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NO EVIDENCE OF BENEFIT FROM CLASS-II COMPRESSION STOCKINGS IN THE PREVENTION OF LOWER-LIMB LYMPHEDEMA AFTER INGUINAL LYMPH NODE DISSECTION: RESULTS OF A RANDOMIZED CONTROLLED TRIAL

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ABSTRACT

Graduated compression stockings have been advocated for prevention of lymphedema after inguinal lymph node dissection (ILND) although scientific evidence of their efficacy in preventing lymphedema is lacking. The primary objective of this study was to assess the efficacy of class II compression stockings for the prevention of lymphedema in cancer patients following ILND. Secondary objectives were to investigate the influence of stockings on the occurrence of wound complications and genital edema, health-related quality of life (HRQoL) and body image. Eighty patients (45 with melanoma, 35 with urogenital tumors) who underwent ILND at two specialized cancer centers were randomly allocated to class II compression stocking use for six months or to a usual care control group. Lymphedema of the leg and genital area, wound complications, HRQoL, and body image were assessed at regular intervals prior to and up to 12 months after ILND. No significant differences were observed between groups in the incidence of edema, median time to the occurrence of edema, incidence of genital edema, frequency of complications, HRQoL, or body image. Based on the results of the current study, routine prescription of class II graduated compression stockings after ILND should be questioned and alternative prevention strategies should be considered.

Keywords: Neoplasms, inguinal nodes, lymphadenectomy, lymphedema, prevention

Inguinal lymph node dissection (ILND) is performed in patients with lymph node metastasis of melanoma, urogenital, or anal tumors. ILND is associated with the frequent occurrence of short- and long-term postoperative complications (1-3). The most notable long-term complication is lymphedema of the leg with incidence varying from 13 to 55% after ILND for melanoma (1,4), 15 to 57% after ILND for penile cancer (5), and up to 69% after ILND in vulvar cancer patients (4,6-8). Risk factors include adjuvant radiotherapy, sartorius muscle transposition, and removal of the great saphenous vein (7,9). Lymphedema can also have a negative

impact on physical appearance, body- and self-image, mobility, health-related quality of life (HRQoL), and finances (10,11).

There is currently no international consensus regarding preventive measures, resulting in considerable variability in postoperative care. A graduated compression stocking has been advocated to prevent edema after inguinal node dissection (12). The efficacy of these stockings in obtaining and maintaining volume reduction for manifest lymphedema in the arm after axillary dissection has been demonstrated (13-15). The efficacy of graduated compression stockings in preventing lymphedema after removal of the (inguinal) lymph nodes has not yet been evaluated in a prospective, randomized trial.

Use of a stocking in the early postoperative period may influence the occurrence of early complications in either a positive or a negative way. The compression may prevent seroma accumulation in the groin but, alternatively, better drainage from the leg towards the groin may stimulate seroma formation. Negative effects may include inflammation of the wound because of friction and lymphedema of the genital area. Stocking use can also have both positive and negative effects on Health Related Quality of Life (HRQoL). If stocking use reduces the risk of lymphedema, it may improve physical and psychosocial functioning. Yet, wearing a stocking may impact negatively on body image and social participation.

The primary objective of this randomized controlled trial was to determine whether six months of postoperative use of a class-II (23-32 mmHg) graduated compression stocking reduces the incidence and severity of lymphedema of the leg after inguinal lymph node dissection. Secondary objectives were to investigate the impact of stocking use on the incidence of post-operative complications, HRQoL, and body image.

METHODS

Patients and Clinical Setting

The study sample was composed of patients from two specialized cancer treatment centers in the Netherlands, The Netherlands Cancer Institute-Antoni van Leeuwenhoek Hospital in Amsterdam and the Erasmus MC-Daniel den Hoed Cancer Center in Rotterdam, who fulfilled the following inclusion criteria: age >18 years, a diagnosis of melanoma, carcinoma of the penis or vulva, and scheduled to undergo ILND with curative intent for proven metastasis or as a prophylactic procedure. Exclusion criteria were: pre-existing lymphedema or prior episode of lymphedema, prior or simultaneous treatment with isolated limb perfusion, a history of deep venous thrombosis of the leg, local skin disease, lack of basic proficiency in the Dutch language, and serious cognitive or psychiatric problems.

