



## Persistent pain after lymph node excision in patients with malignant melanoma is neuropathic

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### ABSTRACT

Persistent postoperative pain is a common complication of surgery, including surgical interventions for cancer. So far, there is limited information about the prevalence and clinical characteristics of pain after lymph node biopsy and dissection in patients with malignant melanoma. In this study, a questionnaire was sent out to all surviving patients (n = 402) after surgery for cutaneous malignant melanoma at the Aalborg Hospital Department of Plastic Surgery, Aalborg, Denmark. Of patients responding, sentinel node biopsy (SNB) and/or lymph node dissection (LND) was performed in 175 patients. All patients with pain and a control group were invited to a clinical examination. Altered sensation and pain were significantly more common after LND (82% and 34%, respectively) than after SNB (32% and 14%, respectively). In patients with LND, 12% reported at least moderate pain and 14% impact of pain on quality of life, while in patients with SNB, 3% reported at least moderate pain and 2% pain impact on quality of life. The most important predictor of pain was sensory abnormalities. At the clinical follow-up, 10 out of 12 patients with pain both met the criteria of the recently proposed grading system for probable neuropathic pain and used descriptors on the DN4 questionnaire suggestive of neuropathic pain. Different patterns of sensory profiles were observed in single patients, suggesting heterogeneous sensory processing within single patients. This study suggested that nerve injury was the main underlying mechanism of persistent pain after lymph node excision.

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### 1. Introduction

Persistent pain is a significant problem after surgery and is well described after hernia repair, thoracotomy, amputation, breast augmentation, and mastectomy, although the underlying mechanisms are still not fully elucidated [2]. Lymph node excision, including sentinel node biopsy (SNB) and lymph node dissection (LND), may also be associated with long-term morbidity, including chronic pain. Studies on pain following lymph node excision have mainly been conducted in patients with breast cancer. Neuropathic pain due to a lesion of the intercostobrachial nerve is considered the most common cause of persistent pain, but pain may also be associated with edema and restrictions of arm movement [20]. Breast cancer patients, however, may have several types of pain, including phantom breast pain and neuropathic pain due to

intercostal nerve or other nerve injury after lumpectomy or mastectomy, as well as pain due to radiation therapy or chemotherapy [9,12], and it may be difficult to distinguish between the pain caused by the lymph node excision and other types of pain. In patients with lymph node excision of malignant melanoma, there are seldom competing causes of pain. Although long-term morbidity including pain has been reported after lymph node excision in melanoma patients, there are no detailed descriptions of the pain symptoms and signs [7,15,17,21].

Malignant melanoma is an aggressive malignancy, and the incidence has been steadily increasing worldwide for the last decades [19]. The therapy is predominantly surgical, with only minor benefits of adjuvant therapy in advanced disease. Current recommendations for treatment of thick melanomas (Breslow thickness  $\geq 1$  mm and/or Clark's level  $\geq$  IV) in Denmark and most international centers are local wide excision supplied with SNB followed by LND if positive nodes are found [8]. The management of microscopically positive lymph nodes is still controversial due to a lack of definite evidence of improved survival [8].

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The aim of this study was to determine the prevalence and severity of persistent pain after lymph node excision in a large unselected population of patients with malignant melanoma followed by a detailed sensory examination in a subgroup of patients to further clarify the underlying mechanisms. We hypothesized that nerve injury with resultant sensory abnormalities is a major underlying cause of persistent postoperative pain after lymph node excision.

## 2. Methods

### 2.1. Design and study population

The study was carried out as a postal questionnaire survey and a clinical follow-up study. All 448 patients who underwent surgical treatment of cutaneous malignant melanoma at the Department of Plastic Surgery at Aalborg Hospital between September 1, 2005 and June 1, 2009 were eligible. Patients with dementia, primary melanoma before the study period, and primary melanoma treated at other departments were excluded. The study included information from medical records and the nationwide Danish Melanoma Group Registry ([www.melanoma.dk](http://www.melanoma.dk)). A detailed questionnaire with a pre-stamped return envelope was mailed to all 402 surviving patients in September 2009 (Fig. 1), and a reminder was sent out 3 months later to nonresponders. Patients were asked to fill out a questionnaire focused on pain after excision of malignant melanomas; these results will be presented separately. Of the 350 patients who answered the questionnaire, 181 patients had undergone lymph node excision (Fig. 1), and these patients answered a separate questionnaire. In June–September 2010, all patients with pain and a gender- and age-matched control group without pain were invited to a clinical examination. Thus, the mean time interval from lymph node excision (SNB) to completion of the questionnaire was 23.4 months (SD = 13.1 months) and to the clinical examination, 33.2 months (SD = 12.3 months). The study was approved by the Danish Data Protection Agency (No. 2009-41-3572) and the Ethical

Committee for the North Denmark Region (No. N-20100032). All patients gave informed written consent for the clinical study.

### 2.2. Surgical and anesthetic procedures

Surgery for malignant melanoma in Denmark follows standardized national protocols according to the histological classification (the Clark level and Breslow invasion depth). In patients with malignant melanomas of a depth  $\geq 1$  mm or Clark level  $\geq$  IV, a surgical excision with a margin of 2 cm combined with an SNB was carried out in general anesthesia, supplied by infiltration analgesia in some patients. An LND was carried out 8–12 days later if the SNB was positive for metastases. General anesthesia involved induction with an intravenous (i.v.) infusion of propofol combined with remifentanyl or fentanyl. The anesthesia was maintained with inhaled sevoflurane. Remifentanyl analgesia was combined with i.v. morphine or a nonsteroidal anti-inflammatory drug (NSAID) perioperatively. Following anesthesia with fentanyl, i.v. morphine or NSAID was supplied postoperatively if needed. Postoperative pain treatment consisted of paracetamol 4 g daily and tramadol 200 mg (optional) for usually no more than 1–2 days. Irradiation, chemotherapy, immunotherapy, or hyperthermic isolated regional limb perfusion was used in a few patients for palliative purposes or for recurrent melanoma in patients with metastatic disease.

