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Clinical importance and surgical management of sentinel lymph nodes in the popliteal fossa of melanoma patients

Amanda A.G. Nijhuis [a, b, *], Ivan D. de A.O. Santos Filho [c], Roger F. Uren [d, e], John F. Thompson [a, e, f], Omgo E. Nieweg [a, e, f]

[a] Melanoma Institute Australia, The University of Sydney, Sydney, Australia
[b] University of Utrecht, Utrecht, the Netherlands
[c] Skin Cancer Department, A.C. Camargo Cancer Center, São Paulo, Brazil
[d] Alfred Nuclear Medicine and Ultrasound, Sydney, Australia
[e] Faculty of Medicine and Health, The University of Sydney, Sydney, Australia
[f] Department of Melanoma and Surgical Oncology, Royal Prince Alfred Hospital, Sydney, Australia

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ABSTRACT

Background and purpose: Patients with a primary melanoma below the knee may have lymphatic drainage to a sentinel node (SN) in the popliteal fossa. The purpose of this study was to analyze lymphatic drainage to this site and to describe clinical features and surgical management of SNs in the popliteal fossa.

Methods: Patients with a primary melanoma below the knee presenting to Melanoma Institute Australia between 1992 and 2013 were analyzed. Those found to have a popliteal SN were evaluated. Data on imaging, SN biopsy, completion lymph node dissection, morbidity and follow-up were analyzed.

Results: Lymphoscintigraphy showed drainage to a popliteal SN in 176 of 3902 cases of melanoma below the knee (4.5%). In 96 of these patients (55%) a popliteal SN biopsy was attempted. The procedure failed to identify the node(s) in seventeen of them (18%). Thirteen of the 79 patients (17%) had a positive popliteal SN and in eight (10%) this was the only positive node. The tumor stage of ten patients (13%) changed as a result of the popliteal node biopsy. A positive popliteal node was associated with an increased risk of recurrence and diminished overall survival. Popliteal SN biopsy did not improve regional control or survival.

Conclusion: Melanomas below the knee infrequently drain to lymph nodes in the popliteal fossa. Although popliteal SN biopsy can be challenging, it is worthwhile, providing improved staging and guiding subsequent management.

Introduction

Sentinel node (SN) tumor status is the most important prognostic factor in patients with a clinically localized melanoma [1,2]. Lymphatic drainage from melanomas on the lower limb typically occurs to groin lymph nodes but melanomas below the knee (on the leg or foot) can also drain to nodes in the popliteal fossa. The popliteal fossa is one of the minor nodal regions that contain just a few lymph nodes. Other minor regions are the epitrochlear fossa and the triangular intermuscular space on the back [3,4]. In some patients, a SN in a minor node field is the only positive lymph node, and failure to harvest it can lead to understaging and undertreatment.

Knowledge of the significance of SNs in the popliteal fossa is limited, as popliteal SN biopsy is performed infrequently. Popliteal drainage has traditionally been associated with melanomas on the heel and lateral margin of the foot but we now know that lymphatic drainage to the popliteal fossa can also occur if the lesion is from other sites on the distal lower limb [5]. Lymphatic drainage to popliteal nodes has been described in 1%–11% of patients with a primary melanoma below the knee [6–20]. These SNs are typically

Abbreviations: Sentinel node, SN.

* Corresponding author. Melanoma Institute Australia, 40 Rocklands Road, North Sydney, NSW, 2065, Australia.
E-mail address: amanda.nijhuis@melanoma.org.au (A.A.G. Nijhuis).

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located below the deep fascia, anterior to the tibial and common fibular nerves and sometimes situated anterior to the popliteal vessels [21]. Performing a SN biopsy in this area can be technically challenging and information on the retrieval rate is sparse. Reported popliteal SN positivity rates vary from 11% to 53%, with only 27 cases included in the largest previous study [6,8,9,13,17–19,22].

Considering the valuable staging and prognostic information provided by SN biopsy and the survival benefit from SN biopsy reported in SN-positive patients with an intermediate Breslow thickness tumor, knowledge of popliteal SN status is likely to have clinical implications [2,23]. The purpose of this study was to describe the incidence, surgical management and clinical relevance of popliteal SNs in a large series of patients with primary melanomas located below the knee.