Study Design

In this multicenter randomized controlled trial, a minimization procedure (16,17) was used to dynamically allocate participants to one of two groups: patient education alone or patient education combined with the use of a class-II graduated compression stocking (23-32mmHg) for six months postoperatively. The minimization algorithm was designed to balance the groups for primary tumor (melanoma or urogenital), additional deep node dissection (yes/no) and indication for adjuvant radiotherapy (yes/no). The allocation procedure was concealed and performed by the clinical trials office of The Netherlands Cancer Institute.

Ethics

The institutional review boards of the participating hospitals approved the trial. All patients provided written informed consent. The trial was registered with the Dutch trial register and the International Standard Randomized Controlled Trial Number Register (ISRCTN23026635).

Lymph Node Dissection

Various types of incisions were used for the operation. An inguinal dissection was always performed, removing the lymph nodes in the area that is confined by the medial surface of the long adductor muscle, the sartorius muscle, an imaginary line just above the inguinal ligament and the adductor canal. The base of the dissection is formed by the femoral vein and artery. The great saphenous vein was preserved if deemed oncologically safe. Prophylactic antibiotics were given according to local protocols. An additional deep dissection was not always performed, but when done included at least the external iliac nodes. It could also encompass common iliac and obturator nodes. Vacuum-drains were placed in the dissected areas. There was no strict protocol for prescription of antibiotics or removal of the drains.

Postoperative Care

On the first postoperative day, patients in both groups were encouraged to sit in a chair with their leg elevated, and they were fully ambulated from day two forward. All patients attended a single, individual education session on minimizing lymphedema risk. Additionally, all patients received an information folder on prevention and treatment of lymphedema. The intervention group was prescribed a full-leg length class-II compression stocking, which was measured to fit before operation and custom made, if necessary. The patients wore the stocking for at least one hour on the second day after the operation. From this day forward, use of the stocking was increased gradually over a maximum period of three days, until it was worn continuously during waking hours. If no lymphedema was present, stocking use was gradually reduced after six months. A physical therapist specialized in the field managed all patients in whom lymphedema developed during follow-up, following professional guidelines. Seroma formation occurring after removal of the vacuum drains was managed with needle aspiration.

Primary Outcome Measure

The primary outcome was the first occurrence of lymphedema in the ipsilateral leg. A specialized physical therapist measured the volume of the leg, using the standardized Kühnke's method of surface measurement (18). This method involves circular measurements at 4 cm intervals that allow the calculation of the volume of the segment. Circumference methods have good reliability and applicability for trend measurement (19,20). The presence of pitting edema was assessed through physical examination. Measurements were scheduled to coincide with regular (control) visits to the treating physician preoperatively (T0), at the time of discharge from the hospital (T1), and at approximately two months (T2), four months (T3), six months (T4) and 12 months (T5) postoperatively. Because the stocking leaves visible marks when removed, the physical therapists performing the outcome assessments could not be blinded, but they were blinded for their previous measurements. We defined lymphedema as a 10% or greater increase from baseline in volume of the proximal or distal half of the thigh or the lower leg. We classified lymphedema as nil ($\leq$10% volume increase compared to the baseline measurement), mild (10-20%), moderate (20-40%) or severe (>40%).

Secondary Outcome Measures

We abstracted the incidence of postoperative complications (infection, wound dehiscence, and seroma formation) within 30 days of the operation prospectively from the medical records. Infection was defined as an inflammation for which oral or intravenous antibiotics were prescribed. Seroma formation was defined as swelling that required needle aspiration that occurred after removal of the wound drain. At each

follow up visit, the physical therapist who performed the follow-up measurements assessed the presence of (pitting) lymphedema in the genital area by physical examination and recorded lymphedema requiring treatment and the reason for such treatment. Use of professional home care because of the stocking was also recorded. At T2, T3, and T4, we used a brief questionnaire to query the user's experiences and compliance (e.g., "Do you find the stockings comfortable to wear?" and "Are you able to put the stocking on without help?").

