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Surgical-site infection following lymph node excision indicates susceptibility for lymphedema: A retrospective cohort study of malignant melanoma patients

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Background and Objectives:

Cancer-related lymphedema is a common complication following lymph node excision. Prevention of lymphedema is essential, as treatment options are limited. Known risk factors are firmly anchored to the cancer treatment itself; however potentially preventable factors such as seroma and surgical-site infection (SSI) have yet to be asserted.

Methods:

All malignant melanoma patients treated with sentinel lymph node biopsy (SNB) and/or complete lymph node dissection (CLND) in the axilla or groin between January 2008 and December 2014 were retrospectively identified. Identified patients were followed until March 2017 for the incidence of lymphedema.

Results:

We identified 70 cases of extremity lymphedema following 640 SNB/CLND. SSI was an independent risk factor for developing lymphedema (HR 8.46, 95%CI 4.37-16.36, p < 0.001), whilst seroma was an independent risk factor for developing SSI (OR 6.92, 95%CI 4.11-12.54, p < 0.001). In addition, the risk of lymphedema was significantly larger following inguinal incisions compared to axillary incisions (HR 2.49, 95%CI 1.36-4.55, p < 0.05).

Conclusion:

SSI was the greatest independent risk factor for developing lymphedema. Additionally, patients’ that developed postoperative seroma were at an increased risk of also developing SSI. Future studies should examine if lymphedema can be prevented, by reducing seroma and SSI.

Keywords: Lymphadenectomy, seroma, surgical wound infection, risk factors
Introduction

Malignant melanoma (MM) has a worldwide increasing incidence\textsuperscript{1}, and can metastasize through lymphatic pathways to regional lymph nodes. Sentinel lymph node biopsy (SNB) is the gold-standard for regional staging of MM\textsuperscript{2}, and in case of positive sentinel lymph nodes, the involved lymph nodes basin is usually removed by complete lymph node dissection (CLND). Although the therapeutic value of CLND is unproven, the procedure is still performed despite the associated morbidity\textsuperscript{3}. Lymphedema is a dreaded complication following lymph node surgery, often characterized by swelling and lymph stasis, which can induce subcutaneous inflammation and fibrosis\textsuperscript{4,5}. Lymphedema of the extremities carries an increased risk of erysipelas, cellulitis and lymphangitis, which is associated with an overall lowered quality of life\textsuperscript{6}. Prevention or reducing the risk of lymphedema is crucial\textsuperscript{7}, as the current treatment options are suboptimal. Early identification of affected patients is of importance, as both conservative and experimental treatments have been shown to be most effective, when initiated early in disease progression\textsuperscript{8,9}. Several inevitable and MM-treatment related risk factors for extremity lymphedema have been identified, such as wide local excision, inguinal lymph node excision, CLND and radiotherapy\textsuperscript{10,11}. However it has been uncertain, whether potentially preventable conditions such as seroma and surgical-site infection (SSI) increases the risk of lymphedema\textsuperscript{12,13}. Hence, the aim of this study was to identify possible risk factors and indicators for lymphedema, in patients undergoing axillary or inguinal SNB/CLND as part of their MM treatment.
Materials and Methods

This study was conducted as a retrospective cohort study and reported according to the recommendations by the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement. Patients diagnosed, staged and treated for MM including SNB and/or CLND in the axilla and groin between 2008 and 2014 at Odense University Hospital, Denmark were identified by surgical procedure codes.

Patient demographics, tumor and lymph node characteristics as well as data related to the surgical procedure were retrieved from registries and medical charts. Treatment codes for seroma drainage in the outpatient clinic were retrieved and registered as a binary variable for each incision within the first three months of SNB/CLND. SSI was registered and defined as any patient treated with oral or intravenous antibiotics on infectious indication to the lymph node incision within one month of SNB/CLND, reoperation or seroma aspiration as recommended by The Center for Disease Control. Reoperation of the surgical site was registered for up to three months, and defined as any opening of the wound or scar while the patient was in general anesthesia.

