

Lymph node dissection in patients with malignant melanoma is associated with high risk of morbidity

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ABSTRACT

INTRODUCTION: Malignant melanoma is one of the most rapidly increasing cancer types globally, and it is by far the most serious skin cancer. Patients with a melanoma ≥ 1 mm in Breslow thickness are offered sentinel node (SN) biopsy and subsequent radical lymph node dissection if the biopsy is positive. The objective in the present paper was to describe post-operative complications in this group of patients. A standard operation and drainage regime was used.

MATERIAL AND METHODS: This was a retrospective study based on 96 consecutive SN-positive patients with primary cutaneous malignant melanoma who underwent subsequent radical axillary or inguinal lymph node dissection. Fisher's exact test and Mann-Whitney U-test were used to evaluate associations.

RESULTS: In all, 57 patients were male and 39 female. A total of 71 had an axillary and 25 an inguinal operation. The median drainage period was seven days (2-15 days). Forty patients developed seroma which needed puncture; three of these cases were chronic, there was no difference between the two groups. Seroma puncture was only associated with infection in the inguinal group ($p = 0.04$). 25% in the axillary group were diagnosed with lymph oedema after three months versus 48% in the inguinal group ($p = 0.04$). A body mass index ≥ 25 kg/m² was associated with a slight, but non-significant increase in complications ($p = 0.08$). No association was found for smoking or co-morbidity.

CONCLUSION: Patients undergoing axillary or inguinal lymph node dissection experience a significant number of complications, especially seroma and lymph oedema. Long-term complications are severe and can profoundly impact the patient's quality of life.

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Malignant melanoma is one of the most rapidly increasing cancer types globally. In Denmark, the incidence of cutaneous malignant melanoma has risen by almost 3% per year over the past four decades [1]. Over 1,900 new cases are registered annually, corresponding to an age standardized incidence of 27/100,000 inhabitants [2]. Approximately 90% of all skin cancer-related deaths are due to cutaneous malignant melanoma [2].

Seroma is a frequent postoperative complication to radical axillary and inguinal lymph node dissections.

Accumulation of fluid is of great inconvenience for the patient; it may cause prolongation of hospital stay, increases the risk of infection, and perhaps also increases the risk of subsequent lymph oedema [3].

The aetiology of seroma formation and how to reduce the incidence is still basically unknown and controversial. Studies suggest that the composition of seroma fluid is of inflammatory origin, while others have hypothesized that seroma originates from open lymph vessels [4, 5]. Anatomical factors are also likely to enhance fluid accumulation. Extensive dissection results in a large dead space beneath the skin flaps. The majority of previous studies have been performed in breast cancer patients. Lymph node dissection after malignant melanoma is somewhat more extensive and results may thus not be fully comparable.

The objective of this study was to describe post-operative complications in malignant melanoma patients after radical axillary or inguinal glandular lymph node dissection.

MATERIAL AND METHODS

Patient material

Between 1 January 2008 and 31 December 2011, 112 patients underwent radical axillary or inguinal lymph node dissection at the Department of Plastic Surgery and Reconstruction, Herlev University Hospital. A total of 16 patients were excluded from this study because they had clinical metastases at the time of surgery.

The study included a total of 96 patients diagnosed with primary malignant melanoma and who had one or more positive lymph nodes after sentinel node (SN) biopsy according to the Danish Melanoma Guidelines [6]. SN biopsy is recommended for patients with primary tumours with a Breslow thickness of ≥ 1 mm and/or Clark level of invasiveness of IV or V, and/or ulcerating primary tumour. The indications for SN biopsy are about to be changed to also include a mitotic index in the primary tumour of ≤ 1 mm) [6] (Figure 1).

Data were collected from the medical files and included age, sex, current smoking, body mass index (BMI), co-morbidity, histology and tumour characteristics such as Clark level, Breslow thickness, ulceration, location, number of sentinel nodes removed, number of sentinel nodes with metastases, number of lymph nodes

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A 64-year-old woman with an acquired naevus on her arm, increased in size and darkness. Histology was a superficially spreading malignant melanoma with regression; therefore, depth and thickness could not be measured. The tumour was excised with a 2-cm margin as in a worst case scenario. The patient declined sentinel node biopsy due to co-morbidity. There has been no relapse within a year.

removed at exauresis, number of lymph nodes with metastases at exauresis, pre-operative antibiotics, time of drain removal, occurrence of any haematoma requiring surgery, infection, seroma, number and volume of aspirations, and occurrence of the following symptoms ≥ 3 months after surgery: pain sensibility disturbances, seroma and lymph oedema.

