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ORIGINAL ARTICLE – MELANOMA

Negative Sentinel Lymph Node Biopsy in Patients with Melanoma: The Patient's Perspective

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ABSTRACT

Background. The majority of patients undergoing sentinel lymph node biopsy (SLNB) for melanoma will have a negative SLN. The long-term sequelae of a negative result are important when discussing this staging investigation with patients. The objective of this study was to assess rates of lymphoedema and quality of life for these patients.

Methods. A prospective, cross-sectional study was performed on patients under routine follow-up with a history of melanoma, who had undergone sentinel lymph node biopsy where no metastasis was found (N0) at a high-volume melanoma centre. Relevant limbs were measured to assess for lymphoedema and patients completed the FACT-M quality of life instrument and a study specific questionnaire.

Results. A total of 102 patients were recruited. Wound complications were observed in 25% and lymphoedema in 2% of patients. Physical and functional well-being scores were lowest in patients seen within 3 months of their SLNB. Functional well-being and quality of life improved over the 2 years following the procedure.

Conclusions. SLNB has low complication rates. The procedure is associated with a short-term impact on patient quality of life and well-being. The vast majority of patients are pleased with the outcomes of this procedure and the information that it provides.

Sentinel lymph node biopsy (SLNB) is utilised in the management of patients diagnosed with primary melanoma to provide optimal risk stratification. In accordance with the American Joint Committee on Cancer (AJCC) 8th edition, a SLNB is required to provide a pathologic stage for patients with melanoma greater than 1 mm in Breslow thickness. This is vital to facilitate optimal clinical decision making and management.[1,2]

Patients with a positive SLNB are at significantly higher risk of recurrence and in the modern era are eligible for highly effective adjuvant systemic therapy as well as undergoing closer surveillance than patients with a negative result.[3,4] Importantly, the majority of patients who undergo SLNB will have no evidence of disease in the sentinel node (N0), which stratifies the patient to a lower clinical stage and recurrence risk.[5,6] For these patients, the benefit of the test is purely the prognostic information it carries. This benefit needs to be weighed against the associated morbidity of SLNB, which although lower than that of lymph node dissection is still of importance.[7] To estimate the value of a test, the risks need to be clearly quantified.

Results from large studies have identified the complications of SLNB to include seroma, infection, and pain, which occur in 10–16% of patients.[8–10] Other potential morbidities include lymphedema and sensory complications. A prior study has identified a higher rate of wound

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complications, which were more common in patients with a positive SLNB compared with those with a negative SLNB.[9]

A prospective study of melanoma patients who had a negative SLNB was performed to assess rates of lymphoedema and quality of life at a single point in time in a high-volume melanoma centre.

METHODS

Data

Consecutive patients attending the melanoma outpatient clinic at Peter MacCallum Cancer Centre, Australia, were screened between 8 December, 2016 and 13 September, 2017. Patients with a prior SLNB, where the lymph node was free of disease (negative SLNB), were identified. Eligible patients were seen at a single time point in a private room in the clinic.

Patients

This was a prospective, cross-sectional study. Patients were eligible if they were diagnosed with their first melanoma, underwent a sentinel lymph node biopsy, the sentinel lymph node biopsy results were negative for melanoma, the patient was aware of these results, able to read and speak English, provided consent, and was at least 18 years of age.

Patients who had previous lymph node surgery in the lymph node basin, separate to this melanoma were excluded. Of note, patients who underwent SLNB in the neck did not undergo lymphoedema measurements.

Lymphoedema measurements were performed by measuring the circumference of the unaffected limb and the limb from which the sentinel nodes were removed. The measurements were made 10 cm proximal and 10 cm distal to the medial epicondyle, 10 cm proximal and 10 cm distal to the medial condyle of the tibia, and 10 cm proximal to the medial malleolus. This was the same technique used to measure lymphoedema in the Multicentre Selective Lymphadenectomy Trial II.[11]

Patient surveys were completed in the clinic or in their own time. The surveys consisted of the Functional Assessment of Cancer Therapy-Melanoma (FACT-M), a study specific five-point Likert scale to determine the patient's opinion on their surgical experience, and a questionnaire to determine demographic details of the patient. FACT-M has good validity and reliability (Cronbach's alpha and test–retest correlations $r > 0.80$) and consists of 51 questions on quality of life, including a module specifically for patients with a melanoma diagnosis.[12] Data regarding acute surgical complications were extracted retrospectively from the medical record.