Lymphedema was defined as patients who received complete decongestive therapy to the correlating extremity. The follow-up program for MM included a minimum of two visits at the oncology department per year. Guidelines dictated that if lymphedema was clinically evident, patients were to be referred to the Department of Physical Rehabilitation for lymphedema evaluation. Referred patients received complete decongestive therapy at the physiotherapist’s clinical evaluation. For this study, patients that received physiotherapeutic lymphedema treatment were identified using a specific treatment code.

For CLND, patients received a single dosage of intravenous perioperative antibiotics (cefuroxime, 1.5g). Department guidelines detailed that drains were to be removed, when the daily output was less than 50 mL or at the 5th postoperative day, however the final decision was at the discretion of
the operating surgeon. Daily drain output volume was registered, as were the total number of days with drains in situ.

All included incision sites were followed from the date of their latest lymph node operation; SNB or CLND, up until the correlated limb was diagnosed with lymphedema, patient migration, death from any cause, or March 2017, whichever came first. Any missing data was added by scrutinizing electronic medical journals.

**Statistical analysis**

Baseline characteristics were described with means ± standard derivation (SD) for continuous parametric variables, median (interquartile range (IQR)) for continuous nonparametric variables and rounded frequencies (%) for categorical variables. STATA 14 (StataCorp. 2015. *Stat Statistical Software: Release 14*. College Station, TX: StataCorp LP) was used for the statistical analysis and conducted with a two-tailed significance level of .05 and reported with 95%CI when applicable. Baseline characteristics were compared between patients with and without lymphedema with an unpaired t-test, Chi-squared or Mann-Whitney test depending on data type and distribution. Skewness and kurtosis test of all variables and groupings was used for normality testing. Age, BMI and statistically significant baseline variables were included in the multivariate analyses. For lymphedema risk analysis, the relevant variables were included in a multivariate cox regression model. Using the same variables, a risk profile was established for SSI using a multivariate logistic regression model. All statistical analyses were completed in collaboration with the Department of Biostatistics and Epidemiology, University of Southern Denmark, Odense, Denmark.
Results

We diagnosed and treated 2507 patients for MM between 2008 and 2014, see Figure 1 for flowchart. SNB and/or CLND were performed in the axilla and/or groin in 560 patients, with a mean tumor thickness of 2.33±0.11mm and a median age of 61(22). In these 560 patients, 640 SNB/CLND were registered, Table 1. The median total follow up time was 1630 (1282) days and 82 patients died within the follow up period. CLND was performed due to a positive SNB in 127 cases of which 13 was found to have additional lymph node metastasis.

During the follow up period, lymphedema was diagnosed in a total number of 70 limbs. The median number of days from SNB/CLND until lymphedema diagnosis was 173 (330) days, Figure 2A. Seroma, SSI and lymphedema occurred more frequently following CLND when compared to SNB (p < 0.05), Table 2 and Figure 2B. These postoperative complications also occurred more often after inguinal operations compared to axillary operations (p < 0.05).

The multivariate cox analysis revealed that SSI was a major indicator for lymphedema (HR 8.46, 95%CI 4.37-16.36, p < 0.001) along with CLND when compared to SNB (HR 3.14 95%CI 1.35-7.31, p < 0.05) and inguinal operation when compared to axillary operation (HR 2.49 95%CI 1.36-4.55, p < 0.05), Table 3. After exclusion of SSI from the multivariate cox regression model, seroma proved to be a statistically significant predictor for lymphedema (HR 1.89, 95%CI 1.07-3.35, p < 0.05). Additionally, postoperative seroma was the greatest risk factor for SSI (OR 7.28, 95%CI 4.18-12.69, p < 0.001) along with CLND (OR 4.48, 95%CI 2.13-9.45, p < 0.05) and inguinal operation (OR 1.99, 95%CI 1.19-3.32, p < 0.05) as revealed in Table 4.