Methods

Prospectively collected information on patients with a melanoma below the knee treated between 1992 and 2013 was retrieved from the research database of Melanoma Institute Australia. All patients signed an informed consent form for entry of their data into the Institute's database and approval of the institutional research committee was obtained prior to commencing the study.

SN biopsy was recommended in patients with an intermediate thickness melanoma (T2 or T3) and discussed in patients with thin (T1b) or thick (T4) melanomas. Lymphoscintigrams were routinely obtained with technetium-99 m antimony trisulfide colloid using dynamic and static imaging. A SN was defined as a lymph node receiving direct lymphatic drainage from the melanoma site [24]. The AJCC-UICC 8th edition staging classification was used.

Patients with palpable popliteal lymph nodes or who had lymphoscintigraphy for recurrent melanoma were excluded. Patients with lymphatic drainage to a popliteal SN on their lymphoscintigram were identified. Patient files were reviewed to collect data on their general characteristics, preoperative imaging, SN biopsy, completion node dissection, morbidity and survival outcome. Patients with a follow-up of less than one month were not included in the follow-up analyses.

Data were analyzed using IBM SPSS Statistics 24 and R [25,26]. Descriptive statistics were used to evaluate outcomes. Normality of distribution was assessed with the Kolmogorov-Smirnov test and the Shapiro Wilk test. Numbers with percentiles, mean values with standard deviation (SD) or medians with interquartile range (IQR) were reported as appropriate. The chi-squared test and Fisher's exact test were used to evaluate recurrence rates. Overall survival curves were produced using the Kaplan Meier method and the survival distribution was tested using the log rank test (Mantel-Cox).

Results

Lymphoscintigraphy and SN biopsy

Between 1992 and 2013, 3820 patients with 3902 primary melanomas below the knee were treated. Lymphoscintigraphy showed drainage to both popliteal and inguinal lymph nodes in 176 cases (4.5%) (Table 1). Exclusive drainage to the popliteal fossa was never seen. The primary tumor location was on the posterior leg in 73 patients (42%), foot in 57 (32%), ankle in 25 (14%), and anterior leg in 21 (12%).

The visualized popliteal SN was not surgically pursued in 80 patients (46%). The reasons were documented in 56 cases (70%). In fifteen (27%), the reason was that the lymphoscintigrams showed a complex drainage pattern with numerous sentinel nodes (often >5) in multiple sites, increasing the anticipated difficulty of the procedure and the associated risk of morbidity. Unfavorable patient characteristics such as advanced age and major comorbidities accounted for fourteen cases (25%). Nine patients (16%) declined SN biopsy, primarily because of fear of lymphedema. Seven patients (13%) participated in the first Multicenter Selective Lymphadenectomy Trial and were randomized to observation without SN biopsy [23]. In six cases (11%), no biopsy was performed because of low risk melanoma features such as a relatively thin primary

Table 1
Patient and tumor characteristics.

Characteristics	Total	No popliteal SN biopsy	Popliteal SN biopsy	Failed biopsy	Missing
Number of patients	176	80	79	17	
Age (SD)	59 (±16)	61 (±18)	58 (±14)	57 (±16)	0
Male	82 (47%)	39 (49%)	36 (46%)	7 (41%)	0
Primary tumor					
Breslow in mm (IQR)	1.8 (1.2–2.8)	1.5 (1.1–2.8)	2.2 (1.5–3.1)	1.4 (1.1–2.3)	1
Ulceration	56 (34%)	21 (27%)	30 (42%)	5 (31%)	12
Mitotic rate per mm^2 (IQR)	3 (1–7)	3 (1–6)	4 (1–8)	5 (1–6)	8
Microsatellite lesions	9 (7.3%)	4 (7.7%)	5 (8.2%)	–	53
In-transit lesions	3 (2.4%)	2 (3.8%)	1 (1.6%)	–	53
Location primary					0
Foot	57 (32%)	27 (34%)	28 (35%)	2 (12%)	
Ankle	25 (14%)	13 (16%)	11 (14%)	1 (6%)	
Posterior leg	73 (42%)	29 (36%)	35 (44%)	9 (53%)	
Anterior leg	21 (12%)	11 (14%)	5 (6%)	5 (29%)	
LN palpable	6 groin 1 ITM*	3 groin	3 groin 1 ITM*	1 groin	0
Successful SN biopsies					0
Popliteal only		–	4	–	
Groin and popliteal		–	75	–	
Groin only		11	–	12	

