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ORIGINAL ARTICLE

Factors associated with melanoma-related limb lymphoedema

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ABSTRACT

Background: Melanoma-related limb lymphoedema is a well-known late effect following sentinel node biopsy (SNB), and lymph node dissection (LND) in patients treated of melanoma. However, data on associated risk factors are sparse. This study aimed to investigate factors associated with melanoma-related limb lymphoedema.

Methods: The present cross-sectional single-center clinical study included patients between 18 and 75 years with American Joint Committee on Cancer Stages I–III melanoma treated with wide local excision (WLE) and unilateral axillary or inguinal SNB and/or completion LND (CLND) or therapeutic LND (TLND). The diagnosis of secondary unilateral limb lymphoedema was based on the history, symptoms, and physical examination and staged according to the International Society of Lymphology (ISL). Data on factors associated with lymphoedema were analysed with binary logistic regression models.

Results: In total, 642 patients were eligible, of which 435 (68%) patients participated in the study. Among these 431 patients, 109 (25%) had lymphoedema of which 48 (44%), and 61 (56%) were classified with ISL Stages I and II–III, respectively. Multivariate analyses identified primary tumour on the limb (odds ratio [OR], 2.28; 95% confidence interval [CI], 1.17–4.56; *p* value .017), inguinal surgery (OR, 6.91; 95% CI, 3.49–14.11; *p* value <.0001), LND (OR, 6.45; 95% CI, 3.18–13.57; *p* value <.0001), and persistent pain at the site of lymph node surgery as factors associated with lymphoedema (OR, 3.52; 95% CI, 1.54–8.19; *p* value .003). Multivariable analysis of ISL Stage II–III lymphoedema further identified limb cellulitis to be associated with lymphoedema (OR 5.74; 95% CI, 2.11–15.99; *p* value .0006).

Conclusions: Melanoma-related limb lymphoedema is associated with inguinal surgery, LND, primary tumour on the limb, persistent pain at the site of lymph node surgery, and cellulitis of the limb. This study highlights the importance of increasing awareness, improving prevention, and treatment of melanoma-related limb lymphoedema.

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Melanoma; extremities; lymphoedema; lymph node excision; risk factors

Introduction

Sentinel lymph node (SN) biopsy (SNB) is considered the gold standard procedure for diagnosing subclinical regional lymph node involvement in selected patients treated for cutaneous melanoma [1,2]. This technique can identify occult regional lymph node metastasis of importance for staging, treatment, prognosis, and clinical trials [3]. In patients undergoing SNB approximately 20% are found to have positive SNs [4–6]. Of these, up to 20% will have additional metastatic nodes found by completion lymph node dissection (CLND) [6–8]. A feared complication following nodal surgery is limb lymphoedema which has a negative impact on patients' quality of life (QoL) [9–11]. The reported prevalence of limb lymphoedema in patients treated for melanoma varies widely ranging from 1 to 15% and 10 to 64% following SNB and LND, respectively [5,10,12–16]. Extensive research has been conducted on risk factors for development of breast cancer-related lymphoedema. However, studies of risk factors associated with limb lymphoedema after treatment of melanoma are sparse [10,12–14,17–22]. Factors associated with lymphoedema have been difficult to identify with certainty as most studies are retrospective with varying or lack of definitions of lymphoedema, heterogeneity with respect to lymphoedema measurement methods, lymphoedema classification, and follow-up intervals, relatively modest numbers, inhomogeneous with respect to extent of node dissection, use of radiotherapy and lack of long-term assessment. [5,14,17,19–21,23–25]. The objective of this study was, therefore, to investigate if certain factors were associated with clinical evident limb lymphoedema after surgical treatment of melanoma.

Methods

This was a single-center, cross-sectional study of adult patients ≤75 years of age treated for cutaneous melanoma,

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Table 1. Baseline characteristics of the study population.

