Lymphology 50 (2017) 120-130

THE VOLUME OF POSTOPERATIVE DRAINAGE FLUID AS A POTENTIAL EARLY PREDICTOR OF LYMPHEDEMA AFTER LYMPH NODE EXCISION FOR METASTATIC MELANOMA

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ABSTRACT

Lymphedema (LE) following lymph node dissection is a major problem for cancer patients, and radiation therapy, extended surgery, groin dissection, obesity, and older age are well-established risk factors of LE. We studied whether these risk factors are further associated with high volumes of postoperative drainage fluid after complete lymph node dissection (CLND) for melanoma metastases. Moreover, we examined whether a high amount of drainage fluid after sentinel lymph node biopsy (SLNB) can predict a high amount of drainage fluid after subsequent CLND. Using descriptive statistics and regression analyses, we analyzed the cumulative volumes of postoperative drainage fluid for 836 melanoma patients with lymph node excision in the axilla or groin. In multiple regression analyses, the well-established risk factors of LE, i.e., increased body mass index, older age, and ilioinguinal versus inguinal versus axillary dissection predicted a high drainage volume after CLND. Of note, a high drainage fluid volume after SLNB also predicted a high drainage volume after subsequent CLND. In patients with groin dissections, who are particularly susceptible to swelling, extended iliac dissection, age above 60, and a cumulative drainage volume of more than 100 ml in the preceding SLNB were predictors of the cumulative drainage volume. We find that common risk factors predict the volume of postoperative drainage fluid after CLND and postoperative LE. Further, high postoperative drainage volume may therefore function as a potential early predictor of LE following CLND.

Keywords: lymph node excision, drains, drainage fluid, lymphedema, risk factors, obesity, age, sentinel node, cancer, melanoma

Radical lymphadenectomy is currently the primary treatment modality for lymph node metastases of melanoma. Unfortunately, this procedure is associated with significant morbidity. Potential complications include wound infection, wound dehiscence, nerve damage, hematoma, prolonged lymphorrhea and seroma. Among these, lymphedema (LE) has the most serious consequences. Given that LE tends to increase over time both in frequency and severity (1-3), this condition burdens patients, physicians and health care systems alike.

The identification of risk factors for LE is mainly based on systematic reviews dealing with breast cancer patients. Beside adjuvant radiation therapy (4), the extent of lymph node excision [sentinel lymph node biopsy (SLNB) versus radical lymphadenectomy, number of excised lymph nodes], and increased body mass index (BMI) are well-established risk factors of LE (5). Several large-scale studies have also demonstrated a negative effect of age (2,4). In melanoma, inguinal and pelvic lymph node dissections are additional risk factors for postoperative swellings (6-8).

After radical lymphadenectomy, most surgeons apply a closed suction drainage system, to prevent complications such as seroma. The association between the post-operative wound drainage volume, seroma formation and postoperative swellings is supported by a considerable body of empirical evidence: It has been shown that patients producing high wound drainage volumes more frequently develop seromas (7,9-10) and that these patients in turn have an increased risk of LE (2,7,11-13).

Based on the hypothesis that a large drainage fluid volume could be an early indicator of postoperative LE, we tested whether the volume of postoperative wound drainage fluid correlates with the well-established risk factors of postoperative LE.

The value of completion lymph node dissection (CLND) within the sentinel lymph node (SLN) procedure is currently a controversial topic (14,15). Consequently, parameters that can preoperatively predict the risk of postoperative swellings are urgently needed when individual decisions in favor or against a completion lymphadenectomy should be made. Therefore, we also assessed whether a high volume of drainage fluid after SLNB might predict a high volume of drainage fluid after subsequent CLND and, thus, constitute a potential risk factor for postoperative swellings.

