Morbidity after lymph node dissection in patients with cancer: Incidence, risk factors, and prevention
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CHAPTER 4

No evidence of benefit from class-II compression stockings in the prevention of lower-limb lymphoedema after inguinal lymph node dissection; Results of a randomized controlled trial

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ABSTRACT

Background and Objective
Graduated compression stockings have been advocated for prevention of lymphoedema after inguinal lymph node dissection (ILND). Scientific evidence of their efficacy in preventing lymphoedema is lacking. The primary objective of this study was to assess the efficacy of class II compression stockings for the prevention of lymphoedema in cancer patients following ILND. Secondary objectives were to investigate the influence of stockings on the occurrence of wound complications and genital oedema, health related quality of life (HRQoL) and body image.

Methods
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. Lymphoedema in 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.

Results
No significant differences were observed between groups in the incidence of oedema, median time to the occurrence of oedema, incidence of genital oedema, frequency of complications, HRQoL or body image.

Conclusion
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.
Introduction

Inguinal lymph node dissection (ILND) is performed in patients with lymph node metastasis of melanoma, urogenital or anal tumours. ILND is associated with the frequent occurrence of short- and long-term postoperative complications 1-3. The most notable long-term complication is lymphoedema of the leg. The incidence of lymphoedema varies from 13 to 55% after ILND for melanoma 1,4,15 to 57 percent after ILND for penile cancer 5 and up to 69% after ILND in vulva cancer patients 4,6-8. Risk factors include adjuvant radiotherapy, sartorius muscle transposition, and removal of the great saphenous vein 7,9. Lymphoedema can 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 oedema after inguinal node dissection 12. The efficacy of these stockings in obtaining and maintaining volume reduction for manifest lymphoedema 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 by the stocking 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 lymphoedema 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 lymphoedema, 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 lymphoedema 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 centres 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 lymphoedema or prior episode of lymphoedema, 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 multicentre 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 on primary tumour (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.

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 this was 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, the 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 lymphoedema risk. Additionally, all patients received an information folder on prevention and treatment of lymphoedema. 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 lymphoedema was present, stocking use was gradually reduced after six months. A physical therapist specialized in the field managed all patients in whom lymphoedema developed during follow-up, following professional guidelines. Seroma formation occurring after removal of the vacuum drains was managed with needle aspiration.

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).

Primary outcome measure
The primary outcome was the first occurrence of lymphoedema 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. The presence of pitting oedema 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 lymphoedema 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 lymphoedema as nil (≤10% volume increase compared to the baseline measurement), slight (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) lymphoedema in the genital area by physical examination and recorded lymphoedema requiring treatment and the reason for such treatment. Use of professional homecare 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 hose 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 and body image at T4 and T5 using a cancer-specific body image scale. In the analysis, we focused on the two SF-36 component scores, one for physical health and one for mental health.

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. We performed statistical power calculations on the assumption of a 40% incidence of lymphoedema 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 lymphoedema 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. A risk reduction of 30% implies that approximately three patients would have to wear a stocking to prevent one extra case of lymphoedema, 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 lymphoedema at 6 and 12 months postoperatively, the incidence of wound complications and genital oedema, and the need for lymphoedema 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 and relevant baseline imbalances. If lymphoedema 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 lymphoedema 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).

Figure 1
Consort diagram of the study

- Enrollment
  - Assessed for eligibility n = 125
  - Excluded n = 45
    - Did not meet inclusion criteria (21)
    - Refused participation (24)
  - Randomized n = 80
    - Allocated to stocking group n = 41
      - Received intervention n = 41
        - Lost to follow up/ censored n = 4
          - Progressive disease (2)
          - Refused due to study burden (2)
        - Discontinued intervention n = 8
          - Discomfort (7)
          - No Oedema (1)
    - Allocated to no-stocking group n = 39
      - Received allocated intervention n = 39
        - Lost to follow up/ censored n = 7
          - Progressive disease (2)
          - Refused due to study burden (1)
          - Refused due to wound complications (1)
          - Discomfort (7)
          - Died (3)
  - 6 months
    - Analyzed n = 37
    - Analyzed n = 32
  - 12 months
    - Lost to follow up/ censored n = 1
      (reason unknown)
    - Lost to follow up/ censored n = 0
    - Analyzed n = 36
    - Analyzed n = 32
Results

Lymphoedema
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. Figure 1 provides the reasons for non-participation and displays the flow of participating patients through 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 lymphoedema (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 lymphoedema (RR = 0.92, 95% CI 0.73 ; 1.16, p = 0.55) (table 2). Sensitivity analysis with a last observation carried forward approach yielded qualitatively similar results. RR’s for all time points are shown in figure 2. Lymphoedema was classified as slight in all but 7 patients (4 in the stocking group and 3 in the control group, all of whom had moderate lymphoedema). Cumulative incidence of lymphoedema was 80% for melanoma patients and 57% for patients with cancer of the urogenital tract.