	$n = 431$
American Joint Committee on Cancer 7th edition (2009), *n* (%)	
Stage I-II	348 (81%)
Stage III	83 (19%)
Lymphoedema following axillary lymph node surgery, *n* (%)	
Sentinel lymph node biopsy alone	10 (5%)
Lymph node dissection	13 (31%)
Lymphoedema following inguinal lymph node surgery, *n* (%)	
Sentinel lymph node biopsy alone	53 (35%)
Lymph node dissection	33 (83%)
Melanoma-related limb lymphoedema, *n* (%)	109 (25%)
International Society of Lymphology (ISL) staging of limb lymphoedema, *n* (%)	
ISL Stage I	48 (44%)
ISL Stage II	59 (54%)
ISL Stage III	2 (2%)
Duration of lymphoedema (years), mean (SD), range	4 (4), 1−18

Stage I–III based on the seventh edition (2009) of the American Joint Committee on Cancer Staging Manual with unilateral axillary or inguinal lymph node surgery, as a SNB and/or LND. CLND was performed in patients with positive SN(s), and therapeutic LND (TLND) in patients with macroscopic disease (i.e., nodal metastases detected clinically or by imaging). The study participants took part in a broader study of health-related QoL (HRQoL) and surgical morbidity in patients treated for melanoma. Patients who were ≥18 and ≤75 years treated of melanoma with wide local excision (WLE) and unilateral axillary or inguinal SLNB and/or LND at least 1 year prior to the study were assessed for eligibility. The exclusion criteria were metastatic or recurrent disease, bilateral lymph node procedures, ilioinguinal lymphadenectomy, failure of SLNB technique, other current cancers other than skin cancer, previous major surgery in ipsi- or contralateral limb, heart failure, mentally not fit, or lymphoedema not related to the treatment of melanoma. The dichotomous outcome was presence of unilateral melanoma-related limb lymphoedema at the time of the study. The diagnosis was based on a detailed history including onset of lymphoedema after lymph node surgery, the patients' symptoms (typically swelling, heaviness, and tiredness in the limb) and a thorough physical examination of the limb at risk and contralateral limb focusing on pitting edema and skin changes was conducted of all study participants by first author at the time of the study [26,27]. If diagnosed with lymphoedema based on symptoms and physical findings at the time of the study, which was at least 12 months post-surgery, the stage was classified according to the International Society of Lymphology (ISL) in Stage I–III with Stage I representing early onset of the condition where there is accumulation of tissue fluid that subsides with limb elevation, edema may be pitting at this stage, Stage II in which limb elevation alone rarely reduces swelling and pitting is manifest or may not be present as tissue fibrosis is more evident, and Stage III in which the tissue is hard (fibrotic), pitting is absent, and skin changes such as thickening, hyperpigmentation, increased skin folds, fat deposits, and warty overgrowths develop [26].

Potential factors associated with lymphoedema were identified based on expert clinical opinion and literature search. These factors were extracted and cross-checked between the prospectively registered national Pathology Register (location, lymph node procedure, and number of lymph nodes removed), the Danish Melanoma Database (location of primary tumour, location and type of lymph node surgery, and dates of surgery), the medical records (sex, gender, BMI at the time of surgery, date of surgery, location of primary tumour, location and type of lymph node surgery, delayed wound healing, postoperative infection, aspiration required, and postoperative cellulitis), as well as by a self-reported questionnaire (smoking, alcohol, and numbers of comorbidity at the time of the study, postoperative infection, and persistent pain) sent to the patients prior to the study. Data from the later were discussed with the patients if the data were contradictory. A postoperative infection was defined as requiring intervention, either antibiotics, and/or surgical. The categorical variable comorbidity was categorized as none or one, or more than one disorder (diabetes, hypertension, depression, and so forth). The limbs and BMI obtain were examined and measurement, respectively by first author at the time of the study.