We assessed HRQoL at T0, T4, and T5 using the Dutch version of the SF-36 Health Survey (21) and body image at T4 and T5 using a cancer-specific body image scale (22). In the analysis, we focused on the two SF-36 component scores, one for physical health and one for mental health (23).

Statistical Analysis

A previously published observational study reported a 39% risk reduction for patients using stockings compared to those who did not, with a 45.8% incidence in the control group (24). We performed statistical power calculations on the assumption of a 40% incidence of lymphedema in the control group. With a total of 72 patients, the study would have 80% power to detect an absolute risk reduction of 30% in the incidence of lymphedema for the patients with a stocking compared to the control group, with a two-sided p value of 0.05, using Fisher's exact test (25). A risk reduction of 30% implies that approximately three patients would have to wear a stocking to prevent one extra case of lymphedema, which we considered clinically acceptable. To account for possible loss to follow-up, the sample size was set at 80 patients.

We generated descriptive statistics for relevant demographic and clinical characteristics at baseline. For baseline comparisons, we used Fisher's exact test for categorical variables and Student's t-test or Mann-Whitney U test for continuous variables. Similarly, we tested for between-group differences in background characteristics resulting from loss to follow-up at each assessment point.

All analyses of primary and secondary outcomes were performed using an intention-to-treat approach. For the incidence of lymphedema at 6 and 12 months postoperatively, the incidence of wound complications and genital edema, and the need for lymphedema treatment, we calculated relative risks (RR) with 95% confidence intervals (95% CI) and corresponding p-values (Fisher's exact test) based on available observations. Additionally, to compare time-to-event between the two groups, we used a Cox proportional hazards model that adjusted for the stratification variables of the minimization procedure (17) and relevant baseline imbalances. If lymphedema occurred in both legs after bilateral dissection, we used the earliest event in the analysis. The model incorporated all available data for all patients. Patients who dropped out of the study before a first occurrence of lymphedema were right censored. We report the adjusted hazard ratio (HR) from the model with a 95% CI.

For all tests, we considered a two-sided p value ≤ 0.05 to be statistically significant. All statistical analyses were performed using SPSS 18 for Windows (IBM SPSS, New York, USA).

RESULTS

Lymphedema

Of 125 eligible patients, 80 (45 with melanoma and 35 with cancer of the urogenital tract) were entered into the study. The median age was 59 years (range 20 - 85). Forty-one patients were allocated to the intervention group and the other 39 to the usual care group. *Fig. 1* provides the reasons for non-participation and displays the flow of participating patients through the study.