* In-transit metastasis on shin.
ITM = In-transit metastasis.
SD = standard deviation.
IQR = Interquartile range.
SN = Sentinel node.
LN = Lymph node.

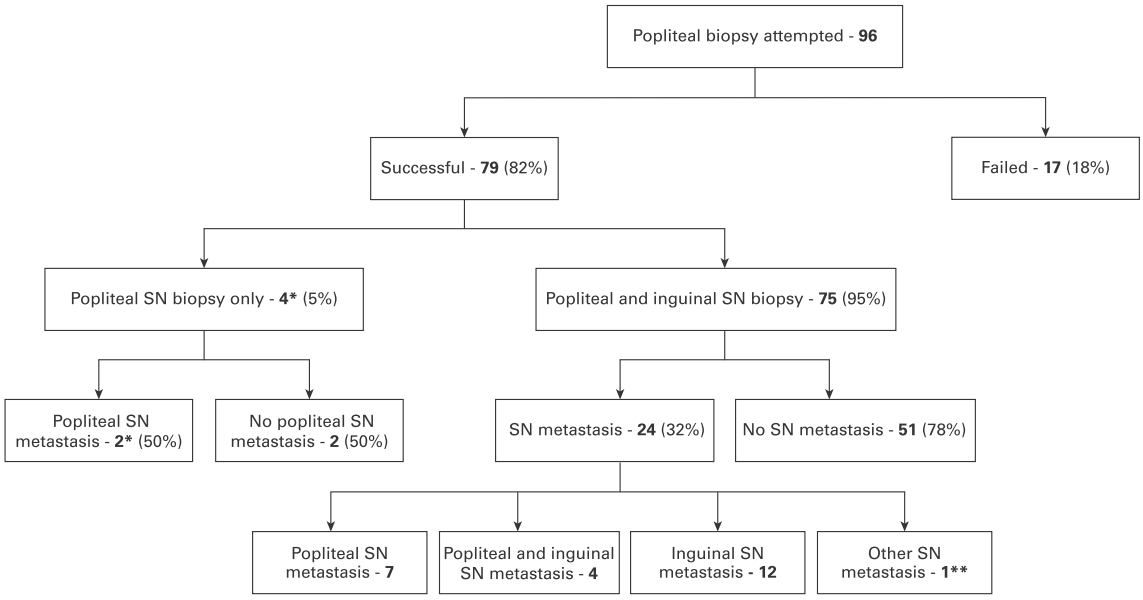

Fig. 1. Flowchart of SN biopsy outcomes. *One patient with palpable groin nodes underwent therapeutic inguinal node dissection at the time of the popliteal SN biopsy. ** One patient had a positive in-transit SN on the anterior leg. SN = sentinel node.

(<1.0 mm Breslow thickness). Other reasons were mentioned in five cases (9%). Eleven of the patients (14%) who did not have a popliteal SN biopsy did undergo a groin SN biopsy, with positive groin nodes in two of them. In three of these eleven patients, there was doubt about the presence of popliteal SNs on review of the lymphoscintigrams; in one other case, the melanoma was thin and the lymphoscintigram showed only faint drainage of radioactive tracer to a popliteal node.

The popliteal fossa was surgically explored in the remaining 96 patients (Fig. 1). No SN was found in twelve of them and the removed specimen did not contain a lymph node in five, resulting in a failure rate of 18%. In two of the latter five patients, the popliteal SNs were described as showing only faint isotope uptake on the lymphoscintigram report.