Surgery and drainage regime

The surgical technique for axillary dissection includes raising of skin flaps at the level of the subcutaneous fascia, removal of all fat and lymph nodes from the axillary vein and below to the level of the fifth rib and in the space between the chest wall and the musculus latissimus dorsi, cranially as far up along the axillary vein as possible, usually to level III, while generally sparing the passing nerves and vessels. The fascia over the muscles is dissected off the muscles and the remaining nerves and vessels appear skeletonized at the end of the procedure.

An inguinal exauresis includes raising of skin flaps at the level of the subcutaneous fascia, removal of all fat and lymph nodes in the triangle between the lateral margin of *m. sartorius*, the medial margin of *m. adductor longus* and cranially from the lower part of the *m. obliquus externus* about 5 cm proximal to the inguinal ligament and down to the apex of the *trigonum femorale*. The fascia over the muscles is dissected off the muscles, and the femoral artery and vein are cleaned as well as the femoral nerve and its divisions, only leaving a thin layer of loose tissue over the nerves. *Vena saphena magna* is sacrificed. The surgery was performed by several of the surgeons in the department and skin flaps were generally raised using a combination of knife and diathermy.

Closed suction drainage was used as a routine, two drains were employed both for axillary and inguinal dissection. One drain was removed on the second day

of surgery and the second drain within seven days, or before if the production was under 30 ml over a 24-hour period. In a few patients, longer drainage was performed. Subsequently, a soft, slightly compressive bandage was placed in the axilla and generally worn for 1-2 days. In case of inguinal operation, a compressive hip bandage was prescribed in combination with immobilization for 24 hours after removal of the last drain.

Complications

Wound infection was defined by the presence of any of the following in the medical records: antibiotics given on clinical suspicion (purulent discharge, redness, warmth and/or swelling); a positive culture of a pathogenic organism from a wound swab; re-operation or drainage with a new drain due to infection.

Wound seroma was defined as a palpable accumulation of fluid at the lymphadenectomy site whether or not aspiration was required. Seromas were aspirated if they were large, painful, tense, associated with infection, or on patient request. Small seromas were usually left to resolve spontaneously. Lymph oedema was defined as postoperative limb swelling persisting beyond three months postoperatively and after a physiotherapist had confirmed the diagnosis.

All patients were seen for clinical controls at three-monthly intervals for two years after treatment and at six-monthly intervals for a further three years if there were no sign of recurrence.

Statistics

Simple descriptive statistics were calculated using Fisher's exact test. For continuous data, a Mann Whitney U-test was used. The level of significance was set at 5%.

Trial registration: not relevant.

RESULTS

A total of 96 patients were identified, 57 (59%) of whom were male and 39 (41%) were female. The median age at time of operation was 62 years (range 25-87 years). The median thickness of the primary tumour was 2.90 mm (range 0.13-24 mm). In all, 67% were superficially spreading melanoma, 24% were nodular malignant melanoma, 6% were unclassified and 3% were unknown. There was no incidence of acral or lentigo maligna melanoma in this material (Table 1).

41% of patients had no co-morbidity, 31% had hypertension, 3% had noninsulin-dependent diabetes mellitus (NIDDM), 2% had insulin-dependent diabetes mellitus (IDDM), 9% had cardiac incompenation, 4% were immune-suppressed and 10% had a co-morbidity classified as "another". 16% had more than one co-morbidity.



TABLE 1

Characteristics of the 96 patients with positive sentinel node biopsy who underwent axillary or inguinal lymph node dissection.

	n	%
Sex		
Male	57	59
Female	39	41
Primary melanoma localization		
Truncus	52	54
Upper extremity	21	22
Lower extremity	19	20
Unknown	4	4
Tumour ulceration		
Yes	17	18
No	66	69
Unclassified	13	14
Primary tumour thickness (Breslow), mm		
≤ 1.0	7	7
1.0-1.99	22	23
2.0-3.99	37	39
≥ 4.0	21	22
Unknown	9	9

Twenty-three (24%) of the patients were smokers and 67 (70%) were non-smokers. The smoking status of six (6%) patients was unknown (data not shown).

