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Assessment of Lymphatic Drainage Through Sentinel Lymph Node Biopsy in Cutaneous Melanoma Using a Radioactive Tracer - Technetium-99m (99mTc)

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Abbreviations:
SLNB: sentinel lymph node biopsy;
SLN: sentinel lymph node;
LDB: lymphatic drainage basin;
CLND: complete lymph node dissection;
WLE: wide local excision;
IHC: immunohistochemistry;
ICG: indocyanine green.

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Rezumat

Evaluarea drenajului limfatic prin identificarea și biopsia de ganglion santinelă în melanomul cutanat folosind trasor radioactiv Technețiu-99m (99mTc)

Introducere: melanomul cutanat prezintă adesea un drenaj limfatic imprevizibil, în special în regiunile trunchiului, capului şi gâtului. Biopsia de ganglion santinelă reprezintă o metodă de prognostic importantă ce evaluează cu precizie starea ganglionilor limfatici regionali şi ghidează conduita terapeutică.
Material şi Metode: acest studiu prospectiv a inclus 104 pacienți diagnosticați cu melanom cutanat, care au beneficiat de identificare şi biopsie de ganglion santinelă folosind un trasor radioactiv. Ganglionii santinelă au fost identificați limfoscintigrafic şi cu ajutorul gamma camerei, apoi evaluați prin examen histopatologic şi imunohistochimic.
Rezultate: rata de identificare a ganglionilor santinelă a fost de 100%. Multiple bazine limfatice de drenaj au fost identificate în 27% dintre cazuri, predominant în regiunile trunchiului, capului şi gâtului. Numărul mediu de ganglioni santinelă identificați a fost de 2.11 limfoscintigrafic şi 3.35 la examenul histopatologic. Au fost descoperite metastaze la nivelul ganglioniilor santinelă la 22,11% dintre pacienți.
Concluzie: identificarea şi biopsia de ganglion santinelă utilizând un trasor radioactiv este utilă mai ales pentru melanomele cutanate localizate la nivelul trunchiului, capului sau gâtului. De asemenea, această tehnică are o rată mai scăzută de fals negativ chiar şi pentru melanomele situate la nivelul membrelor.

Cuvinte cheie: melanom cutanat, biopsie de ganglion santinelă, trasor radioactiv, drenaj limfatic multiplu

Abstract

Background: cutaneous melanoma has often unpredictable lymphatic drainage patterns, especially at the level of the trunk, head and neck regions. Sentinel lymph node biopsy (SLNB) is an important prognostic tool that accurately assesses regional lymph node involvement and guides therapeutic decisions.

Material and Methods: this prospective study involved 104 patients diagnosed with cutaneous melanoma who underwent SLNB using a radioactive tracer. Sentinel lymph nodes (SLN) were identified via lymphoscintigraphy and gamma camera guidance, followed by histopathological and immunohistochemical evaluation.

Results: the SLNB identification rate was 100%. Multiple lymphatic drainage basins (LDB) were identified in 27% of cases, predominantly in trunk, head, and neck regions. The mean number of SLN identified was 2.11 by lymphoscintigraphy and 3.35 by histopathology. SLN metastases were present in 22.11% of patients.

Conclusions: SLNB with a radioactive tracer is particularly useful for cutaneous melanomas of the trunk, head or neck. This technique also has less false negative results for melanomas located at the lever of the limbs.

Key words: cutaneous melanoma, sentinel lymph node biopsy, radioactive tracer, multiple lymphatic drainage

Introduction

Melanoma has the highest mortality rate among skin cancers and its incidence has steadily increased over the past 50 years (1). In 2022 were reported 331.722 new cases and 58.667 deaths worldwide, with the highest incidence in Australia and New Zealand; in Romania it was the 12th most common type of cancer with 2.247 new cases and 541 deaths (2).

One of the ways cutaneous melanoma spreads is through the lymphatic pathway, which makes the status of regional lymph nodes an important prognostic factor (3,4). Marie Philibert Constant Sappey described almost 150 years ago a symmetrical and predictable pattern of lymphatic drainage, which was widely accepted and used for over a century (5). However, the development of lymphoscintigraphy brought new insights that questioned some of Sappey's conclusions and it was demonstrated that lymphatic drainage could be unpredictable in about 30% of cases of cutaneous melanoma (6). While drainage patterns are relatively consistent in the limbs, the trunk, the head and the neck have more complex and variable networks (7). This complexity highlights the importance of lymphoscintigraphy in accurately identifying the regional lymphatic drainage pathways (8).