SNB was carried out after preoperative injection of radiocolloid (Technetium-99m-labeled human albumin colloid) intradermally around the scar of the excision of the melanoma to identify the lymphatic drainage. The sentinel nodes were identified preoperatively by dynamic images and perioperatively by a handheld  $\gamma$ -probe. A small incision in the skin was made at the hot spot, and the sentinel nodes (usually 1–3) were carefully excised. Pelvic and extraregional sentinel nodes were not excised. The technique was the same in all locations.

Axillary LND was performed as en bloc resection of the lymphatic and fatty tissue of levels I, II, and III of the axilla. In general, the pectoralis minor was not divided. The long thoracic nerves (C5, C6,

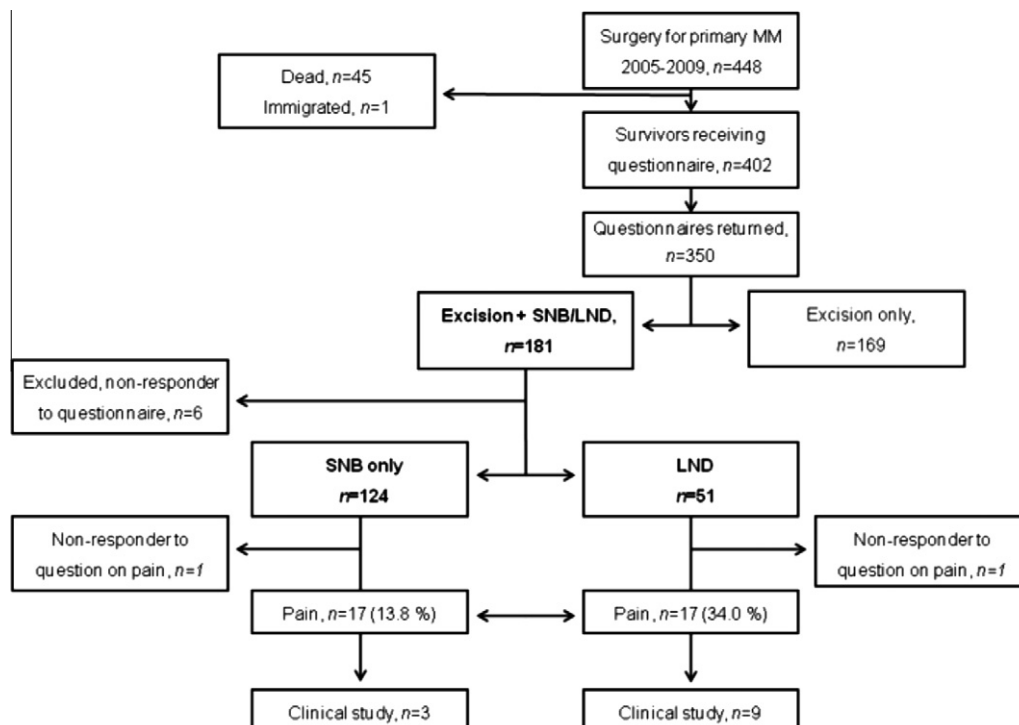


Fig. 1. Study flowchart. MM, malignant melanoma; SNB, sentinel node biopsy; LND, lymph node dissection.

C7) and the thoracodorsal nerves (C6, C7, C8) were identified and preserved. The intercostobrachial nerve (a branch of the second intercostal nerve) was not identified. Superficial inguinal LND was performed through a vertical incision crossing the inguinal ligament and en bloc dissection of the contents of the trigonum femorale, including the anterior nodes on the abdominal wall. The lateral femoral cutaneous nerve was preserved if seen on its way through the fascia of the sartorius muscle, but most often it was not identified. Only patients with clinical or radiological evidence of iliac or pelvic lymph nodes underwent a deep inguinal LND with dissection of glands through incision of the abdominal muscles. Prophylactic antibiotics were not given routinely. Patients with micro- or macrometastases of the neck were admitted to the Department of Ear, Nose, and Throat Surgery, where a neck LND was performed.

### 2.3. Questionnaire and measures

#### 2.3.1. Questionnaire

The questionnaire included information about sensory changes (hyposensitivity and hypersensitivity) and how bothered patients were by the sensory changes. Patients with pain in the areas of surgical removal of lymph nodes during the last month completed questions on onset, frequency, and duration of pain. Pain descriptors were assessed using a nonvalidated translation of the self-administered 7-item neuropathic pain diagnostic (DN4) questionnaire [4]. Intensities of worst and average pain, spontaneous pain, pain by touching the painful area, upon movement, and by a slight pressure to the painful area within the past 24 hours were recorded on a numeric rating scale (NRS, 0–10: 0 = no pain and 10 = worst pain imaginable). The location of the surgical field and the areas of pain were marked on a body chart. The patients were asked if the pain affected their quality of life, sleep, mood, daily living, and social life. Also, other causes of pain and surgery and use of medication were reported. All medical records from the department and the Danish Melanoma Group Registry were searched for baseline information, surgical technique and findings, histology, and complications of surgery.

