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ARTICLE

# Late arm and shoulder problems after axillary therapeutic lymph node dissection in patients with melanoma

Hans P. Gullestad[a,b], Gro Haugen[c] and Sophie D. Fosså[d]

[a]Division of Plastic Surgery, Department of Surgical Oncology, The Norwegian Radium Hospital, Oslo University Hospital, Oslo, Norway; [b]Division of Oncoplastic Surgery, The Norwegian Radium Hospital, Oslo University Hospital, Oslo, Norway; [c]Section for Cancer Rehabilitation, Department of Clinical Service, The Norwegian Radium Hospital, Oslo University Hospital, Oslo, Norway; [d]Department of Clinical Cancer Research, The Norwegian Radium Hospital, Oslo University Hospital, Oslo, Norway

**ABSTRACT**

**Introduction:** Lymphedema is exempted, only a few studies have dealt with the late adverse effects in melanoma patients who have undergone axillary therapeutic lymph node dissection (ATLND) for the clinical nodal disease. We evaluated the data on late arm/shoulder problems (ASPs) reported by the patients and daily life impairment after ATLND and identified the risk factors.

**Material and methods:** Between 2008 and 2014, 82 patients underwent full en bloc Level I-III ATLND. After a median of 56 months (range 34–104), 76 patients (compliance: 93%) rated their ASPs and daily life dysfunction in a questionnaire, leading to the calculation of individual a Symptom/Problem Summary Score and a Function Summary Score. Multivariate analyses identified risk factors.

**Results:** Two groups of patients were identified. Group 1: no or mild ASPs, $n = 56$ (74%). Group 2: at least one moderate, severe and very severe ASP, $n = 20$ (26%). Overall, lymphedema, numbness and restricted arm movements represented the most frequent ASPs. Based on the distribution of the summary scores, about 60% of the patients reported no or only mild symptoms/problems and no or mild dysfunction. More than mild impairment of daily life was reported by five patients. On multivariate analyses, increasing tumor size and decreasing age were identified as risk factors.

**Conclusion:** Our sample shows that ATLND in melanoma patients with the clinically detectable disease can be performed without a major risk of late ASPs and impaired daily life. Increasing tumor size and decreasing age at the surgery are risk factors for developing ASP-related dysfunction.

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## Introduction

Worldwide, the incidence of melanoma has increased over the last decades [1]. The incidence increases with age and affects mostly elderly men. The regional nodal status is considered a more powerful survival predictor than primary tumor features.

Any lymph node surgery can induce early or late post-operative problems in patients with clinically evident regional node metastases. Late side effects after therapeutic lymph node dissection (TLND) refer to symptoms that are absent or subclinical at the end of the primary treatment but become manifest later.

Late ASPs are important when evaluating the full beneficial effect of cancer treatment [2,3]. An interval of at least 24 months after surgery for non-irradiated patients and 3.9 years for irradiated patients has been recommended before evaluating late ASPs after breast cancer surgery [4,5]. Nesvold et al. [6] indicated that self-rated late ASPs essentially remain unchanged over time (four to seven years post-operative).

In most studies, lymphedema has been the focus of interest, but experience from breast cancer survivors emphasize that pain and restricted movement of the shoulder are more common than lymphedema and are significantly associated with disability [7].

Several authors have described a complication rate for TLND ranging from 37 to 53% in melanoma, mainly with focus on infection, seroma and arm swelling, and with higher rates after inguinal surgery compared to axillary surgery [8–12]. After axillary therapeutic lymph node dissection (ATLND), an increasing body mass index (BMI) and the quantity of removed metastatic lymph nodes are considered to be risk factors for the development of ASPs, lymphedema in particular [13–15]. There is relatively little data describing late side effects such as pain in arm/shoulder and restricted arm/shoulder mobility, assessed by melanoma patients themselves. Starritt et al. [16] reported that 31% of the patients felt that their ‘ability to perform daily activities’ had been impaired after axillary dissection, but the perception of the functional deficit did not correlate well with the actual lymphedema.