Regional complete lymph node dissection (CLND) was historically the only method for diagnosing and treating lymph node involvement, but this procedure is associated with significant morbidity (9). The sentinel lymph node biopsy (SLNB) has revolutionized surgical and diagnostic approaches in oncology. Ramon M. Cabanas introduced this concept in 1977. He observed a predictable pattern of lymphatic drainage in penile cancer and identified the first lymph node to receive lymphatic drainage from the tumor. In this

article, Cabanas proposed that the presence of metastases in the sentinel node could guide the need for more extensive lymphadenectomy (10). The concept of the sentinel lymph node was extended and refined by Donald L. Morton. In 1992, Morton and his team at the John Wayne Cancer Institute in California demonstrated that sentinel lymph node biopsy could be effectively applied in cutaneous melanoma to detect metastases at an early stage (11). Neoplastic cells from the primary tumor initially metastasize to the first lymph node(s) along the lymphatic pathway. This node is identified and excised during surgery. If the sentinel node is not invaded, the likelihood of other lymph nodes in the same anatomical region being involved is low. Morton perfected the technique by using vital dye and a radioactive tracer to locate the sentinel lymph node during surgery. This protocol allowed for precise identification of sentinel nodes, reducing the need for unnecessary extensive CLND.

The aim of this study is the assessment of the results of SLNB in cutaneous melanoma using a radioactive tracer.

Material and Methods

We conducted a prospective study involving 104 patients diagnosed with cutaneous melanoma who underwent surgery at Prof. Dr. Alexandru Trestioreanu Oncology Institute of Bucharest, Surgical Oncology 2 Department, between January 2022 and December 2023. The study complied with current legislation on personal data protection and the standards set by the ethics committee.

The diagnosis was made by excisional biopsy of the primary tumor and the procedure was done in Dermatology or Plastic Surgery clinics around the country. The tumor board recommended SLNB to all patients, and for 74 of them wide local excision (WLE) to achieve safe oncological margins. Staging was done according to the eighth edition of the American Joint Committee on Cancer (*Table 1*). SLNB was done at 4 to 14 weeks after excisional biopsy for all patients with clinically node-negative ≥ T1b and for special cases of T1a patients: 3 mitoses/mm^2, a positive deep margin or when Breslow thickness cannot be reliably determined (12). After clinical examination, the patients underwent blood tests, a full body CT scan and locoregional ultrasound of the lymph nodes.

A dose of 10 to 120 MBq sodium pertechnetate (^{99m}Tc) labeled nanocolloidal human serum albumin (Nanoscan®) was used for every patient. The radiocolloid was injected pericicatricial and intradermally (2-6 injections) at the Clinical Nuclear Medicine Laboratory of the Prof. Dr. Alexandru Trestioreanu Oncology Institute in Bucharest and at Gauss Clinics Bucharest and dynamic lymphoscintigraphy images were recorded in order to track all the migration pathways and the corresponding lymph nodes and

Table 1. Primary Tumor Melanoma Staging System - Eighth edition of the American Joint Committee on Cancer (AJCC8) - Gershenwald, Scolyer, et al. Melanoma. In Amin, M.B., Edge, S.B., Greene, F.L., et al. (Eds.) AJCC Cancer Staging Manual. 8th Ed. New York: Springer; 2017

T Category	Thickness	Ulceration status
Tis (melanoma *in situ*)	Not applicable	Not applicable
T1	≤ 1.0 mm	Unknown or unspecified
T1a	<0.8 mm	Without ulceration
T1b	<0.8 mm	With ulceration
	0.8-1.0 mm	With or without ulceration
T2	>1.0-2.0 mm	Unknown or unspecified
T2a	>1.0-2.0 mm	Without ulceration
T2b	>1.0-2.0 mm	With ulceration
T3	>2.0-4.0 mm	Unknown or unspecified
T3a	>2.0-4.0 mm	Without ulceration
T3b	>2.0-4.0 mm	With ulceration
T4	>4.0 mm	Unknown or unspecified
T4a	>4.0 mm	Without ulceration
T4b	>4.0 mm	With ulceration