#### 2.3.2. Clinical study

In this part, patients with pain completed the same questionnaire as described above and, in addition, a nonvalidated translation of the Neuropathic Pain Symptom Inventory [5] and the 10-item DN4 [4]. Evoked pain and unpleasantness to stroking the skin slowly with a brush (SENSELab Brush 05, Somedic AB, Hörby, Sweden) and thermo rolls of 20 °C and 40 °C (Somedic AB), single pinprick (Semmes-Weinstein monofilament, estimated force 745 mN, Stoelting, IL, USA), and repetitive pinprick (2 Hz for 30 s) were assessed using an NRS (0–10) on the affected and the contralateral side in randomized order via a computer-generated randomization list [3,6,11]. In all subjects, the character of sensation to cold and warm stimulation was also recorded. The area of spontaneous pain was marked, and while the subject was not looking at the test site, the areas of decreased and increased sensation to pinprick and brush were marked, starting well outside the affected area and moving towards the scar area with increments of 1 cm. The areas were calculated in square centimeters using a standard program (Quantify; K.L.O.N.K, Sorø, Denmark). Lymphedema was evaluated by estimating upper or lower limb volumes by circumferential measurement of the upper or lower extremities at 10-cm intervals. The arm volume was obtained by starting the measurement at the styloid process of the ulna, and the leg volume was obtained by starting at the medial malleolus. The volume was calculated using the formula proposed by Kosir et al.:  $\text{volume} = h * [(Ct \cdot Ct) + (Ct \cdot Cb) + (Cb \cdot Cb)] / (12 \cdot \pi)$  with  $h$  = length (10 cm);  $Ct$  = circumference of the top of the arm/leg;  $Cb$  = circumference of the bottom of the arm/leg [14]. Restricted range of motion and pain during

shoulder abduction to 90°, placing the hand in the neck, hip flexion to 90°, and hip abduction and extension to 30° were assessed. All patients were examined by the same person (KAR).

### 2.4. Statistical analysis

The statistical analyses were carried out in SPSS version 13 (SPSS Inc., Chicago, IL, USA). All  $P$ -values <0.05 were considered statistically significant. Baseline data were described by mean (SD) if normally distributed or median (range). Binary variables were analyzed by  $\chi^2$  and Fisher's exact test.  $T$ -test and Mann-Whitney  $U$ -test were carried out for continuous variables. Odds ratios (OR) with 95% confidence intervals were calculated using standard  $2 \times 2$  tables. There were not enough cases for multiple logistic regression analysis.

## 3. Results

### 3.1. Questionnaire study

#### 3.1.1. Patients

Three-hundred fifty-four patients returned the questionnaire, and 350 answers could be assessed (response rate 87.1%) (Fig. 1). Lymph node excision was performed in 181 of the 350 patients, of which 175 (97%) responded to the second part of the questionnaire on pain after lymph node excision.

Table 1 describes baseline data in the study population. Mean age was 59.4 years (SD = 14.5 years), and 49.7% were women. Women were significantly younger than men (56.6 years [SD = 14.2 years] vs 62.1 years [SD = 14.3 years],  $P = 0.011$ ,  $t$ -test).

LND was performed in 51 patients (29.1%); 47 had both SNB and LND, and 4 had only LND because of metastatic disease. The remaining 124 patients had SNB only. The location for lymph node excision was the axilla (unilateral in 78 and bilateral in 26), groin (unilateral in 58 and bilateral in 5), and neck (unilateral in 16 and bilateral in 2). Ten patients had surgery in more than one location (a combination of axilla, groin, or neck). SNB was followed by minor surgical complications (seroma, signs of infection treated with peroral antibiotics, or hematoma) in 15 of 181 patients (8.5%), and a major complication (abscess leading to surgical intervention) in one patient (0.6%). Following LND, complications were more frequent, with 19 of 51 patients (37.3%) experiencing a minor surgical complication (seroma, infection treated with peroral antibiotics, or hematoma) and 8 patients (15.7%) a major surgical complication leading to intervention (abscess, postoperative bleeding leading to reoperation, or infection treated with intravenous antibiotics).

#### 3.1.2. Sensory abnormalities

Eighty-one of 174 patients (46.6%) reported sensory changes as a consequence of their lymph node excision, 37.9% described hyposensitivity, and 19.0% hypersensitivity (Table 1, Fig. 2). Altered sensation was significantly more common in those with LND than those with SNB only (82.4% and 31.7%, respectively, OR 10.1 [4.5–122.7]) (Fig. 2).

Fifty-four patients (81.8%) with hyposensitivity were bothered daily by this (median NRS 2, range 1–10), while 93.9% of patients with hypersensitivity were bothered daily by this (median NRS 4, range 1–10). Of all responders, 13.2% (23 of 174) were at least moderately bothered (NRS > 3) by either hypo- or hypersensitivity.

#### 3.1.3. Pain

Thirty-four of 173 patients (19.7%) reported pain following lymph node excision within the last month and 17.3% reported chronic pain, defined as constant pain or pain at least once weekly for at least 3 months. Pain was significantly more common in

**Table 1**  
Baseline data of the study population and patients with and without pain as a consequence of sentinel node biopsy (SNB) (n = 123, one did not answer the questions on pain) and lymph node dissection (LND) (n = 50, one did not answer the questions on pain) for malignant melanoma.