Statistical analysis

The differences between the baseline patient, treatment, and melanoma characteristics of the participants and non-participants were tested with Student's *t*-tests, chi-square tests, Fisher's exact tests, and Mann–Whitney U tests [9]. A binary logistic regression model was used for describing and analysing risk factors for lymphoedema. The results of the logistic regression models were presented as odds ratios (ORs) (95% confidence interval [CI]) and *p* values. Covariates were tested including patient factors (sex, age, smoking, and BMI) and cancer and treatment-related factors (primary tumour location, location and type of lymph node surgery, calendar year of surgery and time since surgery, postoperative infection or delayed wound healing at lymph node surgery site, aspiration required, cellulitis of the limb, and persistent pain at the lymph node surgery site) as independent variables with the presence of limb lymphoedema as the dependent variable using logistic regression. The identified factors associated with lymphoedema with *p* values <.1 were further tested in a multivariable regression model including all these covariates. Statistical tests were 2-sided and *p* values below .05 were considered to indicate a significant difference. The statistical analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA).

The study was approved by the Danish Regional Committee on Biomedical Research Ethics (journal no.: H-4-2014-127), the Danish Data Protection Agency (2012-58-0004, local journal no.: HEH-2015-003, I-Suite no.: 03436), the Danish Melanoma Group, and registered with Clinical Trials.gov (Identifier: NCT02352623) as part of a broader study into HRQoL following treatment of melanoma. All patients gave written informed consent prior to participation in the study.

Results

We identified 642 eligible adult patients ≤75 years of age, who had been treated for cutaneous melanoma with WLE and

Table 2. Univariate analysis of factors associated with melanoma-related limb lymphedema.

	Lymphoedema		Unadjusted analyses[a]		
	No, $n = 322$ (75%)	Yes, $n = 109$ (25%)	OR	95% CI	p Value
Patient factors					
Sex, *n* (%)					
Female (reference)	154 (68.8)	70 (31.2)			
Male	168 (81.2)	39 (18.8)	0.51	(0.33–0.80)	.003
Age in years at study[b], mean (SD)	54.6 (11.9)	49.8 (12.4)	0.97	(0.95–0.99)	.0004
Smoking, *n* (%)					
Non-smoker (reference)	279 (75.6)	90 (24.3)			
Smoker	42 (68.9)	19 (31.2)	1.40	(0.78–2.53)	.26
Alcohol consumption, *n* (%)					
≤14 units/week (reference)	290 (73.8)	103 (26.2)			
>14 units/week	32 (84.2)	6 (15.8)	0.53	(0.21–1.3)	.16
Number of comorbidities[c], *n* (%)					
0–1 comorbidity (reference)	279 (74.0)	98 (26.0)			
>1 comorbidities	43 (79.6)	11 (20.4)	0.73	(0.36–1.47)	.38
BMI[b] at time of study, mean (SD)	26.8 (4.7)	26.8 (4.2)	1.00	(0.95–1.05)	.90
BMI[b] at time of surgery, mean (SD)	26.4 (4.4)	25.9 (4.0)	0.97	(0.92–1.02)	.27
Cancer and treatment related factors					
Primary tumour location, n (%)					
Trunk or head & neck[d] (reference)	184 (86.0)	30 (14.0)			
Limb	138 (63.6)	79 (36.4)	3.51	(2.18–5.64)	<.0001
Location of lymph node surgery, n (%)					
Axillary (reference)	217 (90.4)	23 (9.6)			
Inguinal	105 (55.0)	86 (45.0)	7.73	(4.61–12.94)	<.0001
Type of lymph node surgery					
Sentinel lymph node biopsy alone (reference)	284 (82.6)	60 (17.4)			
Lymph node clearance	38 (43.7)	49 (56.3)	6.10	(3.68–10.13)	<.0001
Number of lymph nodes (LN) removed at the SNB procedure, mean (SD)	1.9 (1.2)	2.1 (1.5)	1.13	(0.97–1.33)	.13
Number LN removed at axillary SNB	2.0 (1.3)	1.8 (1.4)	0.89	(0.62–1.27)	0.52
Number LN removed at inguinal SNB	1.7 (1.1)	2.2 (1.6)	1.33	(1.06–1.68)	.014
Calendar year of surgery, median, range	2011 (1999-2015)	2011 (1997-2015)	0.98	(0.93–1.04)	.51
Time since surgery (years), mean (SD), range	4.5 (3.6)	4.8 (3.9)	1.02	(0.96–1.08)	.51
Delayed wound healing at the lymph node surgery site					
No (reference)	313 (76.2)	98 (23.8)			
Yes	9 (45.0)	11 (55.0)	3.90	(1.57–9.69)	.003
Postoperative infection at the lymph node surgery site[e], *n* (%)					
No (reference)	287 (80.2)	71 (19.8)			
Yes	35 (48.0)	28 (52.0)	4.39	(2.59–7.44)	<.0001
Aspiration required, *n* (%)					
No (reference)	289 (80.3)	71 (19.7)			
Yes	33 (46.5)	38 (53.5)	4.69	(2.75–7.99)	<.0001
Persistent pain at the lymph node surgery site, *n* (%)					
No (reference)	297 (77.8)	85 (22.2)			
Yes	25 (51.0)	24 (59.0)	3.35	(1.82–6.17)	.0001
Cellulitis of the limb[f], *n* (%)					
No (reference)	310 (76.4)	96 (23.6)			
Yes	11 (45.8)	13 (54.2)	3.82	(1.66–8.8)	.002