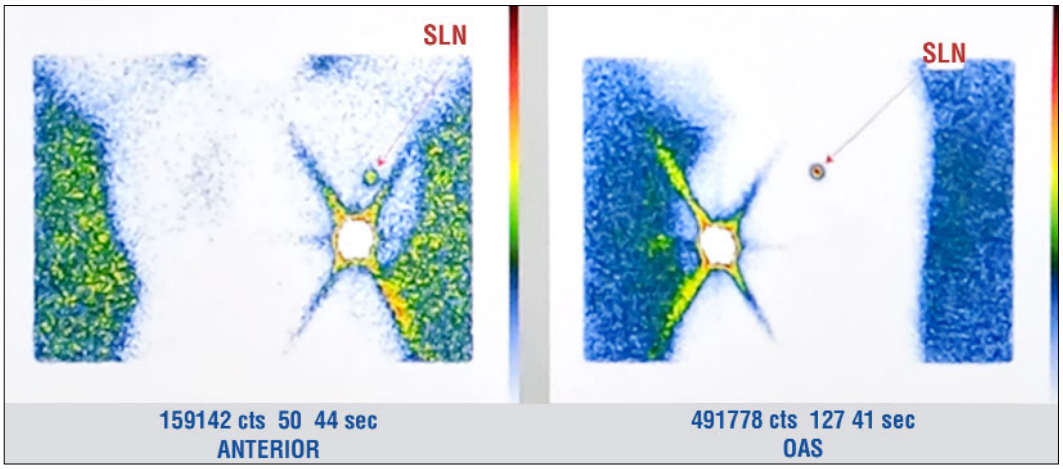


Figure 1. Dynamic lymphoscintigraphy images recorded at 50 and 127 seconds for primary tumor at the level of left pectoral region with corresponding drainage to a left axillary lymph node

mark them on the skin (*Fig. 1*). This protocol was done either one day before the surgery or at least 6 hours before the intervention (usually in the morning).

We used before the surgery a "BriTec - Europrobe 3.2" gamma camera to confirm that the radioactive signal is present and is corresponding to the skin mark. The identification of the lymphatic drainage basins facilitate the surgical planning by selecting the initial and possible subsequent positions of the patient on the operating table in order to facilitate a proper access to the areas of surgical interest. If the drainage basin is close to the surgical scar, then it is recommended to perform first a WLE in order to have a more accurate and without interference identification of SLN. After the incision is made, with the help of gamma camera, we identify lymph nodes emitting a radioactive signal (*Fig. 2*), which are then excised and sent for histopathological examination. In this study, any lymph node with a signal greater than 10% of the value of the lymph node with the maximum signal was also considered a sentinel lymph node. Additionally, in some cases, non-sentinel lymph nodes were excised when adenopathies without a radioactive signal were encountered. For macroscopically high suspicious lymph nodes (size, consistency, color), an immediate histopathological examination was performed. Otherwise, the excised lymph nodes were routinely examined by paraffin sections and underwent also immunohistochemistry (IHC) examination.

Results

The mean age of the patients was 56.7 and median 59.0 years, the male-to-female ratio was 1.12 and the urban-to-rural ratio was 2.05. The Breslow index ranged from 0.5 to 13.0 mm with a mean of 3.05 and a median of

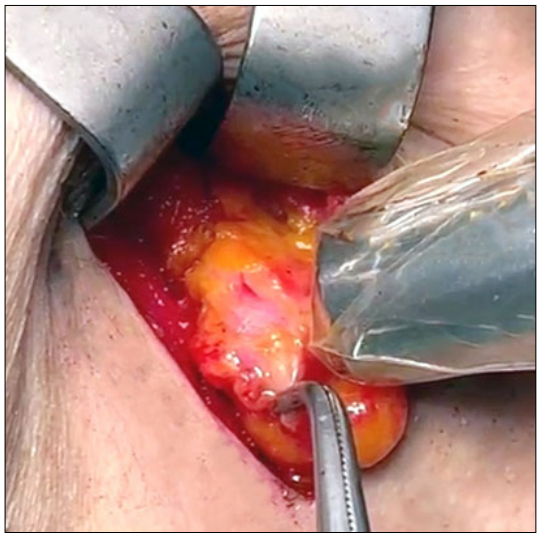


Figure 2. Intraoperative aspect of SLN identification and biopsy

Table 2. The number of identified lymphatic drainage basins at preoperative lymphoscintigraphy for cutaneous melanoma patients who underwent SLNB at IOB between 2022-2023

IOB	No. of patients	1 LDB	2 LDB	3 LDB	4 LDB
2022-2023	104	76 (73.08%)	26 (25.00%)	1 (0.96%)	1 (0.96%)

2.2 mm. The SLN identification rate was 100%. Among the 104 patients, 72 (69.23%) required additional WLE of the scar to achieve oncologically safe resection margins. At the preoperative lymphoscintigraphy, 76 patients (73.07%) had one lymphatic drainage basin (LDB), 26 patients (25.00%) had two LDB, one patient had three LDB, and one patient had four LDB (*Table 2*).