## Aim of the study

The aim of this retrospective study was to evaluate data reported by the patients themselves regarding late ASPs after ATLND in melanoma patients with clinical nodal disease, describing their impact on daily life and to identify possible risk factors of late ASPs.

## Material and methods

This survey took place in 2017. Patients treated for clinical stages III and IV melanoma were identified from a prospective database which registered all melanoma patients who underwent ATLND at

**CONTACT** Hans P. Gullestad hpg@ous-hf.no Division of Oncoplastic Surgery, The Norwegian Radium Hospital, Oslo University Hospital, Oslo, Norway

the plastic surgery unit at The Norwegian Radium Hospital, Oslo University Hospital, between 2009 and 2014.

All patients fulfilled the following inclusion criteria:

1. Stage III or stage IV disease with lymphadenectomy of the axilla
2. >24 months from ATLND to survey
3. No other oncological treatment for melanoma prior to surgery (radiotherapy, cytotoxic agent, immunotherapy)
4. No other malignant diagnosis
5. No age restriction
6. Clinically detectable nodal disease verified by fine needle aspiration cytology (79%), biopsy (8%), node picking (12%) or previous incomplete nodal dissection (1%).
7. Surgery: All patients underwent full en bloc axillary dissection (levels I–III). This involved the complete clearance of the axillary content up to the apex of the axilla defined by the musculus subclavius tendon. The pectoral minor muscle, which is embraced by the clavio-pectoral fascia, was detached from the coracoid process and divided inferiorly at its attachment to the chest wall and removed allowing en bloc excision of level III nodes medial to the superior part of the pectoral minor muscle. The intercostal-brachial nerve was routinely sacrificed to achieve radicality, while the thoracodorsal- and long thoracic nerves were preserved [17]. When a tumor was close to or affecting the nerves, radicality prevailed.
8. Physiotherapy: All patients followed the same physiotherapy regime, not only to prevent arm swelling/lymphedema, but also to avoid restricted arm/shoulder movement and chronic pain as much as possible [18]. All the patients received individual pre-operative information/counselling as well as post-operative mobilization of arm/shoulder by a trained physiotherapist. The arm was kept in a sling from the first post-operative day. Sagittal movements were started on the second post-operative day. No movement restrictions were imposed after the drain(s) was removed, and the patients were encouraged to exercise/motion daily. Pressure garments were not used routinely. Post-hospital physiotherapy by a local physiotherapist was recommended on an individual basis if needed. Any later physiotherapy, either requested by the patients themselves or recommended by the physiotherapist was reported in the survey. Patients assessed for lymphedema were objectively measured with volumetric calculations based on circumferential assessments as this is more practical and less time consuming than the 'water displacement technique'.

## Measures

1. Demographical- and treatment characteristics for each patient were extracted from the hospital's melanoma database. The quantity of removed metastatic lymph nodes was provided by the pathologist's report. The quantity of nodes from previous node picking and prior incomplete nodal dissections were included in the final count. In large tumor masses, where the pathologist could not clearly distinguish between one solid tumor and several melted nodes, the entire tumor size was recorded (Table 1a).
2. Late effects: The questionnaire was based on Kwan's arm problem scale (KAPS) [19]. KAPS was originally designed for breast cancer survivors to evaluate persistent ASPs based on the patient's evaluation. The reliability of the Norwegian version of KAPS has been documented by Nesvold et al. [20]. KAPS consists of a symptom/problem *subscale* with eight items Q1–Q8, rating arm/shoulder function, pain, stiffness and swelling, and a subscale affecting specific functions activities of daily life (ADL). Three items (Q9–Q11) are relevant for both genders, while Q12–Q13 explore functions most relevant for women (Table 1). All 13 items are rated on a five point Likert scale from 1 (no symptoms/problems or same as before) to 5 (very severe symptoms/problems or unable to perform).