The number of seroma aspirations proportionally increased the risk of subsequent lymphedema as shown in Figure 3A. Seroma aspirations also increased the risk of SSI as shown in Figure 3B and subsequent lymphedema as presented in Figure 3C.
**Discussion**

In this study, we mapped risk factors for developing extremity lymphedema and unraveled how a cascade of postoperative events leads to an increased lymphedema risk. Our study suggests that SSI may mediate lymphedema onset following SNB and CLND in the axilla and groin. We found seroma to be the most predominant postoperative complication, and linked to an increased risk of subsequent SSI. **Seroma indicated an increased risk of lymphedema, however as seroma were often followed by infection, a multivariate analysis of both variables lead to the effect being mediated through infection.** Additionally, removal of lymph nodes in the groin was associated with a greater risk of postoperative seroma, SSI, reoperation and lymphedema development when compared to lymph node removal in the axilla. These findings may aid clinicians in identifying patients with a high risk of developing lymphedema.

The majority of lymphedema risk factor studies are conducted in breast- and urogenital cancer populations\textsuperscript{16,17}. The surgical treatment of these cancers is often complemented with adjuvant radiation and systemic therapy, which is rarely the case for MM patients and is the reason why studies on MM patients are needed. **In this study, lymphedema occurred more frequently after inguinal incisions compared to axillary incisions, which is consistent with literature\textsuperscript{10,12}.** Obesity and increasing age has previously been associated with a risk of lymphedema\textsuperscript{18}, however in this study, these parameters were not found to be independent risk factors.

The surgical divisions of lymphatic vessels during lymph node resection were likely the major causes of seroma formation and subsequent extremity lymphedema. Seroma has been assumed to origin from inflammatory lymphovascular leakage\textsuperscript{19}, jeopardize wound healing and **possibly provide an entry for infection.** The increased risk of lymphedema for patients with SSI may be elucidated by the immunological response. The immunological host response to a bacterial infection is a sustained release of bradykinin, which impairs physiological lymphatic function\textsuperscript{20}. The net
effect is then a sequestration of macromolecules and fluid, which further distorts the lymphatic system. The findings herein, which associates seroma to lymphedema is consistent with our previous publication in breast cancer patients\textsuperscript{21}, and a study by Ul-mulk et al. who found an association between seroma and SSI following inguinal CLND\textsuperscript{22}, but not axillary CLND.

A few minor limitations apply to this study, and should be acknowledged when interpreting our findings. Due to the retrospective nature of our cohort, the definition of lymphedema depended not on excessive volume measures or inhibited lymph flow patterns. Instead we used a pragmatic approach and identified all patients who had received physiotherapeutic lymphedema treatment.

The incidence of lymphedema is known to vary between studies\textsuperscript{17}, depending on its definition and the length of follow up. In this study, lymphedema was defined as the need for lymphotherapeutic treatment, and the incidence were found to be in the high-end spectrum of previous reporting\textsuperscript{17,23}.

Owing to our definition of lymphedema, it is possible that we may have included patients with milder cases of lymphedema, which would not have met circumferential or volumetric thresholds in prospective trials\textsuperscript{17}. In the same context, we defined seroma as a fluid aspiration from the surgical site, without an assigned lower volumetric limit. Furthermore, we made no distinguishing between superficial and deeper levels of SSI, but merely on the necessitation of antibiotic treatment.

Early diagnosis and treatment is crucial for curbing lymphedema, but currently there is little emphasis on diagnosing lymphedema after ended cancer treatment\textsuperscript{24}. Patients, at high risk of developing lymphedema, could benefit from a high-efficacy screening program effectuated at follow-up consultations. Previous studies have stressed lymph flow imaging as an essential tool for a precise lymphedema diagnosis, and indocyanine green lymphography has so far shown to be an efficient bedside tool for diagnosing even subclinical lymphedema\textsuperscript{25,26}. Theoretically, a reduction in the number of patients with postoperative seroma and SSI, may also lead to a reduction in the number of patients with lymphedema. Despite the prophylactic effort of antiseptic skin preparations
and systemic perioperative antibiotic treatment, SSI still occurs to a wide extent. The most straightforward solution could be a long-term antibiotic prescription, however concerns of multi-resistant strains have been raised, and have therefore not been recommended for clean surgeries\textsuperscript{27}. Hypothermia is a known hotbed for infection\textsuperscript{28}, and a more prudent approach could therefore be to maintain normothermia at the surgical site. Similarly, the optimal intervention for seroma prevention following CLND has not been found as of yet\textsuperscript{29}, nevertheless has incisional Negative Pressure Wound Therapy (iNPWT) so far shown promising results in the prevention of seroma and wound infection across several incision sites\textsuperscript{30,31}. While there is a deficiency on high quality iNPWT efficacy trials following oncological procedures, the initial results for lymphedema prevention are encouraging\textsuperscript{32}.