Primary tumor location was for 50 patients (48.07%) at the level of the limbs, for 50 (48.07%) at the level of the trunk, and for 4 (3.84%) at the level of the head and neck (Table 3). Among patients with tumors on the limbs, 47 out of 50 had predictable drainage (axillary or inguinal ipsilateral). In two cases, there were multiple drainage to both the popliteal and inguinal regions for lower limb tumors (*Fig. 3 A*) and in one case, there was drainage to the right subclavicular and right axillary region for a tumor located on the shoulder (*Fig. 3 B*).

The mean number of SLN identified at lymphoscintigraphy was 2.11; median 2 and the mean number of sentinel lymph nodes identified at histopathological exam was 3.35; median 3 (*Fig. 4*). In addition to the sentinel lymph nodes, 46 patients (44.23%) also had non-sentinel lymph nodes excised with a mean of 2.32 and a median of 2 (*Fig. 5*).

Out of the 104 patients, 23 (22.11%) had metastasis at the level of the sentinel lymph nodes and 6 in non-sentinel lymph nodes (5.77%). In 8 cases, at the IHC examination, metastatic invasion was discovered (4 cases with micrometastasis), even though there was initially no suspicion during the paraffin examination. While in 2 cases, a previously suspected metastasis was ruled out.

In 13 cases (12.5%), an immediate intraoperative histopathological examination was performed and in 8 out of 13 lymph node metastases were identified. CLND was performed in 5 patients in the same surgery (4.80%).

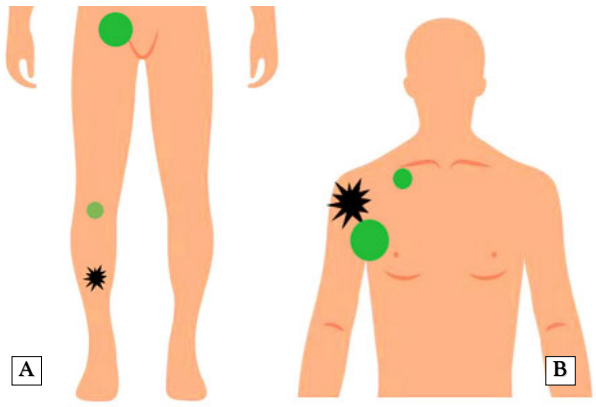


Figure 3. Unpredictable (additional) lymphatic drainage to the popliteal region (A) – 2 cases, and to the subclavic lar region (B) – 1 case.

Discussion

The average age of diagnosis and male to female ratio is similar to literature and confirms that cutaneous melanoma is more frequent for males after the age of 50 (13); but the higher (2.05 times) urban incidence might suggest diagnostic failure in rural areas – which is a concerning public health problem that needs to be investigated further.

Except for melanomas located on the limbs, those on the trunk, head, or neck have unpredictable lymphatic drainage. Thus, when using a radioactive isotope, in addition to identifying the number of SLN, lymphoscintigraphy allows for the visualization of LDBs. During surgery, a gamma camera helps identify the lymph nodes with the strongest signal, which are then excised and analyzed at the histopathologic exam. This is especially useful because of the possibility of multiple

Figure 4. Distribution of the number of sentinel lymph nodes identified by lympho-scintigraphy and at the histopathological exam

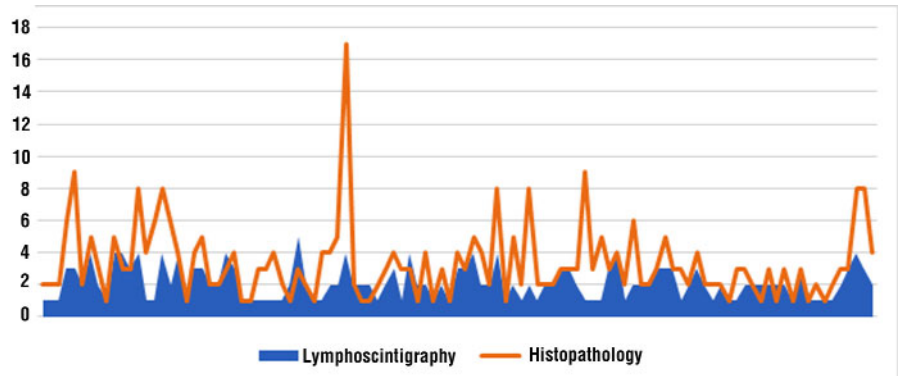


Figure 5. Ratio of the number of SLN and total number of lymph nodes (SLN+ nonSLN) identified at the histopathological examination (46 patients)

