REVIEW ARTICLE

The Lymphatic Drain of Below-Knee Malignant Melanoma: Is the Popliteal Fossa a Ghost Station?

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Abstract

Sentinel lymph node biopsy is fundamental in the staging of primary cutaneous melanoma (PCL), but reported lymphoscintigraphic patterns are very heterogeneous. In this systematic review, we evaluated the role of the popliteal station in below-knee PCL. A systematic search of literature through was conducted on the electronic databases PubMed, SCOPUS, and Web of Science (WOS) to identify eligible studies. A total of 22 studies (n=5673 patients) were included. During the analysis of the included articles, it was not possible to classify patients into the 3 Menes popliteal drainage pattern, obtained by lymphoscintigraphy. The analysis of lymphatic drainage in patients undergoing lymphoscintigraphy for melanoma of the lower extremities below the knee was reported in 5637 patients and the type of lymphatic popliteal drainage was reported only in 5.64% (320 patients). The rate of popliteal lymph nodes melanoma metastases was 1.49%: they were located exclusively at the popliteal level in 0.60%, at the popliteal and inguinal levels in 0.39%, at the popliteal and iliac level in 0.02%, and at the groin level in 0.48%. In conclusion, the most common lymphoscintigraphic pattern is represented by popliteal nodes in-transit or interval nodes, so metastases from below-knee melanomas commonly transit through popliteal nodes stations and arrive to inguinal nodes stations. The popliteal nodes are the primary station in about 5.64% of cases. Larger studies are needed to corroborate these findings.

Keywords Primary cutaneous melanoma · Popliteal lymph nodes · Sentinel nodes

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Introduction

Sentinel lymph node biopsy (SLNB) represents a fundamental step in the staging and prognosis of patients with primary cutaneous melanoma (PCN) [1]. It is defined as the lymph node that first drains the lymph of a specific area of skin and is based on Halsted theory of stepwise dissemination of tumor cells from peritumoral lymphatics to the sentinel lymph node (SLN), and then to more distant lymph nodes. The candidates of SLNB are those with thick melanomas (Breslow thickness cut-off of 0.75 mm and 1 mm as per the National Comprehensive Cancer Network (NCCN) [2], and American Joint Committee on Cancer (AJCC) respectively) [3], or thinner melanoma in the presence of ulceration, high mitotic rate, and/or lymphovascular invasion [2]. The identification of these lymph nodes is performed via injection of tracers into the peritumoral site [3, 4]. The current guidelines, according to the AJCC 8th edition [3] and the guidelines of the Italian Association of Medical Oncologists (AIOM) [5], changed the recommendation for SLN-positive cases. Although in the previous guidelines, these patients were managed with completion lymph node dissection (CLND), presently SLN positivity is not a mandatory indication for a CLND but lymph node dissection currently is indicated in macroscopic nodal disease (Stage IIIB+). Lymphatic drainage for most anatomical areas is variable, but it appears to be more predictable in the lower limbs (below-knee) [6], in which traditionally two main drainage routes are recognized:

– A major pathway, which originates from the medial edge of the foot and develops parallel to the great saphenous vein draining to the inguinal lymph nodes.
– A minor pathway, that originates from the lateral edge of the foot and runs along the small saphenous vein thus draining into the popliteal lymph nodes.

The introduction of the sentinel lymph node technique with lymphoscintigraphy has led to a better understanding of these drainage pathways of melanomas, challenging previous anatomical knowledge. For instance, Menes et al. reported 3 different patterns of drainage of melanoma of leg to the popliteal nodes as obtained by lymphoscintigraphic examination of patients with a SLN-positive biopsy [7] (Fig. 1a–c).

The aim of this systematic literature review is to evaluate the role of the popliteal basin in the lymphatic drain of below-knee melanoma and in SLNB.

Methods

Study Guidelines, Protocol, and Registration

This systematic review and meta-analysis was performed following the Cochrane Handbook for Systematic Reviews of

Fig. 1 **a**–**c** Patterns of drainage of melanoma of leg according to ▶ classification by Menes

Interventions guidelines [8], and reported as per the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [9].