PATIENTS AND METHODS

Patients and Medical Procedures

Between January 1999 and December 2015, 836 patients with primary melanomas received axillary or inguinal SLNB at the Göttingen University Medical Center. Indications, technical aspects of SLNB, and details of pathological processing of primary melanomas and SLNs have been described previously (16,17). Patients with SLN metastases were offered a CLND, except those with metastases in more than one nodal basin. Delayed CLNDs were performed when isolated nodal basin recurrences were detected in patients who had not received an immediate CLND. We used established, standard surgical techniques of CLND. In the case of axillary metastasis, excision of level-I to level-III nodes was our standard procedure. The minor pectoral muscle was not excised or divided, but the fascia of its lateral aspect resected. In patients with groin metastases, either an inguinal dissection or the more extended ilioinguinal dissection was performed. A spindle-shaped strip of overlying skin was routinely excised together with the inguinal nodes, thus reducing the need for skin flap preparation. The upper part of the great saphenous vein was routinely included into the specimen. We did not transpose the sartorius muscle to cover the femoral vessels.

Patients received thromboprophylaxis (Enoxaparin 20-40 mg once a day and surgical stockings). We routinely performed lymph node surgery under general anesthesia using conventional scissors for tissue cutting and bipolar tweezers for sealing of lymph and small blood vessels. Larger blood vessels were ligated using Vicryl 4-0 (Ethicon, Norderstedt, Germany). After lymph node excision, a single closed suction drainage tube (Redon drain, pfm, Cologne, Germany) was placed through a separate incision. In patients with SLNB, we removed the drain after two days at the earliest, or when the daily amount of drainage fluid decreased to <20 ml. After CLND, we removed the drain when the daily amount of drainage fluid was below 30 ml or after 14 days, provided prolonged excessive lymph drainage (>100 ml/d) was absent.

Data Collection

We had prospectively recorded the following variables in an electronic database: age at the time of primary diagnosis, gender, body mass index (BMI), location, vertical tumor thickness (Breslow index), ulceration of the primary melanoma, pathologic status of the SLNs, and nodal basin recurrences. The main outcome variable was the cumulative total volume of postoperative drainage fluid according to the five different types of lymph node surgery (axillary SLNB, inguinal SLNB, axillary CLND, inguinal CLND, ilioinguinal CLND). The drainage duration was also recorded. In patients with bidirectional lymphatic drainage, we considered the nodal basin showing the largest amount of drainage fluid.

The Ethics Committee of the Göttingen University Medical Center approved this retrospective observational study (No. 2/12/07).

Statistical Analysis

For statistical analyses, SAS (version 9.4, SAS Institute Inc.) and Statistica (version 12, StatSoft) programs were used. Means, standard deviations (SD), and ranges were determined for normally distributed variables; medians, quartiles, and ranges for non-normally distributed variables. Categorical variables were described by their absolute and relative frequencies. For comparison of independent groups of categorical as well as non-normally distributed metric variables, we applied the Mann Whitney U test or the Kruskal Wallis test (in case of >2 groups). For the comparison of dependent groups of non-normally-distributed metric variables, we used the Wilcoxon signed rank test.

The influence of potential risk factors on the square root of the cumulative lymph drainage volume was analyzed using linear regression models. The influence of potential risk factors on the drainage duration was studied using Cox regression models. Starting with all predictors having a p-value of <0.2 in simple regression analyses, multiple regression models with backward selection (exclusion criterion p>0.05) were calculated. We did not adjust for multiplicity in this hypothesis-generating study and therefore the p-values are used as descriptive measures.

RESULTS

Patient and Tumor Characteristics

Of the 836 patients included in this study, 413 (49%) were men and 423 (51%) were women. The mean age was 57.1 years (SD 16.6, range 5 - 90 years) and the mean BMI was 27.9 kg/m^2 (SD 5.3, range 14.8 - 53.5). The primary melanomas were located in the trunk for 364 patients (44%), and in the extremities in 472 patients (56%). The median Breslow thickness of the primary melanomas was 1.5 mm (inter quartile range (IQR) 1 - 2.8, range 0.35 - 20.0). The T classification (18) was T1 in 212 cases (25%), T2 in 311 cases (37%), T3 in 195 cases (23%), T4 in 111 cases (13%), and TX in 7 cases (1%). Of the 793 patients with available data for epidermal ulceration, 209 (27%) had ulcerated primary tumors. After SLNB, 232 (28%) patients were classified as SLN-positive. We performed a total of 174 CLNDs. Of those, 153 (88%) were performed immediately after the diagnosis of SLN metastasis, whereas 21 (12%) were performed as delayed lymph node dissections in patients with false-negative SLNBs. In this group, the mean time to isolated nodal basin recurrence was 13.7 months (SD 12.1, range 5 - 22). The patients' characteristics according to the type of lymph node excision performed are shown in *Table 1.*