Statistical Analysis

Data analyses were conducted using the SAS.[13] Patient characteristics and factors of interest associated with an increased risk of lymphoedema were analysed using descriptive statistics. To assess whether factors of interest were associated with quality of life outcomes, robust regression with Huber M-estimation were used. The multivariable model included covariates that were significant ($p < 0.10$) in univariable model. Missing values were not imputed. All applicable statistical tests were two-sided and were performed using a 5% significance level.

RESULTS

A total of 105 patients were invited to participate, and 102 patients were recruited. Each patient was seen at one time point following their procedure. Two patients were not able to read or write English, and one patient did not agree to participate. Nineteen were seen within 3 months, 13 between 4 and 6 months, 21 between 7 and 12 months, 24 between 13 and 24 months, and 25 patients more than 24 months after their procedure. Forty-five percent were female, with a median age at enrolment of 60 years. The median BMI at the time of surgery was 27.9 kg/m^2 (Table 1).

Melanomas were located on the upper limb (30%), lower limb (35%), trunk (22%), and head and neck region (13%) (Table 1). Seventy-five percent underwent primary closure, of whom 20% had a local flap and 6% required a skin graft.

The axilla (44%) and groin (36%) were the main sentinel node basins involved, with a small number in the neck (17%), supracondylar region (1%), and popliteal fossa (1%) (Table 2). Eighty-seven percent had a single nodal basin sampled.

Limb measurements yielded a mean (range) discrepancy in upper limb circumference of 0.71 (range 0–2.3) cm and lower limb circumference of 0.91 (range 0–9.5) cm. Two patients (2%) had lymphoedema as defined by a greater than 3 cm difference in limb circumference. Patient 1 had a discrepancy of 9.5 cm, was overweight (body mass index [BMI] 25 kg/m^2), had a primary wound closure, underwent SLNB in the inguinal region, and had lymphoedema measurements measured between 7 and 12 months. Patient 2 had a discrepancy of 5.5 cm, was obese (BMI 43.4 kg/m^2), had a local flap closure, underwent SLNB in the

TABLE 1 Patient demographics and primary tumour characteristics

	Total (N = 102)
Sex	
Female	46 (45%)
Male	56 (55%)
Age at enrolment (yr)	
Median [Range]	60 [29–81]
BMI at surgery (kg/m^2)	
Median [Range]	26.9 [15.2–49.2]
Melanoma site	
Upper limb	31 (30%)
Lower limb	36 (35%)
Trunk	22 (22%)
Head and neck	13 (13%)
Ulceration	
No	81 (83%)
Yes	17 (17%)
Missing	4
Mitotic count	
0	19 (21%)
$\geq$ 1	73 (79%)
Missing	10
Breslow thickness (mm)	
0.1 < 1.0	23 (23%)
1.1–2.0	54 (53%)
2.1–4.0	17 (17%)
> 4.0	7 (7%)
Missing	1

inguinal region, and had lymphoedema measurements measured between 13 and 24 months. Predictors of lymphedema were not investigated due to the low event rate.

Postoperative wound complications were seen in 25% of patients; however, only 2% of patients had surgical complications greater than Clavien Grade II. Acute wound complications included graft failure, seroma or haematoma requiring drainage, wound dehiscence, wound infection, deep vein thrombus, and accessory nerve palsy. One patient had complete heart block that required emergency coronary bypass surgery.

Patients who were seen in clinic within 3 months of undergoing SLNB reported lower physical and functional well-being scores compared with patients who were seen later than 3 months (Fig. 1a, b). Physical well-being scores were similar across all other time points, whereas functional well-being scores showed a trend toward improvement over the 2 years following SLNB. Male patients reported higher physical well-being and FACT-M quality of life (QoL) scores than female patients (mean difference [95% CI]: 0.75 [0.03, 1.47], 6.76, [1.00, 12.51], physical and FACT-M QoL, respectively).