Search Strategy

A thorough systematic search of literature through February 2020 was conducted by 2 independent reviewers (RC and FB) on the electronic databases PubMed, SCOPUS, and Web of Science (WOS) to identify studies eligible for inclusion using search strategies in Tables 1 and 2 below.
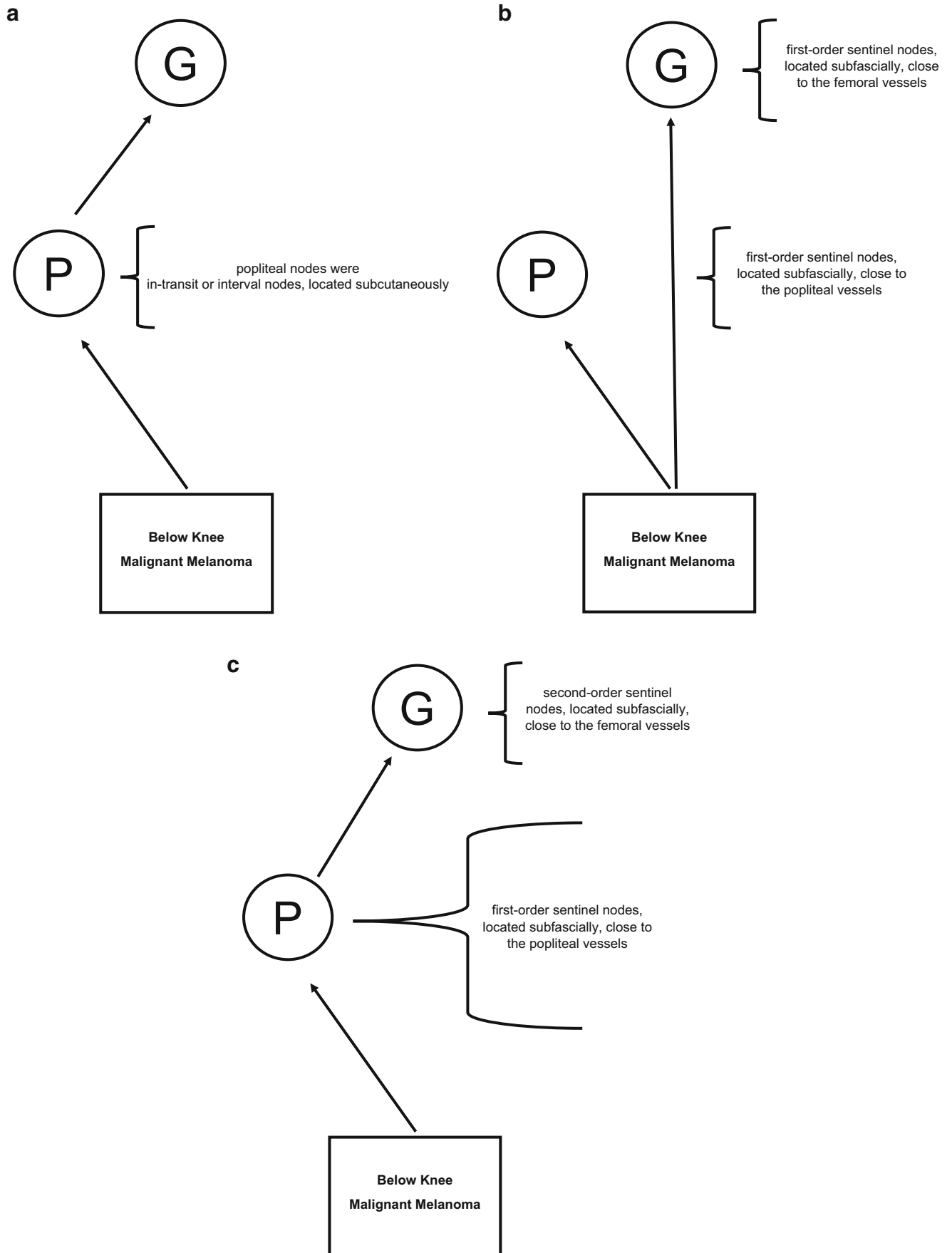
No language restriction was applied. Full texts of records remaining after initial screening by title and abstract were assessed to determine study eligibility. When the articles were published by the same study group and there was an overlap of the search period, only the most recent article was included to avoid duplication of data. The PubMed function "related articles" was used to extend the search and a reference list of all the included studies was analyzed. A search on Google Books was done for the analysis of the grey literature (https://books.google.com).