Volume of Drainage Fluid and Drainage Duration

The cumulative volumes of drainage fluid accumulated before the removal of the Redon tube were available for 727 patients (*Table 2*). After axillary SLNB the median drainage volume was lower compared to that after inguinal SLNE (25 ml vs. 45 ml; p<0.01). Accordingly, the drainage duration

TABLE 1
Patient Characteristics According to the Type of Lymph Node Excision

Type of dissection	Axillary SLNB	Inguinal SLNB	Axillary SLNB+ CLND	Inguinal SLNB+ CLND	Inguinal SLNB +Ilioinguinal CLND
Number of patients (%)	413 (49%)	250 (30%)	95 (11%)	33 (4%)	45 (5%)
Median number of lymph nodes excised, IQR (range)	2, 1-2 (1 – 10)	2, 1-3 (1 – 14)	16, 12-19 (3 – 35)	8, 7-12 (1 – 16)	15, 12-19 (2 – 23)
Median tumor thickness / mm, IQR (range)	1.4, 1-2.5 (0.35 – 12.2)	1.5, 1-2.5 (0.35 – 14)	1.9, 1.3-3.6 (0.6 – 20)	2.1, 1.3-2.8 (0.4 - 8.5)	2.8, 1.9-3.6 (0.6 - 10)
Epidermal ulceration					
Ulceration present	91 (24%)	55 (23%)	31 (34%)	9 (28%)	23 (51%)
Ulceration absent	296 (76%)	183 (77%)	60 (66%)	23 (72%)	22 (49%)
Not available	26	12	4	1	0
Age					
Mean age / yr±SD (range)	59.3±16.1 (5 – 90)	57.3±16.8 (18 - 88)	51.7±17.2 (9 - 81)	51.6±17.5 (12 – 80)	51.6±14.3 (18 – 81)
BMI					
Mean BMI / kg/m²±SD (range)	28.4±5.3 (14.8 -53.5)	27.6±5.3 (19.6 – 49.2)	27.7±5.7 (17.8 – 48.9)	27.2±4.3 (18.9 – 36.0)	26.7±4.5 (20.7 – 39.2)
Sex					
Male	233 (56%)	84 (34%)	58 (61%)	12 (36%)	26 (58%)
Female	180 (44%)	166 (66%)	37 (39%)	21 (64%)	19 (42%)
Site of the primary tumor					
Head/neck + trunk	250 (61%)	31 (12%)	71 (75%)	10 (30%)	2 (4%)
Extremity	163 (39%)	219 (88%)	24 (25%)	23 (70%)	43 (96%)
T classification					
T1	123 (30%)	64 (26%)	16 (17%)	7 (21%)	2 (4%)
T2	154 (37%)	99 (40%)	36 (38%)	9 (27%)	13 (29%)
T3	87 (21%)	55 (22%)	23 (24%)	11 (33%)	19 (42%)
T4	44 (11%)	30 (12%)	20 (21%)	6 (18%)	11 (24%)
TX	5 (1%)	2 (1%)	0 (0%)	0 (0%)	0 (0%)

TABLE 2
Cumulative Drainage Fluid Volumes and Time to Removal of the Redon Drains According to the Type of Lymph Node Excision Performed

Type of lymph node excision	N	Median cumulative volume of postoperative drainage fluid, IQR (range)	Median cumulative drainage duration, IQR (range)
Axillary SLNB	434	25 ml, 10-60 (0 – 1000)	2 days, 2-3 (0 – 14)
Inguinal SLNB	293	45 ml, 18-105 (1 – 3460)	2 days, 2-4 (1 – 15)
Axillary CLND	91	1065 ml, 685-1570 (30 – 3620)	11 days, 8-14 (0 – 21)
Inguinal CLND	32	1310 ml, 525-1788 (20 – 4500)	14 days, 7-14 (0 – 15)
Illioinguinal CLND	41	2200 ml, 1120-2640 (190 – 5339)	14 days, 10-15 (5 – 20)

was longer (descriptive measures given in *Table 2*, p<0.01). Comparing the median volumes and durations after CLND, the drainage volume was smallest and the duration was shortest after axillary CLND, the second smallest and second shortest were recorded after inguinal CLND, and the largest and longest after ilio-inguinal CLND (volumes: 1,065 ml vs. 1,310 ml vs. 2,200 ml, respectively). The descriptive measures for the drainage volumes and durations are displayed in *Table 2*.