Patient characteristic	Total population	Patients with SNB only (n = 123)			Patients with LND (n = 50)		
		Patients with pain	Patients without pain	P-value or OR (95% CI)	Patients with pain	Patients without pain	P-value or OR (95% CI)
Number of patients	175	17	106		17	33	
Age, years, mean (SD)	59.4 (14.5)	54.3 (12.5)	60.1 (14.1)	0.11 <sup>a</sup>	57.2 (12.4)	59.8 (17.1)	0.59 <sup>a</sup>
Sex, women, n (%)	87 (49.7)	10 (58.8)	49 (46.2)	1.6 (0.6–4.7)	11 (64.7)	16 (48.5)	1.9 (0.6–6.5)
Time since SNB, months, mean (SD)	23.4 (13.1)	25.6 (12.8)	23.7 (13.6)	0.59 <sup>a</sup>	22.4 (11.9)	22.1 (12.9)	0.93 <sup>a</sup>
Sensory disturbances (n = 174), n (%)	81 (46.6)	13 (76.5)	26 (24.8)	<b>9.9 (3.0–33.0)</b>	17 (100)	25 (75.6)	<b>0.039<sup>b</sup></b>
Hyposensitivity (n = 174), n (%)	66 (37.9)	7 (41.1)	20 (19.0)	<b>3.0 (1.0–8.8)</b>	16 (94.1)	23 (69.7)	7.0 (0.8–59.9)
Hypersensitivity (n = 174), n (%)	33 (19.0)	9 (52.9)	7 (21.2)	<b>4.2 (1.2–14.8)</b>	6 (35.3)	11 (10.5)	<b>4.7 (1.4–15.4)</b>
Pain following melanoma excision	21 (12.0)	6 (35.3)	8 (7.5)	<b>6.7 (2.0–22.8)</b>	3 (17.6)	4 (12.1)	1.6 (0.3–7.9)
Pain elsewhere (n = 167) <sup>c</sup>	30 (18.0)	5 (29.4)	17 (17.0)	2.0 (0.6–6.5)	2 (11.8)	5 (16.1)	0.7 (0.1–4.0)
Complications	40 (22.9)	2 (11.8)	8 (6.4)	1.6 (0.3–8.4)	11 (64.7)	19 (57.6)	1.4 (0.4–4.5)
Localization of surgery <sup>d</sup>							
Axillary, n (%)	104 (59.4)	13 (76.4)	62 (58.5)	2.3 (0.7–7.5)	10 (58.8)	19 (57.6)	1.1 (0.3–3.5)
Inguinal, n (%)	63 (36.0)	4 (23.5)	38 (35.8)	0.55 (0.2–1.8)	7 (41.2)	13 (39.4)	1.1 (0.3–3.5)
Neck, n (%)	18 (10.3)	2 (11.8)	12 (11.3)	1.0 (0.2–5.1)	0 (0)	3 (9.1)	0.54 <sup>b</sup>
Adjuvant therapy <sup>e</sup>	10 (5.7)	0 (0)	1 (0.9)	1.0 (1.0–1.0)	1 (6.0)	8 (24.2)	0.20 (0.02–1.7)

Bold text indicates significant differences.

OR, odds ratio (chi-squared) with 95% confidence interval (CI).

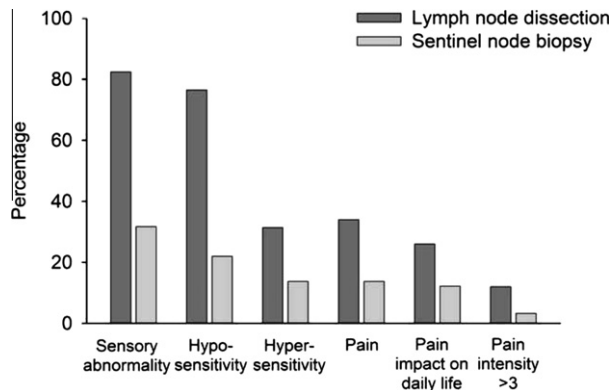
<sup>a</sup> t-Test.

<sup>b</sup> Fisher's exact test, OR cannot be calculated.

<sup>c</sup> The most common pains reported were osteoarthritis (n = 16), neurological cause including migraine, multiple sclerosis or Parkinson disease (n = 9) and abdominal/gynecological pain (n = 4).

<sup>d</sup> More than one location (including bilateral) in 43 patients.

<sup>e</sup> Irradiation therapy (n = 3), immunotherapy with interleukin-2 or interferon treatment (n = 4), chemotherapy (peroral temodal) (n = 5), and isolated regional hyperthermic perfusion of the lower extremity (n = 1).



**Fig. 2.** Sensory disturbances and pain after lymph node excision in patients with malignant melanoma. Percentage of patients reporting sensory abnormality (hypo- and/or hypersensitivity), pain, pain impact on daily life, and at least moderate pain (pain intensity > 3 on numeric rating scale, range 0–10) following lymph node dissection (n = 51) and sentinel node biopsy (n = 124).

patients with LND than in patients with SNB only (34.0% vs 13.8%, OR 3.2; 1.5–7.0) (Fig. 2).