Selection Criteria

All titles and abstracts selected were evaluated by an initial double-blind screening by RC and FB. To be included in the review, a study had to report data about lymphoscintigraphy in patients with melanoma from the lower limbs below the level of the knee. Subsequently, the full texts of these selected articles were independently re-evaluated for suitability and inclusion in the systematic review. In cases of overlap between multiple articles published by the same researchers, only the most recent study was included to avoid double counting. Letter-to-editor, editorials, conference extracts, and studies with incomplete or irrelevant data were excluded.

Data Extraction and Quality Assessment

For each study, the following information was extracted by 2 independent reviewers (PC and RC) based on the model of the CHARMS Checklist (Critical Appraisal and Data Extraction for Systematic Reviews of Prediction Modelling Studies) (Supplement 1) [10]. Methodological quality of the included studies was assessed using the first eight entries of the Methodological Index for Non-Randomized Studies (MINORS) tool [11]. The analysis was carried out in a double-blind fashion by RC and CB. The items score were 0 (not shown); 1 (reported but inadequate); 2 (reported and adequate). The ideal global score is 16 for non-comparative studies.

a

G

P { popliteal nodes were
in-transit or interval nodes, located subcutaneously

Below Knee
Malignant Melanoma

b

G { first-order sentinel nodes,
located subfascially, close
to the femoral vessels

P { first-order sentinel nodes,
located subfascially, close to
the popliteal vessels

Below Knee
Malignant Melanoma

c

G { second-order sentinel
nodes, located subfascially,
close to the femoral vessels

P { first-order sentinel nodes,
located subfascially, close to
the popliteal vessels

Below Knee
Malignant Melanoma

Table 1 Search strategy for PubMed

1	(popliteal[All Fields] AND fossa[All Fields]) AND ("melanoma"[MeSH Terms] OR "melanoma"[All Fields])
2	(popliteal[All Fields] AND fossa[All Fields]) AND ("dissection"[MeSH Terms] OR "dissection"[All Fields])
3	(popliteal[All Fields] AND fossa[All Fields]) AND ("lymphoscintigraphy"[MeSH Terms] OR "lymphoscintigraphy"[All Fields])

Study Outcomes

The primary outcome was the type of popliteal node drainage in patients undergoing lymphoscintigraphy for melanoma of the lower limbs below the knee (as per the classification by Menes et al.) [7]. The secondary outcomes were the melanoma metastasis rate in patients with positive popliteal sentinel node, the type of popliteal lymphadenectomy, the type of surgical access technique at popliteal fossa, the overall survival (OS), and the disease-free survival (DFS).

Meta-Analytical Synthesis Methods

Due to the high heterogeneity displayed by the included studies, pooling of data was not performed. Instead, the results were summarized in a "summary of findings table" and a narration provided.

Results

The initial search yielded 348 potentially relevant articles. Following the removal of duplicates and primary screening, 25 articles were assessed by full text for eligibility in the meta-analysis. Of these, 3 were excluded because the primary and secondary outcomes of the study did not match that of this review (Supplement 2) [12–14]. Thus, a total of 22 articles were included in this systematic review (Fig. 2).

Characteristics of the Included Studies and Quality Assessment

A total of 22 studies (n= 5673 patients) were included from the literature [7, 15–35]. We have added to these articles another unpublished case report of a patient treated at our Surgical Unit of Melanoma Surgery (Table 3).

Table 2 Search strategy for SCOPUS and Web of Science

1	Popliteal AND fossa AND melanoma
2	Popliteal AND fossa AND dissection
3	Popliteal AND fossa AND lymphoscintigraphy

Majority of the studies were performed in Asia (9 studies, n=221 patients), followed from Europe (6 studies, n=320 patients) and the America (Brazil and USA) (6 studies, n=1312 patients). Only one study was from Oceania region (Australia, n=3820 patients).

The year of publication of the included studies ranged from 2002 to 2019. Most of the included patients were females (54.8%). The average age of patients with positive popliteal involvement is 58 years. Rarely, melanomas can occur at a younger age, as described in a case report by Febrero et al. [18] in which the patient in question was 17-year-old. Similarly, in an observational study that Barrasa. et al. published in the Journal of the American College of Surgeons in 2011, one of the enrolled patients was 19-year-old [32]. However, considering all the cases, the incidence is higher around the 5th-6th decade. The greater number of cases of metastasis in the popliteal fossa around the 5th–6th decade is certainly due to a higher incidence of melanoma itself. The average Breslow thickness was 2.86 mm.