When the 160 patients with available data for wound drainage volumes for both SLNB and CLND were analyzed, the drainage volume after SLNB (median 30 ml) was lower than the drainage volume after CLND (median 1,240 ml, p<0.01). A lower volume in favor of SLNB was also observed when the subgroups with axillary (20 vs. 1,045 ml, p<0.01) or inguinal (40 vs. 1,600, p<0.01) lymph node excision were analyzed separately (*Fig. 1*).

Drainage Volumes and Drainage Durations after CLND in Relation to Risk Factors of Postoperative Swellings / Lymphedema

Wound drainage volumes after CLND

We studied only the 164 patients with available data for the drainage volumes of both SLNB and subsequent CLND in the same nodal basin. The association between cumulative drainage volumes after CLND and risk factors for swellings was investigated by multiple linear regression analysis (*Table 3*). The site of the CLND strongly influenced the drainage volume after CLND (axillary lowest, ilioinguinal highest; overall p<0.01). The higher the BMI and age of the patients, the higher were the drainage volumes (both p<0.01). Men tended to produce higher drainage volume than women (in all patients p=0.29, in patients with axillary CLND <0.01). Higher drainage volumes after SLNB were associated with higher drainage volumes

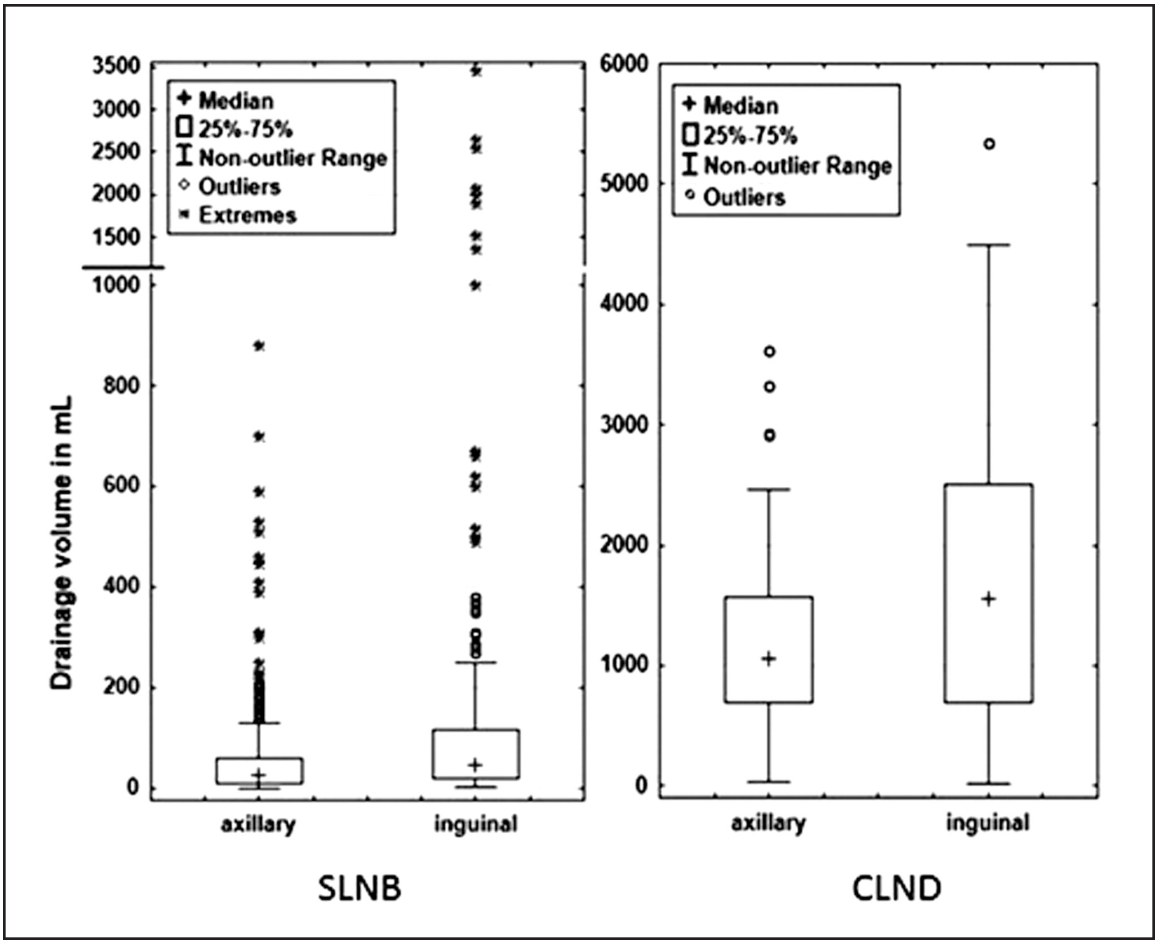

Fig. 1. Cumulative volumes of drainage fluid according to type and location of the lymph node excision. SLNB – sentinel lymph node biopsy, CLND – complete lymph node dissection.

after CLND (p<0.01, *Fig. 2*). The number of removed lymph nodes had no relevant effect.

Groin dissection is especially critical with respect to postoperative swellings. In the multiple regression analysis of dichotomized factors of clinical importance, independent factors predicting a high drainage volume after groin CLND were: a drainage volume after SLNB of more than 100 ml after the preceding inguinal SLNB, the more extended iliac dissection, and age over 60 (*Table 3*).

Wound drainage duration after CLND

In a multivariate Cox model, the site of the CLND (global p=0.01, axillary vs. inguinal: Hazard ratio (HR) 1.25, 95% CI 0.83-1.90, p=0.28; ilioinguinal vs. inguinal: HR 0.68, 95% CI 0.42 -1.09, p=0.11), the BMI (HR 0.95; 95% CI 0.92-0.98; p<0.01) and age (HR 0.98; 95% CI 0.97-0.99; p<0.01) turned out to be independent as risk factors of prolonged drainage duration after CLND.

DISCUSSION

Surgeons treating nodal metastasis in melanoma patients are well aware of the problem of LE after radical lymph node dissection. Axillary CLND has been