[a]Univariable logistic regression analyses with lymphoedema as the dependent variable.
[b]Age and BMI were tested as continuous variables. BMI: body mass index, kg/m^2.
[c]Comorbidity was defined as an unrelated illness or disease requiring treatment e.g., hypertension or asthma.
[d]Only five patients had primary tumour located in neck region draining to the axilla only.
[e]Requiring antibiotics and/or drainage of the wound.
[f]Requiring antibiotics.
OR: odds ratio; 95% CI: 95% confidence interval; SD: standard deviation

axillary or inguinal SNB and/or CLND/TLND from 1 January 1997 to 26 February 2015 at our department. Of these, 69 declined to participate (of which the majority reported lack of time as the main reason for not participating) and 138 did not respond, corresponding to a participation rate of 68%. The differences between patient, treatment and melanoma characteristics of the participants and non-participants were not clinically relevant, as shown elsewhere [9]. The patients were enrolled in the study between 5 February 2015 and 26 February 2016. Overall, 109 (25%) of 431 patients had clinically symptomatic melanoma-related limb lymphoedema as presented in Table 1. The characteristics of melanoma-related limb lymphoedema and the negative impact hereof on HRQoL has been described elsewhere [9].

Most patients with lymphoedema ($n = 99$ (91%)) developed lymphoedema within the first year. Two patients reported lymphoedema immediately postoperatively which resolved within 1year. These two patients were not included in the group with lymphoedema. A few patients reported lymphoedema which was reclassified as paraesthesia based upon symptoms and clinical examination.

In the axillary LND group, five patients underwent TLND, of which 3 (60%) developed lymphoedema. In the inguinal LND group, only one patient underwent TLND. This patient did not develop lymphoedema. The results of the univariate analyses are shown in Table 2. The results of multivariable logistic regression are shown in Table 3. Four variables were associated with the presence of lymphoedema; primary

Table 3. Multivariate analyses of factors associated with melanoma-related limb lymphoedema.