The average score of the MINORS table, of the included studies was 11.27 (moderate risk) (Supplement 3).

Primary Outcomes

During the analysis of the included articles, it was not possible to classify patients into the 3 Menes popliteal drainage pattern, obtained by lymphoscintigraphy [7]:

- "prima via" (popliteal nodes as in-transit or interval nodes, located subcutaneously);
- "secunda via" (popliteal and inguinal nodes as both first-order sentinel nodes, located subfascially, close to the popliteal and inguinal vessels);
- "tertia via" (popliteal nodes as first-order sentinel, located subfascially close to the popliteal vessels, and inguinal nodes as second-order sentinel, located subfascially close to the inguinal vessels).

In effect, most of the patients described in the included articles reviewed do not performed this classification. Furthermore, a lot of articles reported the presence of transit metastasis at popliteal station [7, 16, 26, 30, 34], but it was possible perform an "ex post" analysis from articles if a popliteal node is subcutaneous or sub-fascial without reviewing imaging.

Fig. 2 PRISMA flow diagram for the included studies
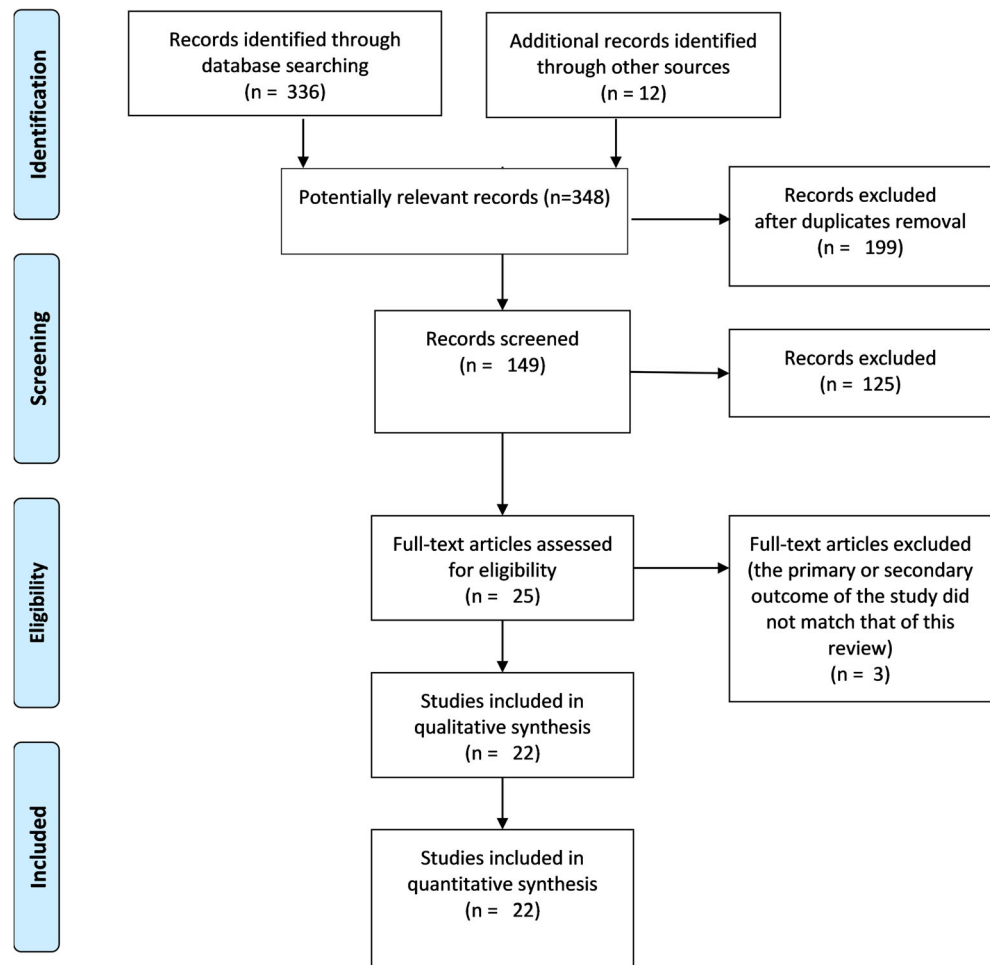
The analysis of lymphatic drainage in patients undergoing lymphoscintigraphy for melanoma of the lower extremities below the knee was reported in 5,637 patients and the lymphatic popliteal drainage was reported only in 5.64% (320 patients).