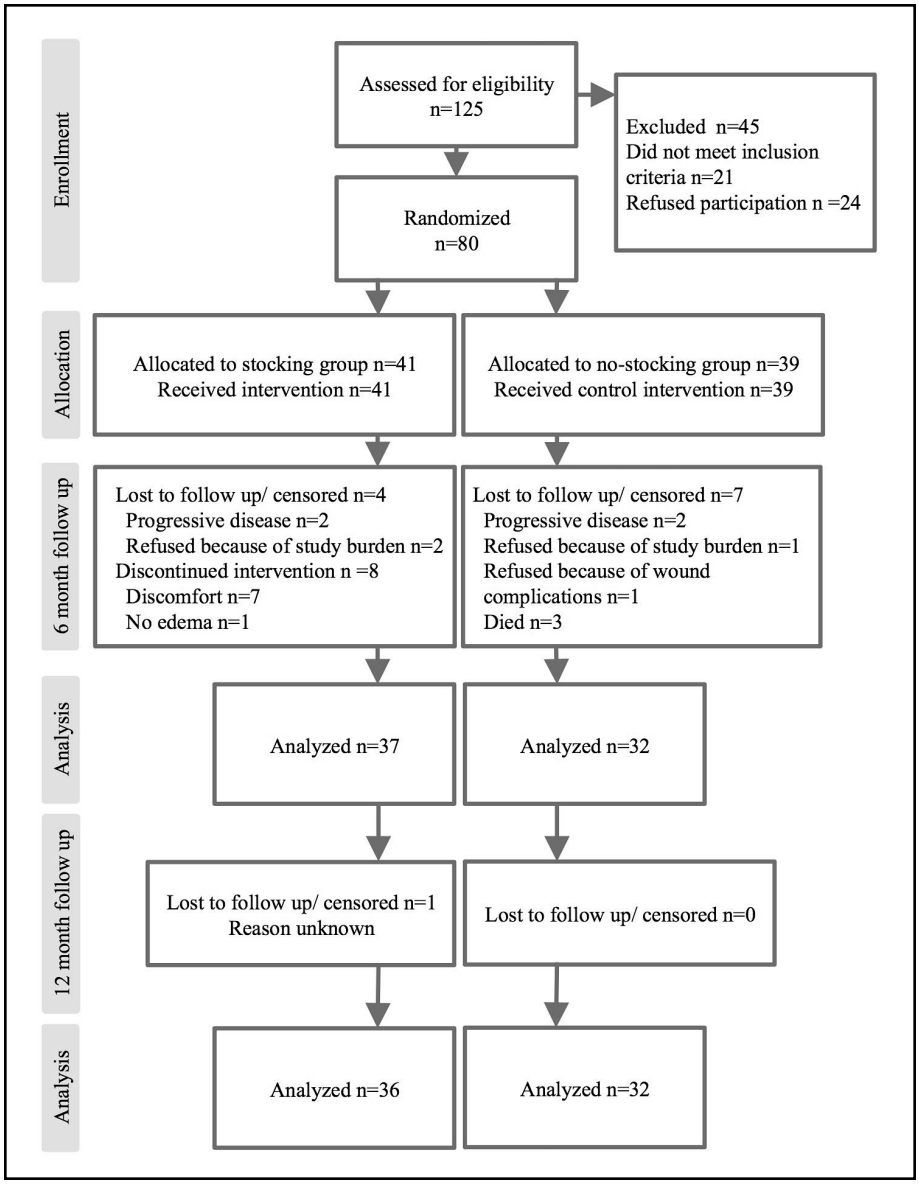

Fig. 1. Consort diagram of the study

The baseline characteristics of the study sample are described in *Table 1*. No significant differences between groups in clinical characteristics were present at baseline or any follow-up point.

At 6 month follow-up (T4), 24 of 37 evaluable patients (65%) in the stocking group and 26 of 32 evaluable patients (81%) in the control group had developed lymphedema (RR = 0.80, 95% CI 0.60 ; 1.07, p = 0.18). At 12 month follow-up (T5), 28 of 36 patients (77%) in the stocking group and 27 of 32 patients (84%) in the control group had developed lymphedema (RR = 0.92, 95% CI 0.73; 1.16, p = 0.55) (*Table 2*). Sensitivity analysis with a last observation carried

TABLE 1
Baseline Descriptives of the Patients

Number of patients	Patients With Stocking 41	Patients Without Stocking 39	p-value
Gender			
Male	20	23	0.38
Female	21	16	
Median age in years (range)	59 (20 - 81)	58 (22 - 85)	0.65
Median body mass index (range)	27.7 (17.9 - 46.1)	24.5 (19.6 - 35.1)	0.46
Number of patients with a melanoma	22	23	1.00
Number of patients with a urogenital tumor	18	17	
Number of dissections			
Unilateral	31	30	1.00
Bilateral	10	9	
Inguino-femoral lymphnode dissection	41	39	1.00
Deep lymphnode dissection:			
External iliac	21	20	1.00
Common iliac	10	11	0.80
Obturator	16	14	0.82
Number of dissections with preservation of the great saphenous vein	10	14	0.34
Number of sartorius muscle transpositions	6	7	0.77
Prophylactic antibiotics			
Yes	9	16	0.09
No	28	20	
Unknown	4	3	
Median number of removed lymph nodes (range)	13 (5 - 55)	12 (3 - 41)	0.88
Patients with initial bed rest	20	20	1.00
Median duration of bed rest in days (range)	2 (1 - 4)	1.5 (1 - 3)	0.98
Days with drainage			
Median (range)	10 (2- 28)	12 (1- 32)	0.54
Number of days until fully ambulated			
Median (range)	3 (1 - 7)	3 (1 - 7)	0.99
Postoperative day of discharge			
Median (range)	7 (1 - 18)	6 (3 - 24)	0.26
Number of patients with postoperative radiotherapy	4	7	0.34
Median duration of follow up in days (range)	336 (63 - 503)	327 (20 - 526)	0.74