**Ethical approval**

This study was registered with the Danish Data Protection Agency (2012-58-0018) and approved by the Danish Health and Medicines Authority (3-3013-1759/1/).

**Conflict of interest**

The authors declare no conflicts of interest.

**Acknowledgments**

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Role of the funding source

The study sponsor was not involved in the study design, the data acquisition, analysis or interpretation, in the manuscript writing or editing or in the decision to submit the manuscript.

References


26. Yamamoto T, Matsuda N, Doi K, et al. The earliest finding of indocyanine green lymphography in asymptomatic limbs of lower extremity lymphedema patients secondary to cancer treatment: the modified dermal backflow stage and concept of subclinical


Figure legends:

Figure 1 legend: Patient selection and subgroupings. This figure shows the flow of malignant melanoma patients in the period of 2008-2014.

Figure 2 legend: Lymphedema following axillary and inguinal lymph node excision. A) Distribution of patients over time without lymphedema stratified by their initial operation. B) Distribution and comparison of operated patients with and without lymphedema, stratified by SNB and CLND at the axilla and groin. P-value denotes the significance level. SNB = Sentinel lymph node biopsy. CLND = Complete lymph node dissection.

Figure 3 legend: Correlations between seroma, infection and lymphedema. A) Distribution of patients over time without lymphedema stratified by the number of seroma aspirations. B) Correlation between patients with surgical-site infection and the number of seroma aspirations. C) Correlation between patients with postoperative surgical-site infection and subsequent lymphedema. P-value denotes the significance level between groups.
Table 1: Incision site and lymphedema characteristics

<table>
<thead>
<tr>
<th>Variables</th>
<th>Total (N=640)</th>
<th>Lymphedema (N=70)</th>
<th>Unaffected (N=570)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (Years)</strong></td>
<td>Mean±SD</td>
<td>58.51±0.59</td>
<td>56.46±1.83</td>
<td>58.76±0.63</td>
</tr>
<tr>
<td><strong>BMI above 30 kg/m²</strong></td>
<td>N(%)</td>
<td>126(20)</td>
<td>12(17)</td>
<td>114(20)</td>
</tr>
<tr>
<td><strong>Sentinel lymph node biopsies</strong></td>
<td>N(%)</td>
<td>493(77)</td>
<td>20(29)</td>
<td>473(83)</td>
</tr>
<tr>
<td><strong>Axillary</strong></td>
<td>N(%)</td>
<td>295(46)</td>
<td>5(7)</td>
<td>290(51)</td>
</tr>
<tr>
<td><strong>Inguinal</strong></td>
<td>N(%)</td>
<td>198(31)</td>
<td>15(21)</td>
<td>183(32)</td>
</tr>
<tr>
<td><strong>Complete lymph node dissections</strong></td>
<td>N(%)</td>
<td>147(23)</td>
<td>50(71)</td>
<td>97(17)</td>
</tr>
<tr>
<td><strong>Axillary</strong></td>
<td>N(%)</td>
<td>67(10)</td>
<td>11(15)</td>
<td>56(10)</td>
</tr>
<tr>
<td><strong>Incl. neck dissection</strong></td>
<td>N(%)</td>
<td>4(1)</td>
<td>2(3)</td>
<td>2(0)</td>
</tr>
<tr>
<td><strong>Inguinal</strong></td>
<td>N(%)</td>
<td>80(13)</td>
<td>39(56)</td>
<td>41(7)</td>
</tr>
<tr>
<td><strong>Incl. Iliac dissection</strong></td>
<td>N(%)</td>
<td>6(1)</td>
<td>6(9)</td>
<td>0(0)</td>
</tr>
<tr>
<td><strong>Drains in situ ≥ 5 days</strong></td>
<td>N(%)</td>
<td>98(15)</td>
<td>38(54)</td>
<td>60(11)</td>
</tr>
<tr>
<td><strong>Total volume in drains</strong></td>
<td>Median(IQR)</td>
<td>575(515)</td>
<td>623.5(480)</td>
<td>510(508)</td>
</tr>
<tr>
<td><strong>Total number of removed lymph nodes</strong></td>
<td>Median(IQR)</td>
<td>2(4)</td>
<td>10(11)</td>
<td>2(3)</td>
</tr>
<tr>
<td><strong>Total number of metastatic lymph nodes</strong></td>
<td>Median(IQR)</td>
<td>0(0)</td>
<td>1(2)</td>
<td>0(0)</td>
</tr>
<tr>
<td><strong>Perinodal growth in metastatic lymph nodes</strong></td>
<td>N(%)</td>
<td>21(3)</td>
<td>10(14)</td>
<td>11(2)</td>
</tr>
<tr>
<td><strong>Surgical-site infection</strong></td>
<td>N(%)</td>
<td>110(17)</td>
<td>52(74)</td>
<td>58(10)</td>
</tr>
<tr>
<td><strong>Reoperation</strong></td>
<td>N(%)</td>
<td>26(4)</td>
<td>16(23)</td>
<td>10(2)</td>
</tr>
<tr>
<td><strong>Seroma</strong></td>
<td>N(%)</td>
<td>130(20)</td>
<td>41(59)</td>
<td>89(16)</td>
</tr>
</tbody>
</table>