Secondary Outcomes

The rate of popliteal lymph node melanoma metastasis was 1.49% (84 patients). Lymph node metastasis was located exclusively at the popliteal level in 0.60% (34 patients), at the popliteal and inguinal levels in 0.39% (22 patients), at the popliteal, and iliac level in 0.02% (1 patient) and at the inguinal level in 0.48% (27 patients) (Fig. 3).

In patients with popliteal sentinel node, the rate of CLND (complete lymph node dissection) was 13.43% (43/320 patients with popliteal drainage). Exclusively popliteal CLND rate was 60.47% (26 patients), while popliteal and inguinal CLND rate was 37.21% (16 patients), and the popliteal and iliac CLND rate was 2.326% (1 patient).

In all studies, the authors used the surgical access technique described by Karakousis by the Z plasty or S-shape technique. During lymphadenectomy, the average number of lymph

nodes removed was 3.9. In 41 patients, the mean follow-up at 39 months was reported and the loss of patients at follow-up was 4.7% (2 patients); the OS was 70.7% (29 patients) and the DFS was 31.7% (13 patients).

Discussion

Metastasis of melanoma to popliteal nodes is a rare pathological condition. The lymphatic drainage of melanomas to the popliteal fossa is uncommon and few cases have been described in the literature [36]. For these reasons, some physicians do not perform the examination of the popliteal region during clinical examination and during lymphoscintigraphy in patients with melanoma of the leg [36]. In contrast, popliteal lymph nodes are the first station for the lymphatic drain of squamous carcinomas and sarcomas below the knee [37–39].

The classic Human Anatomy textbooks describe the popliteal lymph nodes as fundamental passage station in the lymphatic drainage of the leg and foot [40]. These nodes are located in the adipose tissue of the popliteal fossa (Fig. 4) near the popliteal vessels (Fig. 5) [41–43].

Table 3 Characteristics of the included studies

| Author, year of publication	Country	Time of enrollment	Type of analysis study	Number of patients enrolled	Age (median)
Bertolli 2015	Brazil	2000–2010	Retrospective observational study	247 (100%)	53
Costa 2008	Brazil	2008	Case report	1 (100%)	65
Covarelli 2013	Italy	2013	Case report	1 (100%)	NR
Febrero 2018	Spain	2018	Case report	1 (100%)	17
Georgeu 2002	U.K.	2002	Case report	1 (100%)	59
Ishihara 2005	Japan	2005	Case report	1 (100%)	43
Kaku 2012	Japan	2012	Case report	1 (100%)	69
Karadag 2017	Turkey	2017	Case report	1 (100%)	60
Kim HY 2009	South Korea	2009	Case report	2 (100%)	60
Kim 2017	South Korea	2006–2015	Retrospective observational study	107 (100%)	60
Kretschmer 2011	Germany	1998–2010	Retrospective observational study	166 (100%)	NR
Pandey 2016	India	2016	Case report	1(100%)	35
Marone 2007	Italy	1996–2005	Retrospective observational study	149 (100%)	NR
McGregor 2018	USA	1992–2012	Retrospective observational study	246 (100%)	NR
Menes 2004	Israel	1993–2003	Retrospective observational study	106 (100%)	55
Parrett 2016	USA	1995–2010	Retrospective observational study	356 (100%)	56
Nijhuis 2019	Australia	1992–2013	Prospective observational study	3820 (100%)	59
Sholar 2005	USA	2004	Case report	1 (100%)	52
Barrasa 2006	Spain	2014-2016	Case report	1 (100%)	68
Soydan 2008	Turkey	2006	Case report	1 (100%)	50
Steen 2011	USA	1971–2010	Retrospective observational study	461 (100%)	55
Tanaka 2013	Japan	2013	Case report	1 (100%)	72
Total		1971–2018		5673 (100%)	58.1

This is the first systematic review of the literature in which the role of popliteal lymph nodes in lymphatic drainage of the leg and foot in patients with melanoma has been assessed. The current review documents that melanoma of distal legs (below the knee) is more frequently observed in patients in the fifth or sixth decade of life, with a higher incidence in women and it is associated with a higher Breslow thickness (average 2.86 mm). From the analysis of lymphoscintigraphy of the lower limbs performed for melanoma located below the knee, results different from those reported in the classic scientific literature emerge. These different types of lymphatic drainage were originally classified by Menes et al. [7] into 3 different patterns as obtained by lymphoscintigraphy in patients with a sentinel node-positive biopsy. This systematic review of the literature evaluated the role of the popliteal lymph nodes with respect to the different lymphoscintigraphic patterns of the leg and foot.