As part of the patient survey, 89% agreed or strongly agreed that "If they were diagnosed with the same melanoma again, they would choose to undergo sentinel lymph node biopsy"; with only 3% of patients disagreeing with the statement. Patients who disagreed with the statement did not have surgical complications or lymphoedema.

Furthermore, 96% agreed or strongly agreed that "The time after their surgery was made less stressful by a negative sentinel lymph node biopsy"; 4% neither agreed nor disagreed with this statement.

DISCUSSION

In the MSLT-I trial, 16% of patients with an intermediate thickness melanoma had a positive sentinel lymph node biopsy. For the remainder of the patients, the clinical benefit was limited to the reassurance offered by optimal risk assessment. It therefore is important to consider the impact this procedure will have on patients' quality of life and physical state. Results from the current study showed that complication rates were low and that patients were generally pleased with the process.

TABLE 2 Sentinel lymph node characteristics and lymphoedema rates

	Time since biopsy (mo)					
	Total (N = 102 patients, 117 basins)	0–3 (N = 19, 25 basins)	4–6 (N = 13, 14 basins)	7–12 (N = 21, 24 basins)	13–24 (N = 24, 26 basins)	> 24 (N = 25, 28 basins)
Sentinel lymph node biopsy site						
Neck	20 (17%)	5 (20%)	3 (21%)	2 (8%)	3 (12%)	7 (25%)
Axilla	51 (44%)	10 (40%)	6 (43%)	11 (46%)	13 (50%)	11 (39%)
Groin	42 (36%)	9 (36%)	5 (36%)	10 (42%)	9 (35%)	9 (32%)
Other	4 (3%)	1 (4%)	0 (0%)	1 (4%)	1 (4%)	1 (4%)
Lymphoedema						
No	100 (98%)	19 (100%)	13 (100%)	20 (95%)	23 (96%)	25 (100%)
Yes	2 (2%)	0 (0%)	0 (0%)	1 (5%)	1 (4%)	0 (0%)

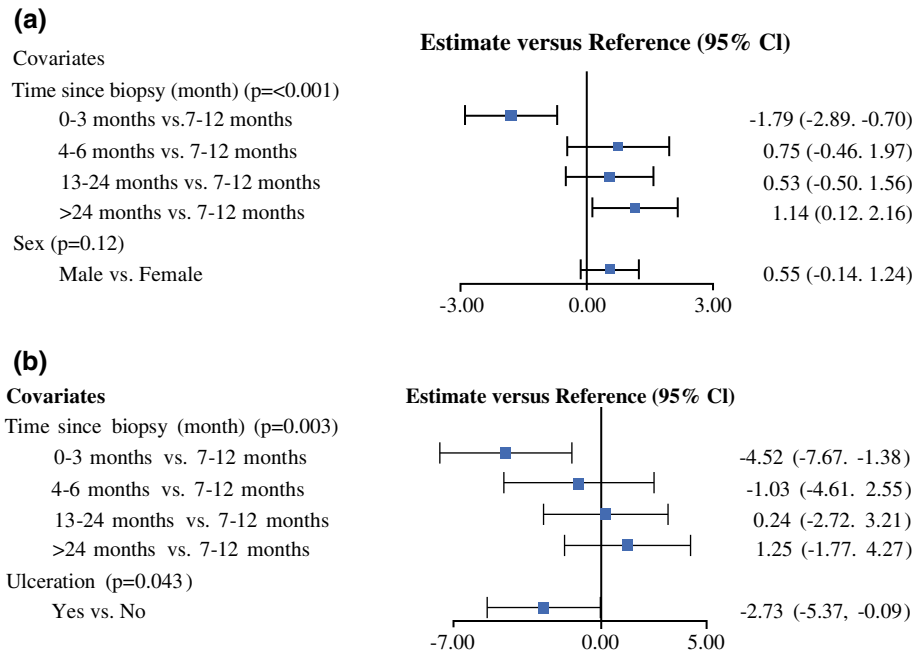

FIG. 1 **a** Factors associated with physical well-being. **b** Factors associated with functional well-being

