of the standard surgical management for vulvar cancer, was frequently associated with postoperative chronic LLL [12, 23]. This may, at least in part, explain the highest prevalence of LLL in patients with vulvar/vaginal cancer also reported in previous studies [3, 4]. More recently, sentinel node dissection became part of the standard surgical treatment in early-stage vulvar cancer, reducing postoperative morbidity without compromising survival rates [24-26]. More studies are required to evaluate whether sentinel lymph node techniques are applicable to various gynecological cancers, which would greatly reduce postoperative morbidity including the prevalence of LLL.

Radiotherapy was not a risk factor for LLL in the present study. Similar results were reported by Gaarenstroom *et al*. [12]. However, previous studies investigated different gynecological malignancies separately and showed a significantly higher incidence of LLL after radiotherapy in patients with uterine cancer [11] and cervical cancer [3]. Werngren *et al*. reported a significantly higher ratio of patients with a history of combined external radio- and brachytherapy developing LLL compared to those exclusively receiving brachytherapy [7]. The present patient sample was more heterogeneous, including patients with various types of gynecological malignancies and receiving radiotherapy with dosages ranging from 20 Gy to 122 Gy. A more detailed analysis of different types and dosages of radiotherapy may provide further insights into its relevance as a risk factor for LLL and should be a subject of future studies. However, the subgroups in this study were too small to be suitable for subgroup analyses.

Interestingly, in the group of patients, a higher BMI had a protective effect for the development of LLL. Other investigators did not find an association between BMI and development of LLL [4, 9]. However, Kizer *et al*. observed in patients with cervical carcinoma that a lower BMI was associated with a significantly increased rate of postoperative complications, including LLL [27]. Furthermore, his group showed that the majority of patients lost weight during treatment. The present authors only documented patients' BMI at the beginning of treatment, which may somewhat limit the conclusions that can be drawn from this particular finding. Moreover, a positive association between BMI and incidence of lymphedema of the upper limb has been well-established in breast cancer patients following axillary lymphadenectomy [28, 29].

Conclusion

The aim of modern therapy of gynecological malignan-

cies is to minimize treatment-related morbidity, without compromising survival rates. Therefore, prevention of LLL through early detection and appropriate treatment, when necessary, has to be an important aim in the care of patients who undergo lymphadenectomy. In order to adequately inform patients and choose the most appropriate treatment option available, the clinician has to be aware of potential risk factors, such as postoperative infection or lymphocyst formation, and the impact of extended LN dissection, specifically within the inguinofemoral region. Until a significant reduction in LLL prevalence has been achieved through individualized therapy, patients should be educated about the risk of developing lymphedema, ways of prevention, symptoms, resources, and options for treatment. Although this is not the primary concern at the time of cancer diagnosis, it may become highly important after therapy.

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