**3.1.3.1. Pain characteristics.** The location of pain is illustrated by Fig. 3. The onset of pain was reported to be within 3 months of surgery in 26 patients, between 3 and 12 months in 5 patients, and after 1 year in 3 patients. Median pain intensity in the past 24 hours was 3 (range 0–10), SNB only: 2.5 (range 0–5), LND: 3.0 (range 0–10); and 10 patients (5.8%) had moderate to severe pain (NRS > 3), SNB: 3.3%, LND: 12.0% (Fig. 2). Five patients reported constant pain and 11 reported daily pain. Of patients with pain, 24 (70.6%) had rest pain with a median pain intensity on the NRS

of 3 (range 1–8), and 18 patients (52.9%) reported pain triggered by a specific motion with a median pain intensity on the NRS of 4 (range 2–10). Fifteen patients (44.1%) reported pain by light pressure on the affected area (median NRS 5, range 1–9); and 8 (23.5%) reported pain by lightly touching the skin (dynamic mechanical allodynia): 2 of 17 with SNB only and 6 of 17 with LND (median NRS 5, range 1–8). Nineteen (57.6%) met the DN4 cutoff criteria for neuropathic pain (3 of 7): 5 of 16 (31%) with SNB only (one missing answer) and 14 of 17 (82%) with LND. Sensations were described as pins and needles by 24 patients, numbness by 18, tingling by 17, burning by 16, electric shocks by 10, itching by 10, and painful cold by 6.

**3.1.3.2. Pain medication and quality of life.** Nine patients used pain medication (pregabalin, paracetamol, aspirin, NSAIDs) for their pain, but only one patient used it (pregabalin) daily. This patient also had a dorsal column stimulator. In 28 patients (16.2%, SNB: 12.2%, LND: 26%) (Fig. 2), pain had an impact on daily life: mood (n = 19), daily activities (n = 18), sleep (n = 15), and social life (n = 13). Nineteen patients (11.0%) reported impact on quality of life by pain; the impact was moderate to severe in 5.2% (SNB: 1.6%, LND: 14.0%). Seventeen patients (9.8% of all patients) reported at least moderate impact on daily life, sleep, mood, or social life.

**3.1.3.3. Predictors of pain.** There was an association between pain and sensory disturbances. Of the 81 patients with altered sensation, 37.0% reported pain, compared with 4.3% of the participants reporting normal sensation (OR 13.0; 43.5–28.4), and both hypersensitivity and hyposensitivity were associated with an increased risk of reporting pain. Within each operation type, sensory abnormality was associated with the presence of pain (Table 1). Patients reporting pain following excision of malignant melanoma also had

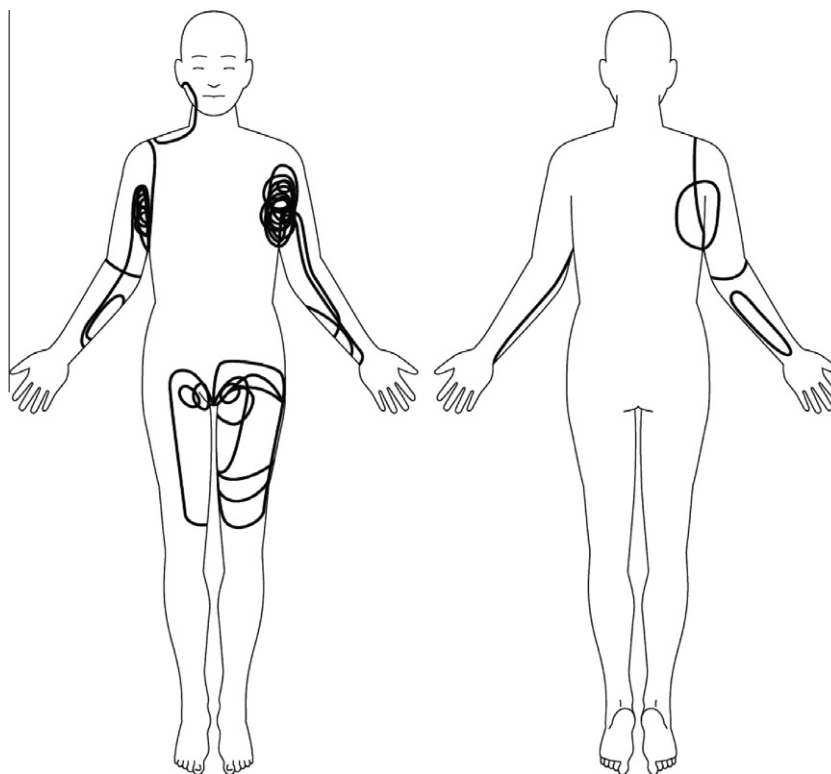


Fig. 3. Areas of pain in 34 patients following lymph node dissection (n = 17) and sentinel node biopsy (n = 17) in the questionnaire study.

a higher prevalence of pain following SNB (Table 1). There was no association between pain and sex, age, localization of surgery, and pain unrelated to their malignant melanoma (Table 1). Surgical complications were not a predictor of pain or sensory abnormality following lymph node excision.

### 3.2. Clinical study

#### 3.2.1. Patients

Twelve of the 34 patients with pain (35.3%) responded to the letter requesting participation in the clinical study, 3 with SNB and 9 with LND. The clinical characteristics of these patients are presented in Table 2. One patient (no. 2) received adjuvant therapy for distant metastasis (interleukin-2, which due to intolerance was switched to peroral temozolomide). One patient (no. 5) clinically had edema and a 14% larger volume of the affected leg compared with the contralateral leg, while there was a deviation of <8% between the affected and the nonaffected side in the remaining patients. This difference was within the range found in a control population of malignant melanoma patients who did not undergo lymph node excision (data not shown) and has not been considered lymphedema in other studies [14,20]. Nineteen pain-free patients were recruited, 15 with SNB (8 axillary, 5 inguinal, 2 neck) and 4 with LND (2 axial and 2 inguinal).