In four of the 79 patients who had a successful popliteal SN biopsy this was the only nodal region that was explored. In one of these patients the reason was documented: he underwent a concurrent therapeutic ipsilateral inguinal node dissection for palpable disease. The lymphoscintigram was presumably made to determine whether there was popliteal drainage as well, but the exact reason was not clearly documented in the patient's records. Both inguinal and popliteal SN biopsies were performed in 75 patients. The popliteal procedure yielded a median of one SN with a maximum of three nodes and the groin procedure a median of two SNs, with a maximum of six. The popliteal lymph nodes were usually just a few millimeters in size and often contained little of the radiopharmaceutical, with low gamma counts when assessed with the gamma detection probe intra-operatively.

In thirteen of the 79 patients (16%), one or more popliteal SNs contained metastatic melanoma. Four of these patients also had inguinal SN involvement and one had palpable groin disease at presentation (Fig. 1). Thus, in eight patients (10%) the popliteal SN was the only tumor-containing node. The finding of a positive popliteal SN altered the AJCC-UICC tumor stage of ten patients (13%).

Postoperative morbidity from the popliteal SN biopsy was reported in one patient (1.3%), who had a wound infection requiring antibiotic treatment. Twenty-one patients (27%) developed lymphedema (generally mild and transient) after SN biopsy of both the groin and popliteal fossa in all but one case.

Completion lymph node dissection

Sixteen of the 26 patients with a positive SN (61%) underwent completion popliteal and/or inguinal lymph node dissection (see Fig. 2). In the subgroup of patients with a positive popliteal SN, only four of the thirteen patients (31%) underwent completion dissection of the popliteal fossa. No additional lymph nodes were found in two of these popliteal operative specimens. In the other two patients, one and two additional lymph nodes were retrieved, all without disease. Popliteal dissection alone was not associated with morbidity. One patient developed lymphedema after combined popliteal and inguinal node dissection.

Follow-up

Follow-up data were available for 170 patients (median follow-up 54 months) (Table 2). Three patients (3.8%) in whom a SN in the popliteal fossa was not pursued, recurred in this region, and there was recurrence in another three patients (4.0%) in whom popliteal SN biopsy had been performed. In one of the latter three, a SN had been positive. Neither the recurrence rate nor the overall survival rate was significantly different for the patients who did or did not undergo popliteal SN biopsy (chi-squared test $P = 0.52$ and log rank test $P = 0.88$ respectively). There was no popliteal recurrence in the seventeen patients in whom the biopsy had failed. Formal dissection of the entire fossa was performed in one of the six patients with a popliteal recurrence, two simply underwent excision of the identified mass and three received radiotherapy, of whom one also received systemic therapy.

Seventeen of the 66 popliteal SN-negative patients developed a recurrence at any site (27%). Patients with a positive popliteal SN did significantly worse, with nine of the thirteen developing a recurrence (69%, Fisher's exact test $P = 0.007$). Overall survival was also significantly reduced in patients with a positive popliteal SN