The median drainage period was seven days (range 2-15 days). Forty (42%) patients developed seroma which needed puncture; 41% in the axillary group and 44% in the inguinal group. The median number of punctures was four (range 1-17) (Table 2). Three of these patients developed chronic seroma (data not shown).

Thirty patients (31%) were diagnosed with lymph oedema and referred for lymph oedema therapy performed by a physiotherapist. Lymph oedema was found

in 25% of the patients in the axillary dissection group and in 48% of patients in the inguinal dissection group ($p = 0.04$) (Table 2).

Overall, there was no association of seroma puncture and infection; however, among the patients with inguinal exaeresis, seven patients who underwent repeated punctures developed infection, in comparison to four who were not punctured ($p = 0.04$). There was no obvious association between seroma and the risk of developing lymph oedema ($p = 0.65$) (Table 2).

Smoking and co-morbidity did not appear to be associated with the risk of any complication, either separately or in total (Table 3). A BMI ≥ 25 kg/m² was associated with an increased risk of any post-operative complication; this, however, was not statistically significant ($p = 0.08$) (Table 3).

DISCUSSION

This study shows that the risk of post-operative seroma and lymph oedema after axillary- and inguinal lymph node dissection in SN-positive melanoma patients was very high. Seroma formation was equally high in the two groups. A very high number of patients with some degree of lymph oedema after three months was also observed. This result was primarily due to patients who had had inguinal lymph node dissection. These results are in good accordance with Serpell et al who found a seroma rate of 46% in inguinal and 32% in axillary lymph node dissection for malignant melanoma, and their finding of lymph oedema was also in line with our results [7]. Our results are also in good accordance with most studies on patients undergoing mastectomy and/or axillary dissection, although much variation in the risk of seroma has been reported (range 2.5% to 51%) [3, 4, 8].

Several studies have been conducted to analyze the



TABLE 2

	Axillary exaeresis (N = 71)		Inguinal exaeresis (N = 25)		Axillary and inguinal exaeresis combined (N = 96)	
	n (%) [range]	p value ^a	n (%) [range]	p value ^b	n (%)	p value ^c
Seroma punctures after removal of last drain						
Yes	29 (41)		11 (44)		40 (42)	0.82
No	42 (59)		14 (56)		56 (58)	
Median number of punctures	5 [1-17]		3 [1-8]			0.67
Infection						
In case of puncture	14 (47)	0.63	7 (70)	0.04	21 (53)	0.14
No puncture	16 (53)		3 (30)		19 (48)	
Lymph oedema after three months						
Yes	18 (25)		12 (48)		30 (31)	0.04
No	53 (75)		13 (52)		66 (69)	
Lymph oedema if						
Seroma puncture	8 (44)	0.60	5 (42)	0.68	13 (43)	0.82
No seroma puncture	10 (56)		7 (58)		17 (57)	

a) Analysis for the axillary group separately; b) Analysis for the inguinal group separately; c) Analysis for the combined group.

Complications after elective lymph node dissection for malignant melanoma metastases diagnosed by sentinel node biopsy in 96 patients.

 TABLE 3

Co-morbidity, certain characteristics, and complications after elective lymph node dissection for malignant melanoma metastases, n = 96 (axillary and inguinal dissections grouped as one). Patients with missing information have been excluded from the analysis in question.

	Any complication (seroma, lymph oedema, infection), n (%)	No complica- tion, n (%)	p value
Any co-morbidity	38 (40)	11 (12)	0.49
No co-morbidity	32 (34)	14 (15)	
Smoking	17 (20)	5 (6)	1.00
No smoking	49 (57)	15 (17)	
BMI \geq 25 kg/m ²	25 (40)	13 (21)	0.08
BMI < 25 kg/m ²	21 (34)	3 (5)	

BMI = body mass index.

chemical and cellular composition of serous fluid from the axilla. In a Dutch prospective study, Bonnema et al analyzed lymph fluid from breast cancer patients and found the fluid to include blood components during the first days after surgery, but these components disappeared rapidly and were replaced by peripheral lymph-like fluid, only lacking fibrinogen [5]. The absence of fibrinogen seems to be an important factor in the formation of seroma. This presumably led to the use of fibrin sealant. However, numerous randomized clinical studies in breast cancer patients have concluded that the use of fibrin does not prevent or reduce the formation of seroma [3, 9, 10-12].