Lymphatic Drainage of SNL

The popliteal lymphatic drainage in patients undergoing lymphoscintigraphy for melanoma of the lower extremities below the knee was reported only in few cases (5.64%).

In these patients, the classification of Menes represents a promising potential challenge that should be better investigated, but it is not clearly validated, according to the too small number of patients having described this popliteal drainage pattern, as presented by Menes [7]. In our systematic review, it was not possible to rank patients into the 3 Menes drainage pattern classification without reviewing the lymphoscintigraphic images of each patient.

In SLN, the most common lymphoscintigraphic pattern ("prima via") was represented by popliteal nodes in-transit
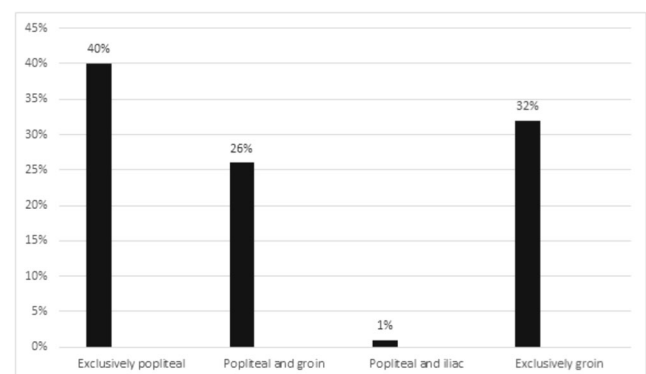
Fig. 3 Rate of popliteal lymph node melanoma metastasis in patients with lymphatic popliteal drainage
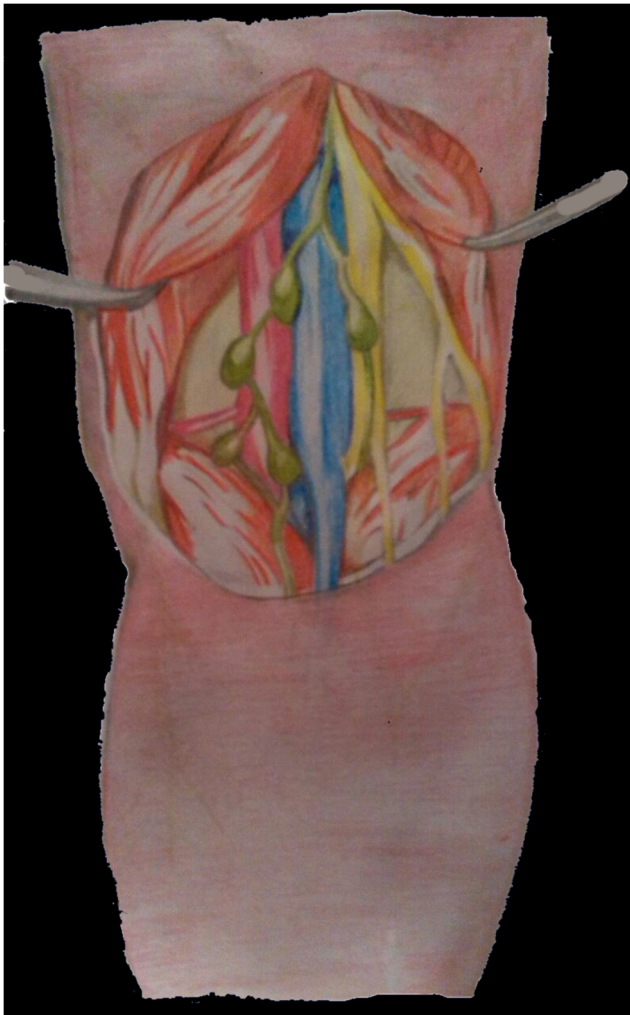
Fig. 4 Relationship between popliteal nodes and vessels in popliteal fossa