	Multivariable logistic regression, adjusted analysis		
	OR	95% CI	*p* value
Patient factors			
Sex			
Female (reference)			
Male	0.92	(0.5–1.7)	.79
Age in years at study[a]	0.99	(0.97–1.01)	.25
Cancer and treatment-related factors			
Primary tumour location			
Trunk or head & neck[b] (reference)			
Limb	2.28	(1.17–4.56)	.017
Location of lymph node surgery			
Axillary (reference)			
Inguinal	6.91	(3.49–14.44)	<.0001
Type of lymph node surgery			
Sentinel lymph node biopsy alone (reference)			
Lymph node dissection	6.45	(3.18–13.57)	<.0001
Delayed wound healing at the lymph node surgery site			
No (reference)			
Yes	0.53	(0.15–1.90)	.32
Postoperative infection at the lymph node surgery site[c]			
No (reference)			
Yes	1.43	(0.65–3.09)	.36
Aspiration required			
No (reference)			
Yes	1.66	(0.80–3.45)	.17
Persistent pain at the lymph node surgery site			
No (reference)			
Yes	3.52	(1.54–8.19)	.003
Cellulitis of the limb[d]			
No (reference)			
Yes	2.15	(0.81–5.82)	.12

[a]Age was tested as continuous variable.
[b]Only five patients had primary tumour located in neck region draining to the axilla only.
[c]Requiring antibiotics and/or drainage of the wound.
[d]Requiring antibiotics.

tumour location on the limb (as to trunk and neck), inguinal lymph node surgery (as to axillary lymph node surgery), lymph node clearance (as to SNB alone), and persistent pain at the lymph node surgery site.

The number of lymph nodes removed at the SNB procedure was not significantly associated with lymphoedema ($p = .091$). However, additional tests were performed where patients who had >5 LNs removed during SNB procedures were re-grouped to the LND group (two and three patients for axillary and inguinal procedures, respectively). This did not change the results (data not shown). An analysis of patients with lymphoedema, ISL Stage II–III ($n = 61$), showed inguinal lymph node surgery (OR 4.70; 95% CI, 2.03–11.69; *p* value .0005), LND (OR 4.95; 95% CI, 2.30–10.77; *p* value <.0001), and cellulitis of the limb (OR 5.74; 95% CI, 2.11–15.99; *p* value .0006) to be associated with lymphoedema in multivariable analysis.

Discussion

In our study, 109 (25%) of 431 patients had melanoma-related limb lymphoedema. These very high numbers exceed findings in most previous studies presumable due to heterogeneity among studies with respect to lymphoedema diagnosis, lymphoedema measurement methods, treatment of lymphoedema at the time of measurement (lowering the volume differences), and follow-up intervals [10,12,14,17,18,22,25].

Other studies have used arbitrary cutoff values, typically defining lymphoedema as volume difference of ≥10% between the limbs [10]. If this criterion was applied on our patients, lymphoedema was only present after axillary and inguinal SNB in 2% and 1% [28]. These percentages are comparable to the study by Morton *et al.* in which 23% of patients reported an increase in limb size following WLE and SNB, but only 2% had limb volume differences of ≥10% [10]. Furthermore, inter-limb volume differences of the upper limbs are particularly misleading if handedness is not considered [29].

Our data suggest that risk of limb lymphoedema after regional lymph node surgery is particularly high with primary tumour location on the limb, after inguinal surgery, LND, in patients with persistent pain at the lymph node site and following cellulitis of the limb. The risk of developing limb lymphoedema after axillary SNB is low (5%) but high following inguinal SNB with lymphoedema found in approx. one in three (35%). The reason for the higher risk of lower limb lymphoedema is likely attributed to several factors including gravity, mobility, posture, and venous disease. LND carries a very high risk of developing lymphoedema in the relevant limb as the procedure disrupts the lymphatic system far more than SNB; one in three after axillary dissection and four in five after groin dissection.

In patients with macroscopic disease TLND is the treatment of choice. However, the paradigm shift in surgical

treatment of melanoma, based on the results of the recent MSLT-II trial and DeCOG trial has decreased the numbers of LND in positive SLNB with units abandoning routine CLND in patients with microscopic disease [30,31]. Contrarily, the number of SLNB procedures performed has increased with the recent eight American Joint Committee on Cancer (AJCC) classification in which the subcategory of T1 has been enlarged. The higher number of patients and better prognosis of this subgroup will lead to far more patients suffering from melanoma-related limb lymphoedema.