#### 3.2.2. Pain and sensory disturbances

Pain onset was within 3 months of surgery in 10 patients, between 3 and 12 months in 1, and more than a year in 1. Eight patients reported constant or daily pain, 3 weekly pain, and 1 (no. 10) reported less frequent pain. Eight patients reported impact of pain on daily activities (Table 2). Only 1 patient (no. 9) took pain medication (not on the day of examination), which included pregabalin, paracetamol, and NSAIDs, and also had a dorsal column stimulator for the pain.

None of the patients had a restricted range of motion for the movements tested, but 8 patients reported pain, all in the affected

side; 1 patient reported pain during hip flexion, 1 during hip flexion and abduction, 4 during shoulder abduction, and 2 during both shoulder abduction and when moving the hand to the neck. Median pain intensity during movement of the affected limb was 3 (range 2–7).

All patients described spontaneous pain, and 7 in addition evoked pain. On bedside clinical examination, evoked pain was found in 9 patients (modalities and intensity in Table 2).

All patients had an area of decreased or increased sensation to mechanical stimuli. Two patients had only hypersensitivity, 3 only hyposensitivity, while 7 had areas of both hypo- and hypersensitivity (Fig. 4). In addition, 8 patients had absent or decreased temperature sensation in the pain-affected area. None of the patients had paradoxical heat sensation upon cold stimulation.

The sensory abnormalities were compatible with neurological abnormalities due to lesions of the medial antebrachial cutaneous nerve, the medial brachial cutaneous nerve, and the intercostobrachial nerves for axillary surgeries and lesions of the femoral branch of the genitofemoral nerve, the ilioinguinal nerve, the lateral femoral cutaneous nerve, the cutaneous branch of the obturator nerve, and the anterior cutaneous branches of the femoral nerve for inguinal surgeries (Fig. 4). In all but 1 patient (no. 8) with spontaneous pain at the time of examination, and in the 4 patients without pain at the time of examination, the area of spontaneous pain was located in an area with sensory abnormality, often within larger areas of abnormal (increased or decreased) sensation (Fig. 4). In addition, sensory abnormalities were present in innervation territories of nerves passing through the surgical field and thus putatively lesioned field (Fig. 4), and evoked and spontaneous pain were distributed in a neuroanatomically plausible area, and thus, the criteria for probable neuropathic pain [24] were met in 11 patients. In addition, 10 patients had a score of 4 or more on the DN4, suggesting probable neuropathic pain. Both criteria for neuropathic pain were present in 10 of 12 patients.

Patients with and without pain were compared with regard to sensory abnormalities, but since it was not possible to match the

**Table 2**

Clinical characteristics of 12 patients reporting pain as a consequence of sentinel node biopsy (SNB) and/or lymph node dissection (LND) in malignant melanoma.

Pt no.	Age, y	Sex	Time since surgery, months	Surgery	Pain intensity average/worst/present (0–10) <sup>a</sup>	Pain impact (0–10) <sup>b</sup>	Spontaneous pain descriptors	Evoked pain descriptors	Evoked pain on examination intensity (0–10) <sup>c</sup>	DN4 score <sup>d</sup>	NPSI dimensions last 24 hours
1	52	F	30	LND Axillary	0/0/1	1	Tight, warm	–	Wu 2	7	Burning, pressing, paroxysmal, evoked, pricking
2	60	F	20	LND Axillary	5/7/5	10	Tight, pins and needles, tingling, numbness, shooting	Shooting pain upon light touch	Brush 2, cold 5, wu 10	8	Pressing, paroxysmal, evoked, pricking
3	44	F	45	LND Inguinal	4/5/0	6	Pins and needles, shooting, dull	Shooting pricking pain upon light touch	Wu 3	7	Burning, pressing, paroxysmal, evoked, pricking
4	57	M	27	LND Axillary	7/7/7	7	Pins and needles, dull	Pricking pain upon light touch	Brush 7	7	Pressing, paroxysmal, evoked, pricking
5	62	F	45	LND axillary	7/5/0	0	Pins and needles, burning	–	–	4	Evoked, pricking
6	53	M	41	SNB Inguinal	1/1/1	0	Tight, tender	–	–	1	Pressing, pricking
7	48	F	15	LND Inguinal	3/3/2	4	Tight, tingling	Tingling when contact with clothes	Brush 3, warm 2, wu 4	6	Burning, pressing, paroxysmal, pricking
8	56	F	42	SNB Axillary	1/1/0	0	Burning	Pain from clothes	Pinprick 1	1	Burning, paroxysmal, pricking
9	43	F	52	LND Axillary	6/6/5	5	Cold, warm, pins and needles, pressing	Shooting pricking pain upon light touch	Brush 4, cold 4, warm 4, pinprick 3, wu 3	9	Burning, pressing, paroxysmal, evoked, pricking
10	65	M	39	LND Axillary	0/0/0	0	Burning	–	–	4	None
11	72	F	20	SNB Neck	6/8/4	5	Tight, pins and needles, warm	Tight sensation upon touch	Cold 2, warm 6, pinprick 3, wu 4	7	Burning, evoked, pricking
12	51	M	22	LND Axillary	5/8/5	5	Pins and needles, dull, tight	–	Pinprick 3, wu 4	6	Burning, paroxysmal, evoked, pricking

NPSI, Neuropathic pain symptom inventory [5]; DN4, Douleur Neuropathique en 4 questions [4]; wu, windup.