A sentinel lymph node biopsy is not a complication-free procedure. Health economists from National Health and Medical Research Council in Sydney, Australia, found that 2% of patients had lymphoedema following this procedure.[14] This study has a similar rate of lymphoedema. There was a trend to a higher rate of lymphoedema in SLNB in the inguinal region. The very low event rate for lymphoedema in the cohort precluded an analysis of patient predictive factors for the development of this adverse outcome.

This current study found an acute wound complication rate of 25%. Ninety-two percent of these complications were Clavien Grade I or II. This is consistent with prior studies with complication rates ranging from 10.1% in the MSLT-1 trial to 31%.[10,15] This variation may be due to inconsistencies in documenting postoperative complications, as well as surgical techniques varying between institutions. Ultimately, however, the rates of complications following a SLNB are low and most complications are low-grade and self-limiting.

Prior studies have offered conflicting results with regards to quality of life. In a study of 221 patients, Thomson et al.[16] found that 34% of patients experienced pain postoperatively and that the pain did not correlate with time since surgery. By contrast and similar to the findings of the current analysis, a study involving 431 patients at the Herlev and Gentofte Hospital in Copenhagen found that health related quality of life scores improved with increased time since surgery and were not associated with the limb affected (upper or lower limb), clinical stage of lymphoedema, duration of lymphoedema or type of surgery (SLNB or CLND), and quality of life.[17] Our study similarly found a lack of evidence to show an association between potential risk factors and postoperative quality of life. An association was identified between primary tumour ulceration and lower postoperative functional well-being scores (mean difference [95% confidence interval (CI): − 2.72 [− 5.25, − 0.18], $p = 0.036$). The reason for this association is unclear given the failure to demonstrate an association with interventions that may have been driven

TABLE 3 FACT-M quality of life scores in comparison to a normative dataset[19]

	Time since biopsy (mo)					Total	Normative dataset
	0–3	4–6	7–12	13–24	> 24		
Physical well-being score (mean)	23.1	25.6	25.1	26	27.4	25.6	24.9
Emotional well-being score (mean)	20.3	19.5	18.6	19.8	18.9	19.4	19.5
Functional well-being score (mean)	18.9	22.7	23.1	23.2	25.3	22.8	21.4
Social well-being score (mean)	24.1	22.3	23.5	22.4	24.1	23.3	20.2

A higher score indicates a better quality of life. The score ranges are as follows: physical well-being 0–28, emotional well-being 0–24, functional well-being 0–28, and social well-being 0–28

by the ulcerated melanoma, e.g., wider margin or complex wound closure. Further studies with larger patient populations may help to clarify whether the presence of ulceration impacts adversely on patient QoL and the reasons for this.

Females diagnosed with cancer have been shown to be more susceptible to psychological distress than males.[18] Consistent with these findings, males (56/102) in the current study reported higher physical well-being and total QoL scores compared to females. Knowledge of baseline level of QoL would have been helpful to better understand this trend.

An inherent limitation of this study is the absence of a comparator group of patients who did not undergo a SLNB. The reason for this was that a control group would be associated with significant institutional selection bias, because they tend to be older with more comorbidities. Furthermore, another limitation was the inability to collect preoperative QoL data and longitudinal follow-up to assess changes in patients QoL over multiple time points. Baseline QoL measurements for patients were unknown, which somewhat limits the ability to clearly identify the contribution of the procedure to QoL. However, using a normative dataset for comparison, our data suggest return of patient QoL to a similar level to the broader population (Table 3).[19]

CONCLUSIONS

Sentinel lymph node biopsy is a procedure that is well-accepted by patients. There is some low-level morbidity and quality of life impairment that is generally self-limiting and improves with time. This is important information to share with patients preoperatively and throughout the initial recovery process to increase understanding and relieve anxiety.

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