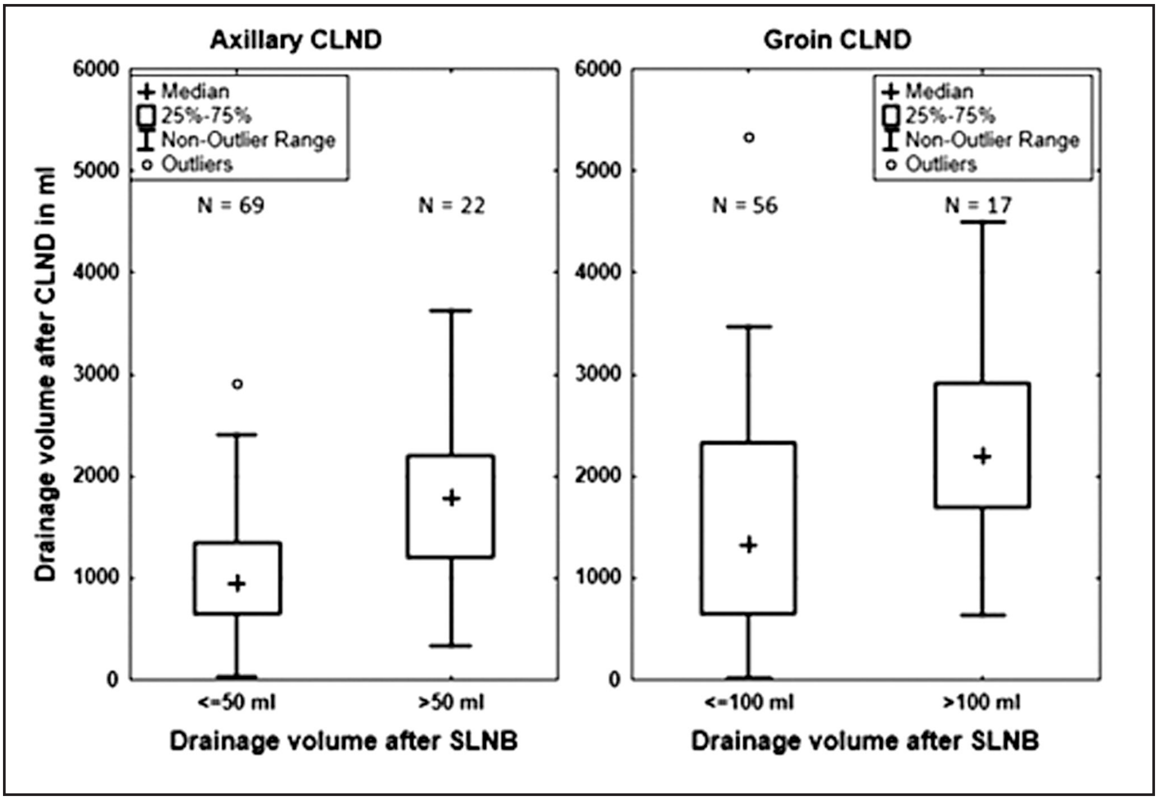

Fig. 2. The left-hand boxplot shows that a high volume of drainage fluid after axillary SLNB of ≤50 ml leads to increased drainage production after subsequent axillary CLND. On the right-hand site, we demonstrate the same relationship for inguinal lymph node excision. High drainage output after groin SLNB of >100 ml leads to increased drainage production after consecutive groin CLND. SLNB – sentinel lymph node biopsy, CLND – complete lymph node dissection.

associated with LE rates ranging from 1% to 35% (19-23) and groin dissection with LE rates between 20% and 62% (6,8,12,21,22, 24,25). Patients undergoing an additional iliac lymph node dissection have been reported to develop LE even more frequently (12,20,25,26). According to systematic reviews, radiation therapy, groin dissection, extended lymph node dissection, overweight or obesity, and higher age are well-established risk factors of LE (5,20,27,28).

In order to prevent seroma formation and to avoid repeated therapeutic punctures (29), most surgeons routinely place a suction drain after lymphadenectomy. However, it is debated whether this procedure affects post-operative complications including LE at all (29,30). There is no strong evidence for or against high or low pressure suction to reduce seroma formation (31). The optimal timing for removal of drainage tubes is also unknown. In most studies, the drainage tube is removed with an output of 30 to 50 ml or less in 24 hours, usually 3 to 17 days postoperatively.