TABLE 2
Univariate Results of Primary and Secondary Outcome Measures

	Patients With Stocking	Patients Without Stocking	Relative Risk (95% CI)	p-value
Lymphedema at 6 months[a]	24	26	0.80 (0.60; 1.07)	0.18
Lymphedema at 12 months[b]	28	27	0.92 (0.73; 1.16)	0.55
Postoperative complications				
Wound breakdown	9	7	1.25 (0.52; 3.03)	0.78
Infection	14	16	0.83 (0.47; 1.47)	0.65
Seroma formation	16	9	1.69 (0.85; 3.37)	0.15
Genital lymphedema	11	14	0.75 (0.39; 1.44)	0.47
Patients requiring treatment for lymphedema	21	22	0.91 (0.61; 1.36)	0.66
Reason for treatment:				
Progressive edema	8	11		
Stiffness because of edema	2	2		
Sensation of heaviness of the leg	4	2		
Abdominal/genital edema	2	2		
Other reasons	5	5		
Patients requiring professional homecare	6	6		

[a] N=37 for the stocking group and 32 for the control group
[b] N=36 for the stocking group and 32 for the control group

forward approach yielded qualitatively similar results. RR's for all time points are shown in *Fig. 2*. Lymphedema was classified as mild in all but 7 patients (4 in the stocking group and 3 in the control group, all of whom had moderate lymphedema). Cumulative incidence of lymphedema was 80% for melanoma patients and 57% for patients with cancer of the urogenital tract.

Genital Edema and Early Complications

There were no statistically significant group differences observed for genital edema or wound complications (*Table 2*). Thirteen patients in the stocking group and 12 patients in the control group developed more than a single wound complication. Genital edema developed in 25 patients (31%) and was resolved in 12 of these patients.

Multivariate Time-to-Event Analysis

Median time to diagnosis of lymphedema was 18 weeks in the intervention group and 12 weeks in the control group. After adjustment for preservation of the great saphenous vein, postoperative radiotherapy, and stratification variables, the hazard ratio was 0.69 (95% CI 0.38 to 1.26, p = 0.23) using 6 month follow-up data, and 0.70 (95% CI 0.40 to 1.24, p = 0.22) using 12 month follow-up data.

Patients' Experiences with the Stocking

Data on experience with the stocking and compliance were available for 33 patients (80%). At T2, 25 of these patients reported wearing the stocking daily. At four and six month follow-up, this practice was the case