Other studies have focused on suction drainage and the ideal time of drain removal after axillary lymph node dissection in breast cancer patients. Jain et al and Kopelman et al both conducted a prospective randomized trial on breast cancer women treated with axillary dissection where 116 and 90 patients, respectively, were randomized to early (on third postoperative day) versus late drain removal (< 35 ml/24 hours) [10, 13]. Both studies concluded that early removal of drains can reduce postoperative discomfort, and drainage was associated with a high pain score [10]. Furthermore, early drain removal shortened hospital stay and seemed to have an economic advantage [13]. Prolonged drainage can potentially increase the risk of infection and perpetuation of drainage due to tissue inflammation, irritation and infection [8, 14].

He et al made a systematic review of randomized controlled trials to evaluate whether breast cancer patients benefit from suction drainage after axillary lymph node dissection [15]. Six randomized controlled trials and a total of 585 patients were included. The study concluded that no drainage resulted in a shorter hospital stay, but seromas occurred more frequently and large-volume seromas required more aspirations. Despite the use of a drain, seroma still occurred in more than half of

the patients and needed aspiration after drain removal [15]. It was reported that frequent aspirations are associated with increased pain and may affect the patient's quality of life [13].

Different variables have been suggested as risk factors for seroma. These include a high body mass index, smoking, surgical technique, duration and amount of drainage, infection, early shoulder movement, skin flap necrosis and delayed wound healing [16]. Several approaches have been used to reduce seroma formation, including mechanical and technical techniques, shoulder immobilization, sclerotherapy and alternative haemostatic agents including fibrin as mentioned above, in addition to quilting of skin flaps [16]. But all of these approaches have failed to identify any single measures that prevent seroma formation [8, 16]. It could be speculated that removal of the fascia over the muscles in melanoma lymph node dissection may increase the risk of seroma formation. Moreover, the oncological benefit of this procedure is not evidence-based, but rather rooted in a conceptual idea that the region should be maximally cleaned. In breast cancer surgery, the fascia is not removed routinely; however, complications are similar to those observed in the present study. In our material, several different surgeons operated patients and thus contributed to complications. Fewer and more specialized surgeons might have yielded better results, but this needs to be evaluated in a prospective study.

Our study found no association between the risk of complications and smoking and co-morbidity. However, a BMI \geq 25 kg/m² was associated with an increased risk of any post-operative complications, although not significantly.

Despite a relatively long drainage time, we had a high number of postoperative seromas, which occurred in 42% of patients who underwent axillary- or inguinal lymph node dissection. Serpell et al speculated that possibly seroma should not be regarded as a true complication, but instead as an inevitable consequence of the operation and that gravity might play a role [7].

A major weakness in this study is the lack of a control group for comparison. Furthermore, this was a retrospective study with the inherited shortcomings of such a study. We set out also to evaluate the occurrence of prolonged pain, but information in the medical records was too inconsistent for this. Most prior studies were performed on breast cancer patients. There are considerable similarities between these patients and melanoma patients undergoing lymph node dissection; however, there are also differences, and seroma formation in the inguinal area has not been thoroughly evaluated. The strength of the study is primarily that we investigated a consecutive and homogenous cohort of patients who were operated with a standard procedure and also

treated postoperatively according to standard postoperative guidelines. There is a need for a randomized study to clarify the optimal drainage regime also taking the patients' perspective into account. Furthermore, a prospective study is needed to identify any risk factors for seroma formation and lymph oedema.

This study allows the conclusion that patients undergoing axillary – or inguinal – lymph node dissection due to positive sentinel nodes in malignant melanoma experience a significant number of complications, especially in the form of seroma and lymph oedema. Long-term complications are, of course, very serious and can profoundly impact the patient's future quality of life. Consequently, it is essential to avoid or at least minimize risk of chronic lymph oedema and pain. Research focusing on new and gentler methods of operation as well as the optimal postoperative regime including rehabilitation are needed.

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CONFLICTS OF INTEREST: none

LITERATURE

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