**Table 1 legend:** This table shows the characteristics of the axillary and inguinal incision sites as a whole and dived based on the lymphedema diagnosis to the correlating limb. P-values denote the difference between the subgroups. n.s = Not significant.

N = Number, SD = Standard deviation, IQR = Interquartile range (Q3-Q1).
Table 2: Overview of the major complications following axillary and inguinal SNB and CLND

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Total (N=640)</th>
<th>Seroma (N=130)</th>
<th>Reoperation (N=26)</th>
<th>SSI (N=110)</th>
<th>Lymphedema (N=70)</th>
<th>Unaffected (N=456)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Axillary CLND</td>
<td>67(100)</td>
<td>30(45)*</td>
<td>4(6)</td>
<td>19(28)*</td>
<td>11(16)*</td>
<td>27 (40)*</td>
</tr>
<tr>
<td>Inguinal CLND</td>
<td>80(100)</td>
<td>54 (68)**</td>
<td>20 (25)**</td>
<td>49 (61)**</td>
<td>39 (49)**</td>
<td>13 (16)**</td>
</tr>
<tr>
<td>Axillary SNB</td>
<td>295(100)</td>
<td>13(4)</td>
<td>0(0)</td>
<td>19 (6)</td>
<td>5 (2)</td>
<td>265 (90)</td>
</tr>
<tr>
<td>Inguinal SNB</td>
<td>198(100)</td>
<td>33 (17)^</td>
<td>2(1)</td>
<td>23 (12)^</td>
<td>15 (8)^</td>
<td>151 (76)^</td>
</tr>
</tbody>
</table>

Table 2 legend: This table shows the postoperative complications following each incision. Surgeries and postoperative complications are reported as a whole and divided based on the number of complications. Unaffected patients had none of the postoperative complications.

SSI = Surgical-site infection, SNB = Sentinel lymph node biopsy, CLND = Complete lymph node dissection, N = Number.

*Denotes a Chi-squared significance level of <0.05 when comparing CLND to SNB.