or interval nodes (Menes pattern 1) [7]. In this common type [7, 16, 26, 30, 34], small lymph nodes were located at the subcutaneously level and represented only a passageway for lymphatics from the leg and directed to the groin. So, the metastasis from Melanoma, located at lower limb under the knee, commonly skip popliteal nodes station and arrive at to inguinal nodes station. Less commonly ("secunda via") [7],
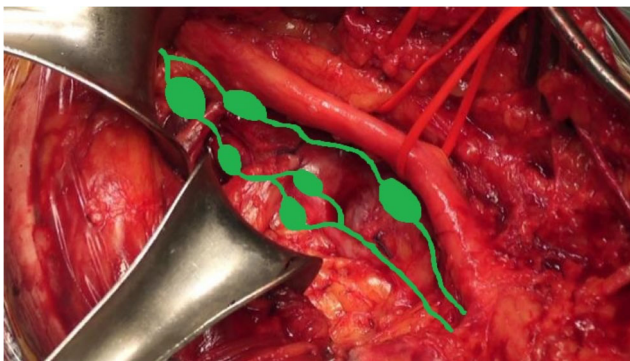
Fig. 5 Intraoperative dissection of popliteal fossa showing relationship between popliteal nodes and vessels

lymphatic flow directs simultaneously through two distinct ways from the leg along the lymphatics located near the great saphenous vein to the inguinal lymph nodes and along lymphatics located near to of the small saphenous vein to the popliteal lymph nodes (Menes pattern 2).

In very rare situations ("tertia via") [7], the efferent path of the lymphatics coming from the leg reaches the subfascial popliteal lymph nodes, and from here, it continues toward the femoral vessels, draining into the deep inguinal lymphatic tissue (Menes pattern 3): popliteal nodes as first-order sentinel, located in the popliteal fossa subfascially close to the popliteal vessels, and inguinal nodes as second-order sentinel, located the popliteal fossa subfascially close to the inguinal vessels.

Proposed Practice Guideline Based on the Menes Pattern for Popliteal Node Dissection

In the "Menes pattern 1," the popliteal basin is jumped and a popliteal lymphadenectomy traditionally is not needed.

In patients with "Menes pattern 2," the simultaneous SLN+ positive at inguinal and popliteal station represents a dilemma for the surgeons and oncologists concerning the choice of performing popliteal lymphadenectomy or no not. In the past, there was an agreement between surgeons and oncologists to perform a step-up approach: first the popliteal lymphadenectomy, and successively the groin lymphadenectomy. The most common complication of this type of sequential popliteal/inguinal lymphadenectomy was the severe lymphedema of the leg. For this reason, in new recommendations from international guidelines, completion lymphadenectomy is no longer the exclusive option in these cases. Lymphadenectomy is only reserved for patients in which clinical lymphadenopathy is encountered during the follow-up.

The Menes pattern 3 is still associated with clinical controversies consequent to the changes reported in the new international guidelines; therefore, new large studies are needed for analyze this small number of patients.

Popliteal Lymph Node Dissection

In this systematic review, only few patients underwent popliteal lymphadenectomy (13.43%); the exclusively popliteal CLND rate was higher (60.47%, 26 patients) than the associated popliteal/inguinal CLND rate (37.21%, 16 patients); the rate of popliteal/iliac CLND (2.33%, 1 patient) was lower. In these cases, the average number of popliteal lymph nodes removed was 3.9. It was not the aim of this systematic review to evaluate the improvement of patient survival possibly related to CLND: this issue has been addressed by many papers and some clinical trials [44]. In these patients with popliteal metastasis from malignant melanoma, the prognosis was very poor. Only 37% of patients who underwent CLND had no evidence of recurrent cancer after an average follow-up of

39 months; in fact, 30% of the cases were still alive with melanoma recurrence and 28% of the cases died from recurrence. New imaging techniques such as photoacoustic ultrasound imaging could improve detection of lymph node micrometastasis [45].

Conclusions

The most common lymphoscintigraphic pattern is represented by popliteal nodes in-transit or interval nodes, so metastases from below-knee melanomas commonly transit through popliteal nodes stations and arrive to inguinal nodes stations. The popliteal nodes are the primary station in about 5.64% of cases. Larger studies are needed to corroborate these findings.

Declarations

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