Genital oedema and early complications
There were no statistically significant group differences observed for genital oedema 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 oedema developed in 25 patients (31%) and was resolved in 12 of these patients.

Multivariate time-to-event analysis.
Median time to diagnosis of lymphoedema 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 was the case 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 lymphoedema and those who did not, although patients with lymphoedema were more likely to rate the stocking as comfortable than patients without lymphoedema.
Table 1  
**Baseline descriptives of the patients**

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

*Deep dissection included at least the external iliac nodes*
Table 2  
*Univariate results of primary and secondary outcome measures.*

<table>
<thead>
<tr>
<th></th>
<th>Patients with stocking</th>
<th>Patients without stocking</th>
<th>Relative Risk (95%CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>number</td>
<td>number</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lymphoedema at 6 months*</td>
<td>24</td>
<td>26</td>
<td>0.80 (0.60 ; 1.07)</td>
<td>0.18</td>
</tr>
<tr>
<td>Lymphoedema at 12 monthsb</td>
<td>28</td>
<td>27</td>
<td>0.92 (0.73 ; 1.16)</td>
<td>0.55</td>
</tr>
<tr>
<td>Postoperative complications</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wound breakdown</td>
<td>9</td>
<td>7</td>
<td>1.25 (0.52 ; 3.03)</td>
<td>0.78</td>
</tr>
<tr>
<td>Infection</td>
<td>14</td>
<td>16</td>
<td>0.83 (0.47 ; 1.47)</td>
<td>0.65</td>
</tr>
<tr>
<td>Seroma formation</td>
<td>16</td>
<td>9</td>
<td>1.69 (0.85 ; 3.37)</td>
<td>0.15</td>
</tr>
<tr>
<td>Genital lymphoedema</td>
<td>11</td>
<td>14</td>
<td>0.75 (0.39 ; 1.44)</td>
<td>0.47</td>
</tr>
<tr>
<td>Patients requiring treatment for lymphoedema</td>
<td>21</td>
<td>22</td>
<td>0.91 (0.61 ; 1.36)</td>
<td>0.66</td>
</tr>
<tr>
<td><em>Reason for treatment:</em></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Progressive oedema</td>
<td>8</td>
<td>11</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stiffness because of oedema</td>
<td>2</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sensation of heaviness of the leg</td>
<td>4</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abdominal/genital oedema</td>
<td>2</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other reasons</td>
<td>5</td>
<td>5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients requiring professional homecare</td>
<td>6</td>
<td>6</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* 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

**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.

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

$^1$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 lymphoedema 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 favour of the intervention group. Considering the apparent absence of harmful effects of the stocking, some might judge this 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 lymphoedema. Estimated time-to-event for lymphoedema 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. 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. 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 lymphoedema risk after axillary lymph node dissection, this is not the case for ILND.
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 lymphoedema, 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 is consistent with the results reported by Sawan et al. It has been suggested that manual lymph drainage with or without the concomitant use of compression garments has the potential to reduce lymphoedema risk. Studies in patients at risk for lymphoedema 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. Further research into this subject is therefore necessary.

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.

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 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 lymphoedema 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 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 lymphoedema and surgical complications, and its randomized controlled design.

Conclusion

Sixty-nine percent of patients with melanoma or urogenital cancer experienced lymphoedema after undergoing inguinal node dissection. The use of a graduated compression stocking did not reduce the incidence of lymphoedema 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.
Figure 2
Relative Risks for lymphoedema (grey dots) with corresponding 95%CI (whiskers), and threshold for a priori defined clinical relevance of the RR (dashed line) based on background risk at each timepoint. N, I0 and I1 indicate number of patients, cumulative incidence for lymphoedema for the stocking group (I1) and the no-stocking group (I0) up to that timepoint.

* Missing data on lymphoedema 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).

Acknowledgment
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REFERENCES