^Denotes a Chi-squared significance level of <0.05 when comparing inguinal to axillary incision.
### Table 3: Risk of lymphedema using a multivariate cox regression model

<table>
<thead>
<tr>
<th>Variable</th>
<th>Hazard Ratio</th>
<th>Confidence interval</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age ≥ 55</td>
<td>1.15</td>
<td>0.70-1.90</td>
<td>n.s</td>
</tr>
<tr>
<td>BMI ≥ 30</td>
<td>0.92</td>
<td>0.49-1.76</td>
<td>n.s</td>
</tr>
<tr>
<td>Complete lymph node dissection</td>
<td>3.14</td>
<td>1.35-7.31</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>Drains in situ ≥ 5 days</td>
<td>1.92</td>
<td>0.92-4.01</td>
<td>n.s</td>
</tr>
<tr>
<td>Inguinal incision</td>
<td>2.49</td>
<td>1.36-4.55</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>Perinodal growth</td>
<td>1.19</td>
<td>0.56-2.50</td>
<td>n.s</td>
</tr>
<tr>
<td>Reoperation</td>
<td>1.26</td>
<td>0.65-2.44</td>
<td>n.s</td>
</tr>
<tr>
<td>Seroma</td>
<td>0.86</td>
<td>0.46-1.60</td>
<td>n.s</td>
</tr>
<tr>
<td>Surgical-site infection</td>
<td>8.46</td>
<td>4.37-16.36</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Total lymph nodes removed ≥ 10</td>
<td>0.86</td>
<td>0.44-1.89</td>
<td>n.s</td>
</tr>
<tr>
<td>Total volume in drains ≥ 700mL</td>
<td>0.63</td>
<td>0.33-1.23</td>
<td>n.s</td>
</tr>
</tbody>
</table>

**Table 3 legend:** This table shows the individual lymphedema hazard ratio, for each variable in the multivariate cox regression. Variables of lymphedema significance in Table 2 were included. P-value denotes the significance level. n.s = Not significant.
Table 4: Risk of surgical-site infection using a multivariate logistic regression model

<table>
<thead>
<tr>
<th>Variable</th>
<th>Odds Ratio</th>
<th>Confidence interval</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age ≥ 55</td>
<td>0.73</td>
<td>0.43-1.21</td>
<td>n.s</td>
</tr>
<tr>
<td>BMI ≥ 30</td>
<td>0.63</td>
<td>0.33-1.22</td>
<td>n.s</td>
</tr>
<tr>
<td>Complete lymph node dissection</td>
<td>4.85</td>
<td>1.74-13.47</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>Drains in situ ≥ 5 days</td>
<td>0.83</td>
<td>0.35-2.00</td>
<td>n.s</td>
</tr>
<tr>
<td>Inguinal incision</td>
<td>2.00</td>
<td>1.16-3.32</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>Perinodal growth</td>
<td>1.87</td>
<td>0.63-5.53</td>
<td>n.s</td>
</tr>
<tr>
<td>Seroma</td>
<td>6.92</td>
<td>4.11-12.54</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Total lymph nodes removed ≥ 10</td>
<td>0.84</td>
<td>0.34-2.12</td>
<td>n.s</td>
</tr>
<tr>
<td>Total volume in drains ≥ 700mL</td>
<td>0.95</td>
<td>0.40-2.23</td>
<td>n.s</td>
</tr>
</tbody>
</table>

Table 4 legend: This table shows the individual risk of each variable for the onset of surgical-site infection. Variables of significance in Table 2 were included. P-value denotes the significance level. n.s = Not significant.
Patients diagnosed with malignant melanoma (n= 2507)

Excluded (n=1947)
- Melanoma in situ, metastasis to other lymph nodes, extensive distant metastasis, declining or not candidate for further treatment.

Eligible subjects (n=560)

Unique incision sites (n=640)

Axillary incisions (n=362)

Sentinel nodes (n=358)

Negative sentinel nodes (n=493)
  
  
  
  Axillary (n=295)
  
  
  
  Inguinal (n=198)

Inguinal incisions (n=278)

Sentinel nodes (n=268)

Axillary lymph node dissections (n=67)
  
  
  
  Macrometastasis (n=4)

Inguinal lymph node dissections (n=80)
  
  
  
  Macrometastasis (n=10)
Figure_2_bestsetConverted.png
Figure_3_bestsetConverted.png