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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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Received 5 July 2017; accepted 12 November 2017

KEYWORDS

Lymphadenectomy;
Seroma;
Surgical wound
infection;
Risk factors

Summary *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.

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Introduction

Malignant melanoma (MM) has a worldwide increasing incidence,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,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.³ Lymphedema is a dreaded complication following lymph node surgery, often characterized by swelling and lymph stasis, which can induce subcutaneous inflammation and fibrosis.^{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.⁶ Prevention or reducing the risk of lymphedema is crucial,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.^{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.^{10,11} However it has been uncertain, whether potentially preventable conditions such as seroma and surgical-site infection (SSI) increases the risk of lymphedema.^{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.¹⁴ 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.¹⁵ 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 \pm standard deviation (SD) for continuous parametric variables, median (interquartile range (IQR)) for continuous nonparametric variables and rounded frequencies (%) for categorical variables. STATA 14 (StataCorp. 2015. *Stata 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 ± 0.11 mm 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 ($p < 0.05$).

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