Table 1. Summary of KWAN's questionnaire.

| | |
|---|---|
| (a) Symptoms and problems | |
| Q1 | How swollen is your arm? |
| Q2 | How much pain do you have in your arm? |
| Q3 | How much pain do you have in your shoulder? |
| Q4 | How stiff is your arm? |
| Q5 | How stiff is your shoulder? |
| Q6 | How well can you use your arm? |
| Q7 | How numb is your arm? |
| Q8 | How well can you move your arm? |
| (b) Specific functions of daily life | |
| Q9 | How well can you brush hair with the arm on the side of surgery? |
| Q10 | How well can you pull sweater over head? |
| Q11 | How well can you reach over head? |
| (c) Specific functions (females only) | |
| Q12 | How well can you fasten bra? |
| Q13 | How well can you do up back zipper? |

Based on the answers concerning Q1–Q8, we identified two groups: Group 1 with a maximum Likert 2 rating (no or mild symptoms, and Group 2 with at least one rating comparable to moderate, severe or very severe problems/dysfunctions.

Following accepted strategies for Quality of life research [21], a Symptom/Problem Summary Score (Q1–Q8) and a Function Summary Score (Q9–Q11) were calculated for each patient, (not considering Q12–Q13 due to gender restriction). Rising Symptom/Problem Summary Scores on a final 0–100 scale reflect increasing patient complaints. Increasing values of the Function Summary Score indicate improving function.

## Statistics

Median and range were calculated from continuous variables with the Mann–Whitney *U* test assessing inter-group differences. Differences between the categorical variables were evaluated by the Chi-square test. Multivariate logistic regression analysis explored the associations between relevant variables and respectively the symptom/problem summary score and the function summary score. The *p*-value was set as $< 0{,}05$ using the IBM SPSS version for PC (IBM Corporation, Armonk, New York, NY).

## Ethics

The study was approved by the Regional Ethical Committee of the South-Eastern Health Region of Norway (REC 2016/1672).

## Results

Of 82 invited patients, 76 returned a completed questionnaire (females $n = 20$, males $n = 56$, response rate = 93%), two of them presenting with Stage IV and 74 of them diagnosed with Stage III. The non-responding patients were similar to responders as to age, BMI, tumor size, number of affected lymph nodes and duration of surgery (data not shown). No patients had post-operative radiotherapy during the follow-up period.

No statistically significant difference emerged between the demographical and medical variables from Group 1 (56 patients)

Table 2. Characteristics.

| | Group 1 ($n = 56$) | Group 2 ($n = 20$) | Univariate analysis $p < .05$ |
|---|---|---|---|
| Gender | | | |
| Male | 41 | 15 | .88 |
| Female | 15 | 5 | |
| Age at surgery[a,b] | 64 (38–83) | 57 (31–83) | .067 |
| BMI[a] | 26 (18–42) | 28 (19–38) | .26 |
| Duration of surgery[a,c] | 105 (70–240) | 116 (69–210) | .339 |
| Follow-up[a,d] | 56 (34–104) | 57 (35–98) | .728 |
| Tumor size[a,e] | 40 (13–105) | 50 (15–130) | .079 |
| No of affected nodes | | | |
| ≤2 | 41 | 16 | .55 |
| >2 | 15 | 4 | |

[a] Median and range.
[b] Years.
[c] Min.
[d] Months.
[e] Millimeters.

and those from Group 2 (20 patients) (Table 2) though high age and increased tumor size tended to be more prevalent in Group 2 than in Group 1 ($p < .1$). Half of the patients from Group 1 ($n = 28$), and 16 out of 20 patients from Group 2 had physiotherapy during follow-up (Table 1b). In Group 2, pressure garments (14/20) and pulsator (3/20) were used for shorter or longer periods (Table 3).

Overall, lymphedema, numbness and restricted arm movements represented the most frequent ASPs in about one of four patients, with at least moderate rating in Group 2 (data not shown). More than mild impairment of daily life was reported by five patients. Four of the 20 evaluable women reported moderate ($n = 1$), severe ($n = 2$) or very severe ($n = 1$) dysfunctions in activities to be typical in women's daily life.