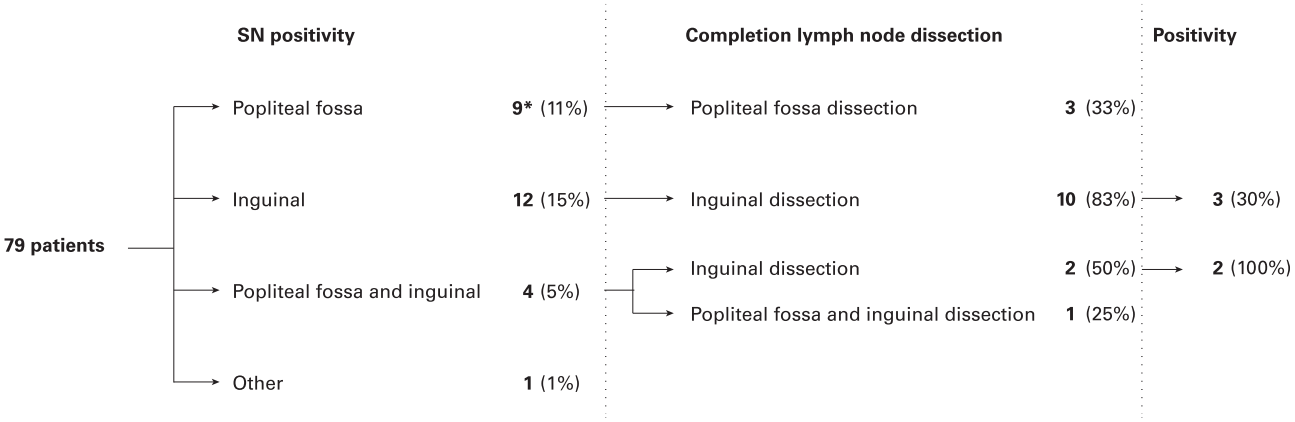

Fig. 2. Completion lymph node dissections with outcomes. *One patient with palpable groin nodes had a therapeutic inguinal lymph node dissection at the time of the popliteal SN biopsy. SN = sentinel node.

Table 2
Follow-up and outcome.

	Total	No popliteal SN biopsy	Popliteal SN biopsy	Failed biopsy
Number of patients with follow-up	170	78	75	17
Follow-up in months (IQR)	54 (27–96)	53 (27–80)	54 (22–101)	59 (44–146)
Recurrence	65 (38%)	31 (40%)	26 (35%)	8 (44%)
First recurrence local recurrence	14	7	4	3
First recurrence in-transit (lower leg)	20	9	6	5
First recurrence regional lymph node (groin)	16	10	6	–
First recurrence systemic	15	5	10	–
Relapse free survival (months, IQR)	23 (10–39)	20 (9–37)	22 (10–30)	49 (16–90)
Popliteal recurrence	6 (3.5%)	3 (3.8%)	3 (4.0%)	–
Groin recurrence	33 (19%)	19 (24%)	13 (17%)	1 (5.9%)
Systemic metastases	39 (23%)	20 (26%)	17 (23%)	2 (12%)
Alive last follow-up	128 (75%)	58 (74%)	56 (75%)	14 (82%)
Status last follow-up				
Alive without recurrence	107 (63%)	45 (57%)	50 (67%)	12 (71%)
Alive with disease	17 (10%)	11 (14%)	5 (6.7%)	1 (5.9%)
Alive, status unknown	4 (2.4%)	2 (2.6%)	1 (1.3%)	1 (5.9%)
Dead, melanoma	29 (17%)	14 (18%)	13 (17%)	2 (12%)
Dead, other cause	4 (2.4%)	2 (2.6%)	1 (1.3%)	1 (5.9%)
Dead, cause unknown	9 (5.3%)	4 (5.1%)	5 (6.7%)	–

IQR = Interquartile range.

when compared to those with a negative popliteal SN (median survival 56 months versus median not reached respectively; log rank test P = 0.011) (Fig. 3).

In seven patients, the popliteal SN was positive but the groin was SN-negative. Two of these seven patients (29%) later developed an inguinal recurrence.

Discussion

Lymphoscintigraphy and SN biopsy

This study of 3820 patients with 3902 primary melanomas below the knee reports the incidence of popliteal SNs and examines their relevance and the clinical implications of popliteal SN biopsy. Of the cohort of 176 patients with drainage to SNs in the popliteal fossa, only 96 (54%) had a SN biopsy in this region. The procedure had a failure rate of 18%. The popliteal SN was found to be positive in 13 of the 79 patients (16%) in whom the procedure was successful. The occurrence of a positive popliteal SN was associated with an increased risk of melanoma recurrence and was associated with a diminished overall survival compared to patients with a negative popliteal SN.

The quality of the lymphoscintigrams is influenced by the size of the radiotracer particles [27]. In this study, Tc-99 m antimony trisulfide colloid was used. This small particle radioactive tracer quickly enters the lymphatic vessels, thereby identifying true SNs with high accuracy on dynamic lymphoscintigrams. Lymphoscintigraphy visualized drainage to nodes in the popliteal fossa in 176 (4.5%) of the patients with a melanoma anywhere below the knee. Previous investigations have been performed but were smaller, including between 57 and 461 patients with melanomas on the distal lower limb. These studies demonstrated popliteal SNs in between 1% and 11% of the patients [6–20].