Primary tumour location in the ipsilateral limb was also significantly associated with lymphoedema. This is likely attributed to two issues: Local damage of draining lymph vessels at the site of the primary tumour excision and the anatomical location of the lymph nodes draining the limb. Lymphatic obstruction by metastatic cells could also theoretically be an explanation for the increased risk in these cases. With the mean follow-up of 5 years in our study of recurrence-free patients, this hypothesis is less likely. Persistent pain at the site of lymph node surgery was highly significantly associated with lymphoedema. Lymphoedema shares many risk factors with the development of chronic pain [32]. Functional impairment has been shown to be associated with both lymphoedema and pain in breast cancer patients [33]. This mechanism may also explain the association with pain and lymphoedema in our study. Lastly, cellulitis of the limb was associated with lymphoedema in patients with ISL Stage II–III. Patients with lymphoedema of all types are prone to episodes of cellulitis due to a local immune deficiency [34]. However, it is also known that cellulitis can lead to damage to the lymphatics [34]. This might explain why cellulitis was only significantly associated with lymphoedema in the subgroup analysis of patients with worse stages of lymphoedema in whom the damage to the lymphatics is more extensive. This emphasizes the importance of detecting and managing cellulitis to avoid development or worsening of lymphoedema. To our knowledge, this is the largest study with clinical assessment of lymphoedema of all ISL stages in patients treated for Stage I–III melanoma. Further strength is full and accurate information on risk factors with an absolute minimum of missing or potentially implausible data. A limitation of the study includes potential selection bias due to strict inclusion and exclusion criteria and 32% eligible non-participants. This selection bias could attribute to the high prevalence of lymphoedema as patients with late effects perhaps were more willing to participate in the study. This argument also applies for other findings in the study. However, it should be noted that the patients were invited to participate in a study assessing HRQoL and surgical morbidity in melanoma patients; and not specifically in a study assessing melanoma-related limb lymphoedema. Furthermore, non-response bias was sought minimized by contacting non-responders by phone. This led to an increased response rate and hence, a better representative of the patient population. A comparison between the participants and non-participants with respect to characteristics regarding patient (age, gender, and time since surgery), melanoma (localization of primary tumour, excision margin, and AJCC stage), and treatment (site and type of lymph node surgery (SNB/LND), number of lymph nodes removed at the SNB and LND procedures and metastatic lymph nodes in the LND specimen) did not reveal clinically significant differences, indicating that the study participants are representative for the study base from which they were selected [9]. We excluded patients with regional lymph node surgery in more than one region in order to potentially increase the sensitivity and specificity of clinical diagnosis of lymphoedema by comparing the operated and contralateral limb. Patients with metastatic disease and patients who had undergone surgery or had diseases which could impact development of lymphoedema were also excluded. Retrospective data on deceased patients were not sought obtained due to lack of documentation of limb lymphoedema. The LND groups were low-risk patients with only non-SN metastases in 4 (10%) patients. There is no reason to believe that the excluded patients should have a lower risk of lymphoedema than the study participants. The main limitation of the study is lack of preoperative assessment of the limbs.

The study highlights the importance of preoperative information of patients undergoing lymph node surgery and systematic postoperative clinical assessment for lymphoedema in these patients at follow-up visits.

A clinical examination focusing on lymphoedema in all patients at risk is of utmost importance as early detection allows for early intervention; presumably minimizing both morbidity and impact on QoL. Noteworthy is the fact that even though the SNB technique greatly minimizes the risk of lymphoedema compared to LND, melanoma caretakers are more likely to encounter lymphoedema in those who have undergone SNB due to the higher number and better prognosis of this group. Our study suggests that more patients undergoing surgical treatment of melanoma experience melanoma-related limb lymphoedema than previously expected [5,10]. The presence of clinical lymphoedema has a negative impact on the QoL in the patients treated for melanoma, regardless of ISL stage [9].