Highly significant inter-group differences emerged in the bivariate analysis of the summary scores (Table 4). Independent of the group's affiliation, at least 60% of the values were within the most favorable quartiles (symptom/problem score < 25; function score >75) (Figure 1). In the multivariate regression analysis including all variables from Table 2, decreasing age at surgery ($p = .02$) and increasing tumor size ($p = .07$) were associated with rising Symptom/Problem Summary Scores. Similar associations emerged for the Function Summary Scores (tumor size: $p < .01$; age at surgery: $p = .04$).

## Discussion

Almost 5 years (median = 56 months) after ATLND for clinically evident nodal metastases in 76 patients with malignant melanoma, followed by specialized physiotherapy, two of three patients reported no or only mild ASPs and reduced arm/shoulder function. Lymphedema, pain and reduced mobility represented the most frequently described complaints. Only 5 patients (7%) described moderate, severe or very severe ASP-related impairment. Decreasing age and increasing size of the lymph node metastases were identified as risk factors.

The 5-year survival for patients undergoing ATLND for macroscopic nodal disease in melanoma ranges between 30 and 50% (in our unit 43%), depending mostly on nodal tumor burden [22]. Some patients may, however, survive for many years; in our sample, overall survival rates of 95 and 80% after 5 and 10 years, respectively, have been confirmed (detailed data not shown). It is therefore essential that the burden of late post-ATLND effects as expressed by the prevalence and severity is as low as possible.

In the literature, the severity of late effects after ATLND for melanoma is not always described in detail, and the timing of the reported complications like 'early' or 'late' makes interpretation of results difficult. However, in Moody et al.'s systematic review and other authors' as well, the prevalence of post-ATLND morbidity ranged from 37 to 53%, mainly related to post-operative problems and lymphedema [8–12]. Though inter-study variability makes direct comparison impossible the published figures indicate essentially more ASP-related complaints than reflected t by the summary scores in our survey.

Table 3. Physiotherapy in post-hospital period.

| | Group 1 ($n = 56$) | Group 2 ($n = 20$) |
|---|---|---|
| No treatment | 28 (50%) | 4 (20%) |
| Arm swelling | 10 (18%) | 6 (30%) |
| Pain/reduced mobility | 12 (21%) | 6 (30%) |
| Arm swelling and pain/reduced mobility | 6 (11%) | 4 (20%) |

Table 4. Problem/Symptom Summary Scores and Function Summary Scores stratified by the group.

| | Group 1, $n = 56$ | Group 2, $n = 20$ | Total, $n = 76$ |
|---|---|---|---|
| Symptoms/problems[a,b] | 3 (0 − 22) | 25 (9 − 75) | 8 (0 − 75) |
| Function[a,b] | 100 (83–100) | 83 (42–100) | 100 (42–100) |

[a] Median, [b] Range; $p < .01$ for (Chi-square) both intergroup comparisons.

After axillary surgery in breast cancer patients, the BMI and the quantity of metastatic lymph nodes are considered risk factors for developing late ASP's, lymphedema in particular. Our survey did not confirm these findings in melanoma patients, probably due to the low number of patients.

### *Lymphedema*

The patients experienced lymphedema as different degrees of arm swelling. Starritt et al. define lymphedema as an increase of arm volume greater than 16% compared to the opposite arm [16]. In our survey, three patients reported very severe problems (Likert 5 on arm swelling) and underwent objective assessment for lymphedema. Each of them fulfilled Starritt's criterion for lymphedema. However, as many as 67 of 76 patients (88%) reported no- or minimal problems with arm swelling.