Of the total patient cohort, 46% of those who had lymphatic drainage to popliteal lymph nodes did not undergo popliteal SN biopsy. The reasons for this were diverse and included patient refusal, lymphoscintigrams with complex drainage patterns, the surgeon's decision, and clinical trial participation. No previous studies have correlated lymphoscintigraphy findings and the popliteal SN biopsy rate. The afferent lymphatic vessels and the lymph nodes are usually not in the subcutaneous tissue but much deeper [28]. This limits the usefulness of blue dye in SN identification and retrieval. The difficulty of popliteal SN biopsy is evident from the reluctance of surgeons to pursue them and the failure rate of 18% in a specialist melanoma unit. In other nodal regions, SNs are retrieved almost without exception at our institution. Three other

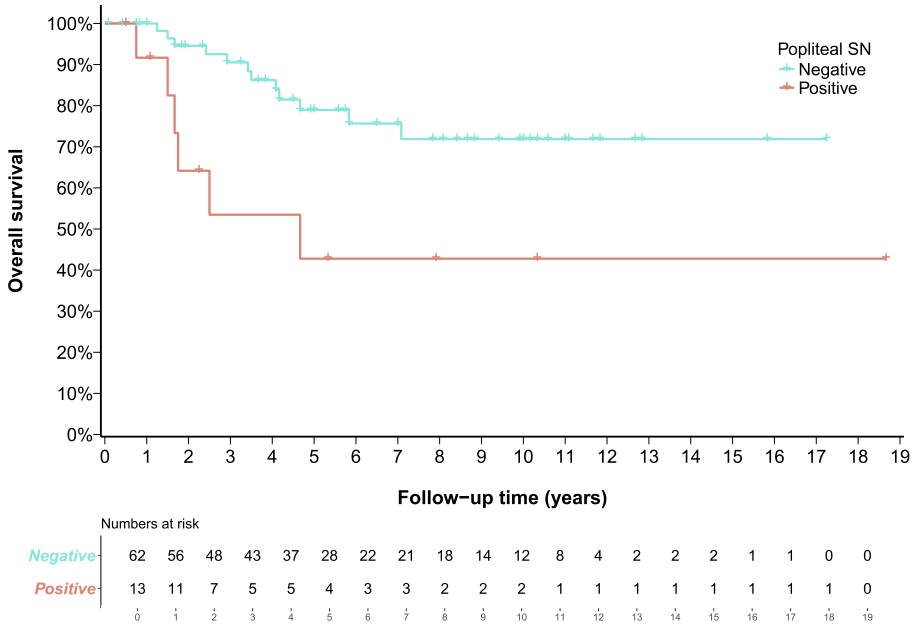

Fig. 3. Overall survival, according to popliteal SN tumor status. SN = sentinel node.

investigators have reported failure rates of 8%, 12% and 62% [9,13,17]. The latter exceptionally high rate was attributed to a low radioactive tracer uptake in the nodes that was sometimes not detectable at the time of surgery. For this reason, the SN procedure should be performed as soon as possible after lymphoscintigraphy.

Retrieved popliteal SNs contained metastases in 16% of the patients, which is in accordance with the experience in other nodal fields [23]. Eleven previous studies reported popliteal SN metastatic rates of 11%–53% [6,8,10,12,13,16–19,22]. This wide range can be attributed to the small patient numbers in these studies, with seven including less than ten patients and the largest reporting 27 patients [6].

The popliteal node was the only positive node in 10% of the patients in the present series. In four other studies this ranged from 4% to 36% [6,8,13,18]. Ten of our patients (13%) were assigned to a higher TNM stage on the basis of popliteal SN positivity. This is relevant in view of current developments in systemic therapy as understaging may prevent patients from receiving potentially beneficial adjuvant therapy or participating in clinical trials of adjuvant therapies [29,30].