Based on multiple regression analyses, we clearly show that a high volume of post-operative drainage fluid after CLND and postoperative LE are predicted by common risk factors. We found that higher age, BMI, CLND vs. SLNB, groin dissection vs. axillary dissection, and ilioinguinal CLND vs. inguinal CLND were strongly associated with an increased amount of postoperative drainage fluid.

TABLE 3
Multiple Regression Analyses of Factors Influencing the Cumulative Postoperative Drainage Volume after CLND, Including the Factors with a P-value of <0.2 on Univariate Simple Regression

Factor	Category	Regression coefficient	95% Confidence Interval	p
All Patients with complete lymph node dissection (CLND)				
Intercept		2.54	-7.14 – 12.22	
Site of CLND	Overall			<0.01
	Axillary vs. inguinal	0.12	-4.21 – 4.45	0.96
	Ilioinguinal vs. inguinal	9.57	4.72 – 14.41	<0.01
Body mass index	/ Kg / m^2	0.67	0.33 – 1.00	<0.01
Age	/ year	0.21	0.11 – 0.32	<0.01
Drainage volume after SLNB	/ ml	0.02	0.01 – 0.02	<0.01
Axillary CLND				
Intercept		1.33	-8.34 – 10.99	
Body mass index	/ Kg / m^2	0.70	0.36 – 1.04	<0.01
Age	/ year	0.19	0.08 – 0.30	<0.01
Gender	Male vs. female	4.64	0.83 – 8.45	<0.01
Groin CLND				
Intercept		25.77	15.50 – 36.04	
Extent of CLND	Inguinal vs. ilioinguinal	-9.39	-15.21 – -3.57	<0.01
Age	/ year	0.30	0.11 – 0.49	<0.01
Drainage volume after SLNB	/ ml	0.02	0.01 – 0.02	<0.01
Groin CLND (dichotomized factors)				
Intercept		56.70	48.46 – 64.95	
Extent of CLND	Inguinal vs. ilioinguinal	-8.96	-15.39 – -2.53	0.01
Age	≤60 vs. >60 years	-8.86	-16.16 – -1.55	0.02
Drainage volume after SLNB	≤100 vs. >100 ml	-9.62	-17.50 – -1.75	0.02