<sup>a</sup> Average and worst pain intensity within the past 24 hours.<sup>b</sup> Pain impact on daily activities (numeric rating scale [NRS] 0–10).<sup>c</sup> Intensity of pain and/or unpleasantness (NRS 0–10) to brush, cold and warm thermo rolls, pinprick and repetitive pinprick (windup) (for pinprick and windup, intensity on contralateral side is subtracted).<sup>d</sup> A score of 4 or higher on the neuropathic pain diagnostic questionnaire DN4 suggests neuropathic pain [4].

location of injury, groups became too small for statistical analyses (Table 3). However, the results do support a higher prevalence of sensory abnormalities, particularly evoked pain, and larger areas of sensory hypersensitivity in patients with pain than in those without pain, also when correcting for type of surgery (Table 3).

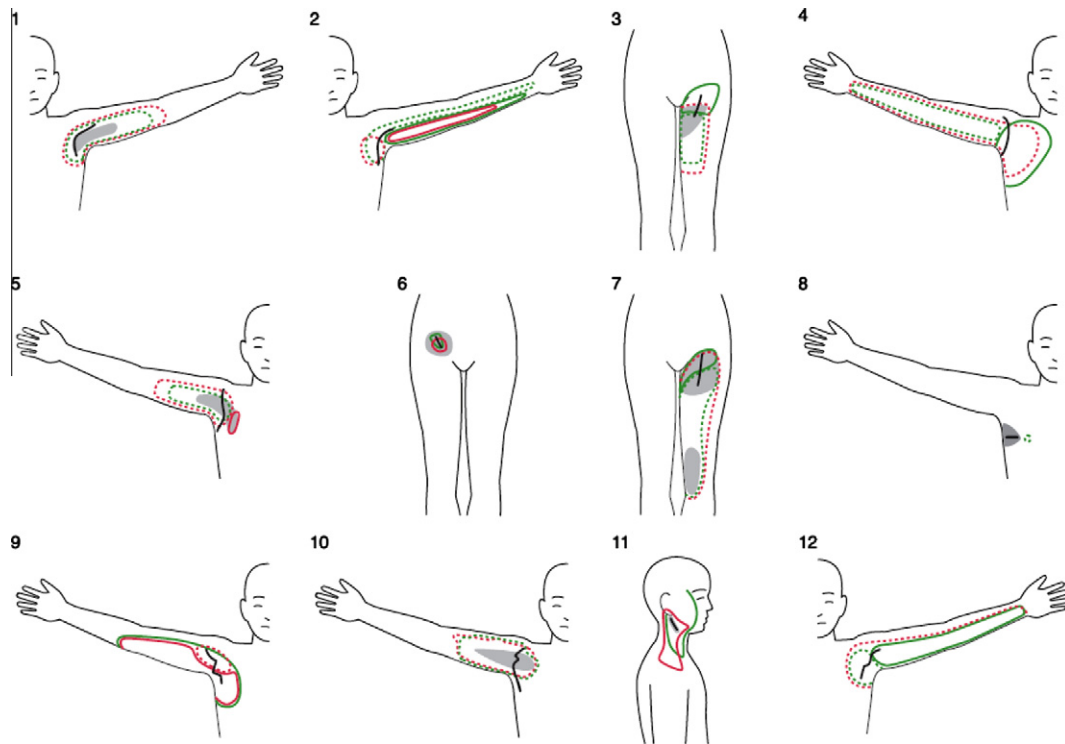
Comparison of patient-reported outcome in questionnaire (changed, decreased, or increased sensitivity for touching the skin) and sensory examination (with a brush) using Cohen's kappa coefficient ( $\kappa$ ) for all 31 subjects showed moderate to excellent agreement (any sensory abnormality:  $\kappa = 0.87$ , decreased sensation:  $\kappa = 0.68$ , and increased sensation:  $\kappa = 0.56$ ).

#### 4. Discussion

In this cross-sectional study, we found that pain within the last month occurred in 14% after SNB and in 34% after LND on average 23 months after surgery for malignant melanoma. After LND, 12% of patients reported at least moderate pain and 14% reported impact of pain on quality of life, while 3% reported at least moderate pain and 2% pain with impact on quality of life after SNB. These figures are higher than previously reported. In 2008, Kretschmer et al. found long-time nerve dysfunction (paresthesia and pain) in 1% of patients after SNB and 9% after LND, and de Vries et al. reported similar quality-of-life and pain outcomes in malignant melanoma patients after SNB with or without LND,

compared with a norm group of the general population [7,15]. None of these studies distinguished between nociceptive and neuropathic pain.

The most important predictor of pain in this study was sensory abnormalities. Hypersensitivity or hyposensitivity within the area of pain is compatible with nerve injury due to a lesion of nerves trespassing the surgical field. In support of this notion, 82% of patients with pain after LND and 31% of patients with SNB met the DN4 cutoff criteria for neuropathic pain. To further analyze for a potential neuropathic underlying mechanism, all patients reporting pain were asked to participate in a clinical follow-up study. The sensory examination was based on a bedside examination, which allows for drawings of the distribution of sensory abnormalities. In this part of the study, 10 of 12 patients fulfilled both the recently proposed grading system for probable neuropathic pain [24] and used descriptors on the DN4 suggestive of neuropathic pain. For the 9 patients with LND, 89% met both criteria for neuropathic pain, while 2 of 3 (66%) of the patients with SNB met both these criteria. The overlap of patients fulfilling the clinical diagnostic criteria and the DN4 criteria for probable neuropathic pain supports the use of DN4 as a screening method, but this is based on a limited number of patients. It is the authors' opinion that a diagnosis of neuropathic pain in the single patient should be based on a pain history and a proper neurological examination according to the diagnostic criteria [25].