In conclusion, this study of the prevalence of and factors associated with clinical melanoma-related limb lymphoedema found very high prevalence of melanoma-related limb lymphoedema associated with LND, inguinal surgery, primary tumour on the limb, persistent pain at the site of lymph node surgery, and cellulitis of the limb. This study highlights the importance of increasing awareness, improving prevention and treatment of melanoma-related limb lymphoedema.

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Disclosure statement

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References

[1] Australian Cancer Network Melanoma Guidelines Revision Working Party. Clinical Practice Guidelines for the Management of Melanoma in Australia and New Zealand. Cancer Council Australia and Australian Cancer Network, Sydney and New Zealand Guidelines Group. 2008.

[2] Han D, Thomas DC, Zager JS, et al. Clinical utilities and biological characteristics of melanoma sentinel lymph nodes. World J Clin Oncol. 2016;7(2):174–188.

[3] Morton DL, Thompson JF, Cochran AJ, et al. Final trial report of sentinel-node biopsy versus nodal observation in melanoma. N Engl J Med. 2014;370(7):599–609.

[4] Gershenwald JE, Thompson W, Mansfield PF, et al. Multi-institutional melanoma lymphatic mapping experience: the prognostic value of sentinel lymph node status in 612 stage I or II melanoma patients. J Clin Oncol. 1999;17(3):976–983.

[5] Moody JA, Ali RF, Carbone AC, et al. Complications of sentinel lymph node biopsy for melanoma – A systematic review of the literature. Eur J Surg Oncol. 2016;43:270–277.

[6] Chakera AH, Drzewiecki KT, Eigtved A, et al. Sentinel node biopsy for melanoma: a study of 241 patients. Melanoma Res. 2004;14(6):521–526.

[7] Voit CA, Oude Ophuis CMC, Ulrich J, et al. Ultrasound of the sentinel node in melanoma patients. Melanoma Res. 2016;26(3):267–271.

[8] Balch CM, Gershenwald JE. Clinical value of the sentinel-node biopsy in primary cutaneous melanoma. N Engl J Med. 2014;370(7):663–664.

[9] Gjorup CA, Groenvold M, Hendel HW, et al. Health-related quality of life in melanoma patients: Impact of melanoma-related limb lymphoedema. Eur J Cancer. 2017;85:122–132.

[10] Morton RL, Tran A, Vessey JY, et al. Quality of life following sentinel node biopsy for primary cutaneous melanoma: health economic implications. Ann Surg Oncol. 2017;24(8):2071–2079.

[11] Faries MB, Thompson JF, Cochran A, et al. The impact on morbidity and length of stay of early versus delayed complete lymphadenectomy in melanoma: results of the multicenter selective lymphadenectomy trial (I). Ann Surg Oncol. 2010;17(12):3324–3329.

[12] Ul-Mulk J, Hölmich LR. Lymph node dissection in patients with malignant melanoma is associated with high risk of morbidity. Dan Med J. 2012;59(6):A4441.

[13] Starritt EC, Joseph D, McKinnon JG, et al. Lymphedema after complete axillary node dissection for melanoma: assessment using a new, objective definition. Ann Surg. 2004;240(5):866–874.

[14] Hyngstrom JR, Chiang YJ, Cromwell KD, et al. Prospective assessment of lymphedema incidence and lymphedema-associated symptoms following lymph node surgery for melanoma. Melanoma Res. 2013;23:1.

[15] Spillane AJ, Saw RPM, Tucker M, et al. Defining lower limb lymphedema after inguinal or ilio-inguinal dissection in patients with melanoma using classification and regression tree analysis. Ann Surg. 2008;248(2):286–293.