The number of previous studies on the factors predicting the amount of drainage fluid is limited. In patients with mastectomy and axillary lymph node dissection, drainage volumes correlated with higher age and obesity (32). In a study dealing with bilateral inguinal lymphadenectomy for penile cancer, high BMI, total number of resected lymph nodes, and ratio of positive lymph nodes were independent predictors of prolonged lymphatic drainage. Young age, however, was associated with longer drainage duration (33), possibly owing to a selection bias due to more radical surgery in younger patients.

In a nuclear medicine study with breast cancer patients, pre-surgery high forearm lymph flow was associated with postoperative LE (34). Our results now extend this study's conclusion that a high lymph flow might be an indicator of lymphatic overload and, eventually, of lymphatic failure. After axillary, inguinal and ilioinguinal CLND, we observed substantial median volumes of drainage fluid of 1055 ml, 1310 ml, and 2200 ml respectively. In a study dealing with elective lymph node dissection, the median drainage volumes after axillary (590 ml) and groin dissection (762 ml) were lower (35).

The most important contribution of our study is the observation that the cumulative drainage volume after radical CLND parallels the drainage volume of the preceding SLNB. Thus, a high volume after SLNB might predict the swelling risk prior to CLND. Assessing benefits and risks of CLND, surgeons must bear in mind the specific circumstances such as side effects for the specific nodal basin, primary melanoma stage, SLN tumor burden, the number of excised and of tumor-involved SLNs, the patients' age and comorbid diseases including obesity. The willingness of the patient to accept postoperative swelling also needs to be considered. Presently, the appropriate extent of lymphadenectomy for melanoma metastasis is controversial in all lymphatic basins. For patients at risk, we perform less extended dissections in daily practice (36). Also, the pelvic part of an ilioinguinal CLND is mostly omitted if only 1-2 SLNs are tumor-positive (37) or if the SLN tumor burden is low (38).

Since swelling is especially problematic after groin dissection, we built a multivariate regression model showing that a post-SLNB drainage volume of >100 ml, age >60 years, and iliac dissection are significant predictors for an increased amount of drainage fluid after groin CLND. In SLN-positive patients with a large drainage volume after the SLNB, CLND or extended lymph node dissection should be performed after careful consideration. A wait-and-see strategy and close scrutiny of the nodal basin by ultrasound B-scans, or inguinal CLND rather than ilioinguinal CLND might be reasonable therapeutic alternatives.

As a potential predictor of LE, the volume of drainage fluid could be considered in planning adjuvant radiation therapy, which would further increase the swelling risk. It should be considered that adjuvant radiation of the node dissection field can improve local disease control but not overall survival (39).

The present observational study, besides its retrospective design, has several limitations. While we can show that the factors predicting increased wound drainage are the same as those heralding LE after CLND, a causal link between the amount of drainage fluid and LE remains to be shown. Moreover, additional factors such as seroma, hypertension, or wound complications may impact on the accrual of swellings (28).

CONCLUSION

Our results in a large cohort of melanoma patients provide compelling evidence that the predictors of a high total volume of drainage fluid after CLND and the well-established risk factors of postoperative LE are essentially identical. This makes the volume of drainage fluid a potential surrogate parameter for the risk of postoperative swellings. The amount of drainage fluid after SLNB predicts the amount of drainage fluid after CLND. Further studies should evaluate whether the cumulative drainage fluid volume after SLNB can be used as a predictor of swellings after a subsequent CLND.

CONFLICT OF INTEREST AND DISCLOSURE

All authors declare that no competing financial interests exist.

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