**Fig. 4.** Areas of sensory abnormality and current spontaneous pain at examination in 12 patients in the clinical study. Gray shade: spontaneous pain, green line: pinprick hyperalgesia, dashed green line: pinprick hypoalgesia, red line: increased sensation to brush, dashed red line: decreased sensation to brush.

**Table 3**

Clinical examination; characteristics of 12 patients with and 19 patients without pain after surgical lymph node excision following malignant melanoma and characteristics of patients with lymph node dissection (LND) and sentinel node biopsy (SNB).

	Total group		Patients with LND		Patients with SNB	
	Pain	No pain	Pain	No pain	Pain	No pain
Number	12	19	10	4	2	15
Age, years, mean (SD)	55.3 (8.6)	52.5 (11.9)	55.4 (9.5)	51.8 (14.5)	54.5 (2.1)	52.7 (11.6)
Sex, women/men, n (% women)	8/4 (67)	12/7 (63)	7/3 (70)	3/1 (75)	1/1 (100)	9/6 (53)
Lymph node dissection, LND, n, (%)	10 (83)	4 (21)	10 (100)	4 (100)	0	0
Brush evoked dysesthesia or pain on examination, %	33	0	40	0	0	0
Cold evoked dysesthesia or pain on examination, %	25	0	30	0	0	0
Warm evoked dysesthesia or pain on exam, %	25	0	30	0	0	0
Pinprick hyperalgesia on examination, %*	33	5	30	0	50	7
Wind up like pain on examination, %*	58	11	70	0	0	13
Decreased touch sensation, %	75	42	90	100	0	27
cm <sup>2</sup> , Median (range)	514 (44–3455)	69 (7–417)	515 (44–3435)	176 (80–417)	0	9 (7–58)
Increased touch sensation, %	42	0	40	0	50	0
cm <sup>2</sup> , Median (range)	146 (5–1488)	0	161 (8–1488)	0	5	0
Decreased pinprick sensation, %	75	37	80	100	50	20
cm <sup>2</sup> , Median (range)	286 (0.2–2797)	16 (3–273)	323 (72–2797)	106 (16–273)	0.24	8 (3–10)
Increased pinprick sensation, %	67	37	70	50	50	33
cm <sup>2</sup> , Median (range)	234 (5–1759)	17 (2–68)	276 (65–1759)	23 (17–29)	5	5 (2–68)

\* Compared to contralateral side.

Based on the close relationship between sensory abnormalities and persistent pain, our study confirms previous suggestions of nerve damage causing persistent postoperative pain [13]. Surgeries with major nerve damage, like amputation and thoracotomy, are more likely to be associated with persistent pain than minor surgeries like herniotomy [13]. In this study, we found a higher prevalence of both pain and sensory abnormalities after LND compared with biopsy, consistent with previous studies documenting a larger morbidity after dissection [16]. Using the same questionnaire in different types of plastic surgery, we have found sensory abnormalities to be the major predictor for persistent postoperative pain,

with ORs ranging from 3.7 to 10.8. The percentages of self-reported sensory abnormalities and pain, respectively, in the different surgical procedures were as follows: LND: 82% and 34%, cosmetic breast augmentation: 76% and 44%, breast reduction surgery: 54% and 28% [23], SNB: 32% and 14%, and excision of malignant melanoma: 32% and 9.7% ([22], Høimyr et al., personal communication). Other predictors found in other studies: young age, gender, and localization of surgery [13] were not found to be a predictor for pain in this study.

Heterogeneous sensory patterns in QST among patients with postsurgical pain have been demonstrated previously [1,10,25],

but the drawings of areas of pain and hypo- and hypersensitivity in this study also illustrate the heterogeneous sensory profiles within single patients. Depending on the site of examination, a quantitative sensory examination as performed, for example, in the German Research Network on Neuropathic Pain [18], will likely demonstrate different sensory profiles within the individual patients. This illustrates the complexity of translating QST examinations at a single location to underlying pain mechanisms in a specific patient.

Methodological limitations of this study include lack of a reference population and a relatively low number of patients participating in the clinical follow-up. Shoulder and hip pain and pain due to lymphedema are likely to be underestimated because we asked for pain developed in the area of lymph node excision. Although none of the patients had a restricted range of motion for the movements tested in the clinical follow-up, 8 of 12 patients reported pain in the affected side during movement of the affected limb. Sensory changes were evaluated on the basis of patient descriptions, which may underestimate sensory changes compared to a clinical examination using different modalities. We did, however, find a good correlation between a person's verbal report and using a brush to evaluate tactile allodynia with a kappa coefficient of  $\kappa = 0.87$ . This is in agreement with previous findings [4]. In addition, the question on sensory abnormalities was asked before any question on pain, and any underreporting of sensory abnormalities is likely to affect pain and pain-free subjects to the same extent.

## 5. Conclusion

In patients with malignant melanoma, sensory disturbances were reported in 82% after LND and 32% after SNB, while persistent pain was reported in 34% and 14%, respectively. Sensory abnormality was a predictor of persistent pain in both conditions. Using the grading system for neuropathic pain and pain descriptors (DN4), neuropathic pain was suggested to explain pain in 82–89% of patients with LND and 31–66% of patients with SNB. Different patterns of sensory profiles were observed in single patients, suggesting heterogeneous sensory processing within individual patients.

## Conflict of interest statement

The authors have no conflicts of interest.

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## Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.pain.2011.07.009.

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