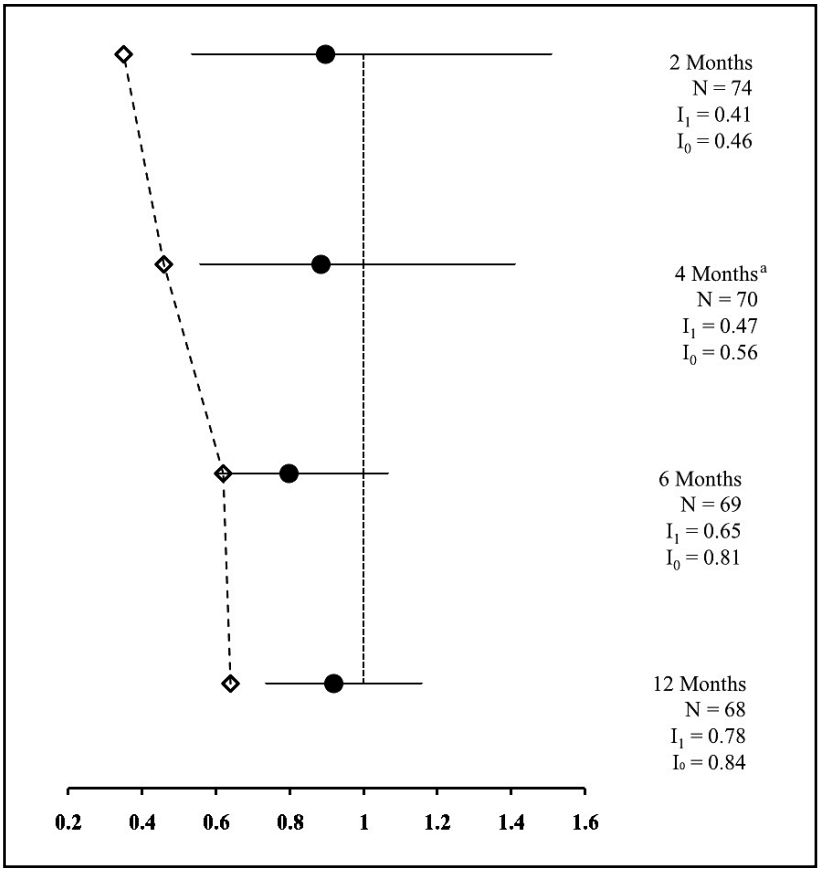

Fig. 2. Relative Risks for lymphedema (black dots) with corresponding 95% CI (whiskers) and threshold for clinical relevance of the RR (diamond markers and dashed line) based on background risk at each time point. I_1 and I_0 denote cumulative incidence of lymphedema at each time point for the intervention group and the control group respectively.
[a]Missing data on lymphedema were imputed using a 'last value carried forward' algorithm, only if the previous and subsequent assessments were available and were the same. In all other cases, missing data were not replaced. In total, 4 missing values were imputed (3 in the intervention group and 1 in the control group).

for 24 patients. Six patients reported requiring assistance in putting on the stocking. At all assessment points, approximately one-third of the patients reported that they deliberately chose clothing that covered up the stocking. Also, approximately one-third of the patients indicated that the stocking was uncomfortable to wear. There were no significant differences in these ratings between patients who had lymphedema and those who did not, although patients with lymphedema were more likely to rate the stocking as comfortable than patients without lymphedema.

HRQoL and Body Image

Standardized mental and physical component scores for the SF-36 could not be calculated for 11 patients at T0 and three patients at T4, due to missing data. HRQoL and BIS data were not evaluable for 21 patients at T4 and 33 patients at T5 due to loss to follow-up for these measures.
The available data indicated no significant differences between the groups at any assessment point (*Table 3*).

TABLE 3
Quality of Life and Body Image Scores

	Patients With Stocking	Patients Without Stocking	Mean Difference (95% CI)	t-value	Df[1]	p-value
T0 (baseline)	n = 36	n = 33				
Mean SPCS[2] (SD)	45.5 (12.2)	47.9 (9.2)	2.4 (-2.8; 7.7)	0.93	67	0.356
Mean SMCS[3] (SD)	48.7 (10.5)	51.5 (10.6)	2.8 (-2.3; 7.8)	1.1	67	0.275
T4 (6 month follow up)	n = 31	n = 25				
Mean SPCS (SD)	43.4 (11.1)	47.5 (9.4)	4.3 (-1.3; 9.9)	1.47	54	0.147
Mean SMCS (SD)	51.2 (9.0)	53.7 (8.6)	2.4 (-2.2; 7.3)	1.29	54	0.202
BIS[4] score	n = 35	n = 25				
Median (min; max)	14 (10; 30)	14 (10; 27)				0.662[5]
T5 (12 month follow up)	= 26	n = 21				
Mean SPCS (SD)	45.7 (11.7)	49.4 (9.0)	3.8 (-2.5; 10.0)	1.22	45	0.228
Mean SMCS (SD)	51.7 (8.4)	52.9 (7.3)	1.3 (-3.4; 6.0)	1.25	45	0.218
BIS[4] score	n = 24	n = 23				
Median (min; max)	15 (10; 34)	16 (10; 25)				0.898[5]

[1]Df = Degrees of freedom, [2]SPCS = Standardized Physical Component Score of MOS-Short Form 36 Health Survey, [3]SMCS =Standardized Mental Component Score of MOS-Short Form 36 Health Survey, [4]BIS= Body Image Scale, [5]P-value as obtained from Mann-Whitney U test

DISCUSSION

There was no statistically significant difference in the incidence or severity of lymphedema between patients who used a class-II graduated compression stocking for a period of six months after ILND and those who did not. The study was powered on the assumption of a 30% risk difference, while the observed relative risk (if real) translates to a 14% risk difference in favor of the intervention group. Considering the apparent absence of harmful effects of the stocking, some might judge this finding as clinically relevant. At the same time, one needs to keep in mind that, based on these results, approximately seven patients would need to use a stocking to prevent one extra case of lymphedema. Estimated time-to-event for lymphedema was longer in the intervention group, but only by 6 weeks.