Completion lymph node dissection

In the time period of the current study, completion lymph node dissection was the recommended treatment when metastatic disease in a SN was identified [21]. Sixty-one percent of the patients with a positive SN underwent completion lymph node dissection. This is in accordance with earlier research from our institution that showed that 62% of all 599 SN positive patients treated between 2004 and 2014 underwent completion lymph node dissection. The decision to refrain from completion lymph node dissection was most often made by the patient. Patients with interval SNs and multiple SNs were less likely to undergo completion lymph node dissection [31]. It is not clear why only 31% of the patients with a positive SN retrieved from the popliteal fossa underwent completion lymph node dissection of this region, but this might be due to concern about the risk of lymphedema or the complexity of the procedure. Patients with a positive groin SN were more likely to undergo completion lymph node dissection than patients with a positive popliteal SN. Additional lymph nodes were found in only two of the four completion popliteal lymph node dissection specimens and all were melanoma-free. A combined total of eleven popliteal completion lymph node dissections has been reported in three other studies [6,8,13]. In two of these, no lymph nodes were found, and only one completion lymph node dissection did yield further metastases [13]. So, the collected literature yields only one additional positive lymph node in fifteen completion node dissections. It appears that either there may be no additional lymph nodes in the popliteal fossa or they may be difficult to remove, as very occasionally patients do recur in this region. Given their small size, the pathologist may also fail to find the nodes in a bulky specimen.

There has been controversy about the management of the inguinal nodes in patients with only a positive popliteal SN [8,9]. One of the aims of our study was to clarify this issue. Unfortunately, the study is limited by its retrospective nature, which renders it prone to selection bias. Furthermore, the total of sixteen popliteal SN-positive patients with only four complete popliteal lymph dissections is clearly insufficient to properly address this matter. Even more importantly, however, the recently published interim results of the Second Multicenter Selective Lymphadenectomy Trial and the German DeCOG study largely obviate the need for clarification, as both trials indicate that completion lymph node dissection does not improve survival if the nodal region is followed with regular ultrasound examination [32,33]. The substantial survival benefit in the SN biopsy arm of the First Multicenter Selective Lymphadenectomy Trial, demonstrated by latent subgroup analysis, appears to be mainly attributable to removal of all disease in the SNs, rather than removal of disease in the non-SNs removed at the time of completion lymph node dissection [23,34].

Follow-up

The overall recurrence rate for the 170 patients with a popliteal SN demonstrated by lymphoscintigraphy and with complete follow-up data available was 40% and for those undergoing

popliteal SN biopsy it was 35%. Other studies report recurrence rates after popliteal SN biopsy of 0%–47% [6,8,13,17]. The 69% overall recurrence rate in the present study for patients with a positive popliteal SN roughly corresponds to rates in two other studies (75% and 100%) [8,17].

Six patients recurred in the popliteal fossa; three had not undergone a SN procedure, one had a positive popliteal SN biopsy and two a negative biopsy. Five of them developed a recurrence in the groin as well. In this small group, popliteal SN biopsy did not improve locoregional control, as patients undergoing popliteal SN biopsy and those observed had a similar rate of popliteal recurrence. However, in the patients who did undergo popliteal SN biopsy, the finding of a positive popliteal node was of prognostic importance, predicting disease recurrence and a worse overall survival compared to popliteal SN-negative patients. Other studies on popliteal SNs have not provided survival data.

Conclusions

Lymphoscintigraphy revealed a SN in the popliteal fossa in 4.5% of the patients with a primary cutaneous melanoma below the knee. Popliteal SN biopsy was performed in only 55% of these patients and harvesting them was challenging, with an 18% failure rate. Patients should be made aware of this high failure rate. Nevertheless, biopsy of SNs in the popliteal fossa is recommended as it can lead to assignation of a higher TNM stage (in 13% of the patients in our study) and is associated with little morbidity. The tumor status of the popliteal node has predictive value for recurrence and overall survival. Completion popliteal lymph node dissection is not beneficial. In patients with an involved popliteal SN, observation with regular ultrasound examination of the region is recommended, rather than a completion lymph node dissection of the popliteal fossa.

Declarations of interest

JFT – has been on an advisory board for and received honoraria and travel support from Bristol Meyers Squibb, Merck Sharp Dome, Provectus Inc and GlaxoSmithKline.

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