[16] de Vries M, Hoekstra HJ, Hoekstra-Weebers JEHM. Quality of life after axillary or groin sentinel lymph node biopsy, with or without completion lymph node dissection, in patients with cutaneous melanoma. Ann Surg Oncol. 2009;16(10):2840–2847.

[17] Voss RK, Cromwell KD, Chiang YJ, et al. The long-term risk of upper-extremity lymphedema is two-fold higher in breast cancer patients than in melanoma patients. J Surg Oncol. 2015;112(8):834–840.

[18] Friedman JF, Sunkara B, Jehnsen JS, et al. Risk factors associated with lymphedema after lymph node dissection in melanoma patients. Am J Surg. 2015;210(6):1178–1184.

[19] Campanholi LL, Duprat Neto JP, Fregnani JHTG. Mathematical model to predict risk for lymphoedema after treatment of cutaneous melanoma. Int J Surg. 2011;9(4):306–309.

[20] Theodore JE, Frankel AJ, Thomas JM, et al. Assessment of morbidity following regional nodal dissection in the axilla and groin for metastatic melanoma. ANZ J Surg. 2016;87: 44–48.

[21] Roaten JB. Identifying risk factors for complications following sentinel lymph node biopsy for melanoma. Arch Surg. 2005;140(1):85.

[22] de Vries M, Vonkeman WG, van Ginkel RJ, et al. Morbidity after inguinal sentinel lymph node biopsy and completion lymph node dissection in patients with cutaneous melanoma. Eur J Surg Oncol. 2006;32(7):785–789.

[23] Sabel MS, Griffith KA, Arora A, et al. Inguinal node dissection for melanoma in the era of sentinel lymph node biopsy. Surgery. 2007;141(6):728–735.

[24] Söderman M, Thomsen JB, Sørensen JA. Complications following inguinal and ilioinguinal lymphadenectomies: a meta-analysis. J Plast Surg Hand Surg. 2016;50(6):315–320.

[25] Cormier JN, Askew RL, Mungovan KS, et al. Lymphedema beyond breast cancer. Cancer. 2010;116(22):5138–5149.

[26] Lymphoedema Framework. Best practice for the management of lymphoedema. International Consensus. London: MEP Ltd; 2006. Available from: http://www.woundsinternational.com/pdf/content_175.pdf

[27] Lee BB, Antignani PL, Baroncelli TA, et al. IUA-ISVI consensus for diagnosis guideline of chronic lymphedema of the limbs. Int Angiol. 2015;34(4):311–332.

[28] Gjorup CA, Hendel HW, Zerahn B, et al. Volume and tissue composition changes measured with dual-energy x-ray absorptiometry in melanoma-related limb lymphedema. Lymphat Res Biol. 2017;15: 274–283.

[29] Gjorup CA, Hendel HW, Klausen TW, et al. Reference values for assessment of unilateral limb lymphedema with dual-energy X-ray absorptiometry. Lymphat Res Biol. 2017;16:75–84.

[30] Faries MB, Thompson JF, Cochran AJ, et al. Completion dissection or observation for sentinel-node metastasis in melanoma. N Engl J Med. 2017;376(23):2211–2222.

[31] Leiter U, Stadler R, Mauch C, et al. Complete lymph node dissection versus no dissection in patients with sentinel lymph node biopsy positive melanoma (DeCOG-SLT): a multicentre, randomised, phase 3 trial. Lancet Oncol. 2016;17(6):757–767.

[32] Andersen KG, Kehlet H. Persistent pain after breast cancer treatment: a critical review of risk factors and strategies for prevention. J Pain. 2011;12(7):725–746.

[33] Gärtner R, Jensen MB, Kronborg L, et al. Self-reported arm-lymphedema and functional impairment after breast cancer treatment-a nationwide study of prevalence and associated factors. Breast. 2010;19(6):506–515.

[34] Keeley VL. Lymphoedema and cellulitis: Chicken or egg? Br J Dermatol. 2008;158(6):1175–1176.