Our findings can be contrasted with those of Karakousis et al, who reported an absolute risk difference of 39% between patients who wore stockings and those who did not (24). That study was observational in nature and thus it may have been biased by confounding. In a recent randomized controlled pilot study of 22 patients with vulvar cancer, increase in leg volume was significantly less in the patients who wore stockings than in those who did not (19). However, when using a clinically relevant cut-off of 10% increase in leg volume, there was no statistically significant difference between the groups. This latter finding is consistent with our results.

In the current study, there were some imbalances at baseline, although none of

them were statistically significant. Median BMI was 3.2 points higher in the stocking-group. Although BMI is associated with lymphedema risk after axillary lymph node dissection, this is not the case for ILND (7,26-28). Preservation of the great saphenous vein and postoperative radiotherapy were more common in the control group. The latter imbalance occurred due to the fact that some patients who were not initially scheduled to undergo radiotherapy actually did so, based on the postoperative pathology report. Since these variables have been associated with increased risk of lymphedema (4,26-28), we performed a Cox-regression analysis that adjusted for these imbalances.

Wound complications occurred frequently in our study, but were not associated significantly with stocking use. This finding is consistent with the results reported by Sawan et al (19).

The intervention in our study consisted of daytime only use of class-II compression stockings. Hypothetically, round the clock use and/or the use of a higher compression class could be more effective. It should be noted, however, that the use of compression stockings for prevention of lymphedema carries with it both direct and indirect costs. Some patients, and especially the elderly, are not able to put on the stocking themselves and thus become dependent on informal or professional caregivers. Round the clock use and/or the use of a higher compression class would likely increase discomfort and/or dependency rates and should also first be tested in a randomized trial.

Because of the intensive follow-up regimen in the current study, all patients who developed swelling of the leg could be diagnosed and treated in a timely manner. Preoperative volume assessment and regularly scheduled follow-up visits, combined with patient education emphasizing the importance of early detection may be more patient-friendly and cost-effective than preventive compression therapy. This approach, too, should be evaluated formally.

It has been suggested that manual lymph drainage with or without the concomitant use of compression garments has the potential to reduce lymphedema risk. Studies in patients at risk for lymphedema after surgical treatment for breast cancer show inconsistent results with regard to the effectiveness of this treatment, and no studies have been done in patients after ILND (29-31). Further research on this issue is therefore necessary.

Some limitations of this study should be noted. First, it was not possible to blind either patient or outcome assessors, which may have introduced some bias. We would note, however, that the Kühnke volumetry method (18) used in our study consists of 18 to 22 circumference measurements per leg. The physical therapists were blinded to their previous assessments at the time of taking measurements, and it is improbable that they could have recalled their findings from several months earlier. Second, the number of patients for whom follow-up ended because of a clinical event other than lymphedema was higher than anticipated, resulting in a somewhat larger chance of a type-II error. Relative risks however, were stable throughout the study. Although more patients were lost to follow-up in the control group than in the intervention group, it is unlikely that this factor biased the results, since the reasons for dropout were not related to the outcome, and there were no significant differences in frequency of known risk factors between the groups at any time point.

Notable strengths of the study were the prospective assessment of lymphedema and surgical complications, and its randomized controlled design.

CONCLUSION

Sixty-nine percent of patients with melanoma or urogenital cancer experienced lymphedema after undergoing inguinal node dissection. The use of a graduated compression stocking did not reduce the incidence of lymphedema by the a priori criterion of 30%,

nor was there a significant salutary effect observed on the incidence of surgical complications, HRQoL, or body image. Based on the results of the current study, routine prescription of class-II graduated compression stockings after ILND should be questioned, and alternative prevention strategies should be considered.

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