### *Numbness*

Silberman et al. [23] reported some degree of arm numbness in 26% of their patients after 1-year follow-up. In Silva Soares et al.'s [24] study, 53% complained of paresthesia affecting the inner region of the affected arm at 35 months. In contrast, 88% of our patients had no or minimal problems with numbness after a

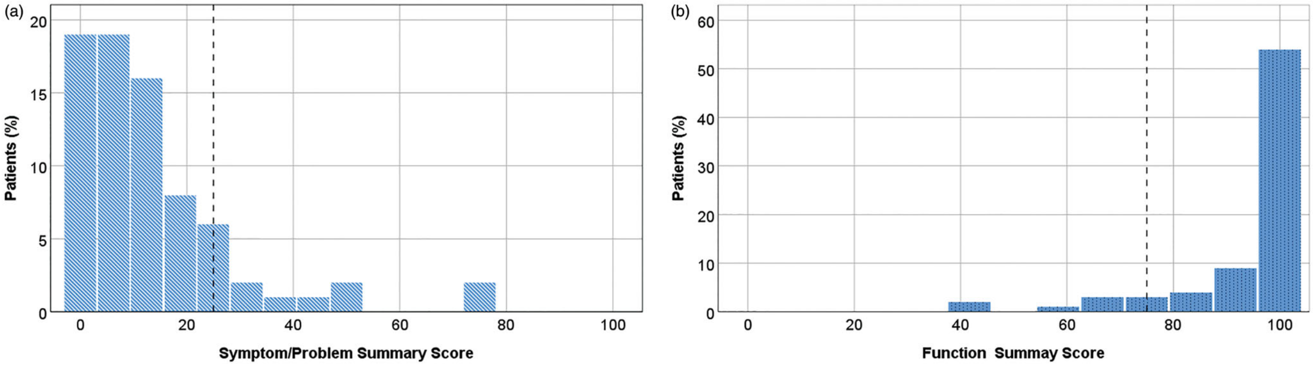

Figure 1. Distribution of Symptom/Problem Summary Scores (a) and Function Summary Scores (b) in 76 patients after therapeutic axillary lymph node dissection for malignant melanoma. The vertical dotted line visualizes the cut-off for the most favorable quartile.

median observation time of close to 5 years (56 months). This percentage is surprisingly low taking into consideration that the inter-costal brachial nerve is sacrificed during the operation. Re-innervation from the periphery over long time represents a probable explanation of the above inter-study variations.

### *Pain/mobility*

Pain and restricted mobility of the arm/shoulder represent serious ASPs in long-term breast cancer survivors [25]. Silva Soares et al. [24] reported limited arm abduction in 24% of the breast cancer survivors and noticed sporadic pain in the arm in 28%. Only three of our patients described severe pain problems localized to arm/shoulder. The numbers are too small to draw definitive conclusions.

### *Physiotherapy*

Our study indicates that at least half of the patients after ATLND of melanoma will benefit from physiotherapy in order to reduce arm swelling and pain as well as to increase their mobility. The median age of the cohort is 62 years (31–83), age may thus play a role. The availability of specialized physiotherapy is probably one of the factors which explain our low number of patients with moderate, severe or very severe ASPs and the limited impairment of daily life in our cohort (7%).

### *Strength and limitation*

The strength of our study is the high response rate (93%) of post-ATLND patients who all have undergone a standard en bloc resection at levels I–III, followed by standardized post-operative physiotherapy. All patients were operated at the same plastic surgical unit at the Norwegian Radium Hospital, referral center for metastasizing melanoma. Median observation time is close to 5 years (56 month). The cross-sectional design and the relatively low number of patients represent the main limitations. The referral practice represents a certain selection bias that cannot be excluded. Further, the KAPS questionnaire was originally designed for breast cancer survivors, whereas we used this instrument in male and female melanoma patients without preceding psychometric testing.

## Conclusion

According to the results based on the survey completed by the patients, the risk of severe ASPs and impairment of daily life after ATLND with subsequent specialized physiotherapy, are small/mild in patients with melanoma with clinical nodal disease. Increasing tumor size and decreasing age at surgery are risk factors for developing ASP-related dysfunctions.

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## Disclosure statement

The authors declare no competing interests as defined by the journal or other interests that might be perceived to influence the results and discussion in this paper.

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