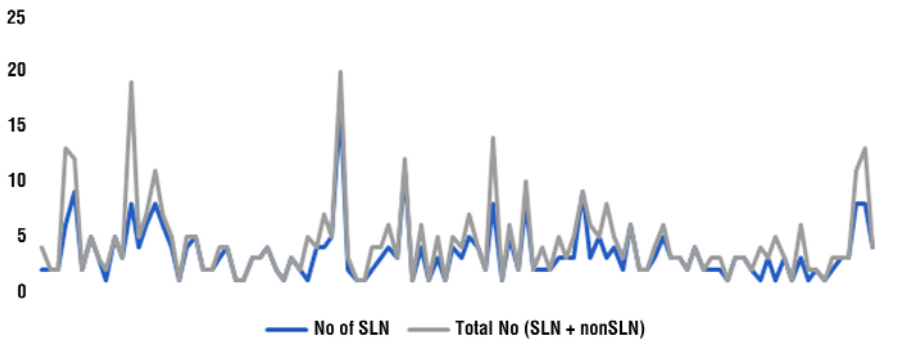
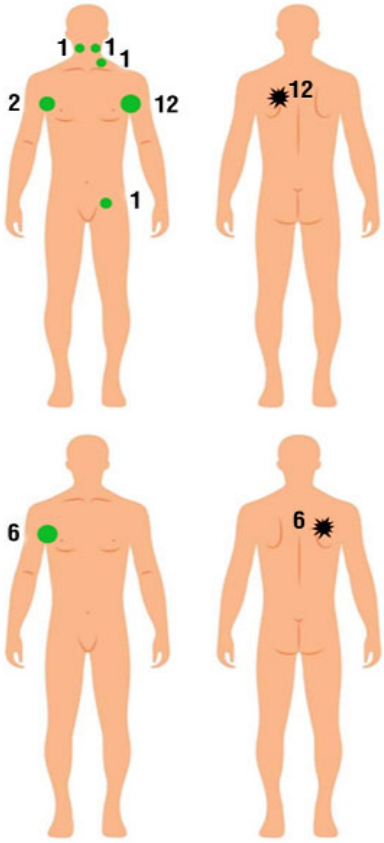
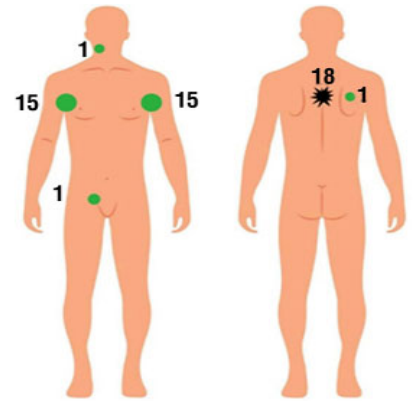


Table 3. Location of the tumors and their drainage basins

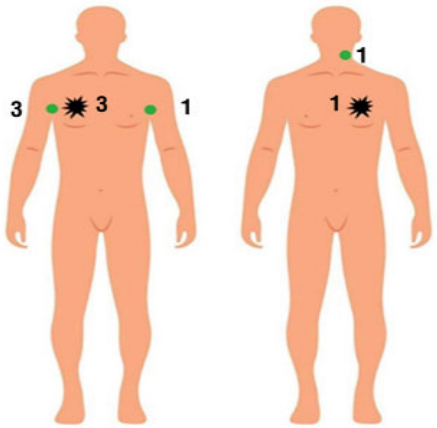


- 12 patients had a primary tumor located in the left scapular region
  - 6 had single axillary drainage on the left side
  - 6 had multiple drainage pathways: left axillary + left supraclavicular, left cervical, right cervical, left inguinal, or right axillary (2 cases)
- 6 patients had a primary tumor located in the right scapular region – all six had single axillary drainage on the right side

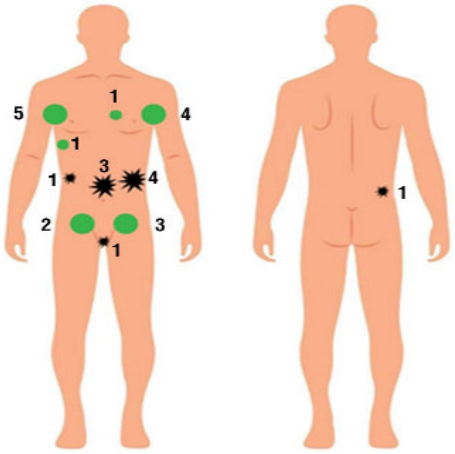
Table 3. Cont'd



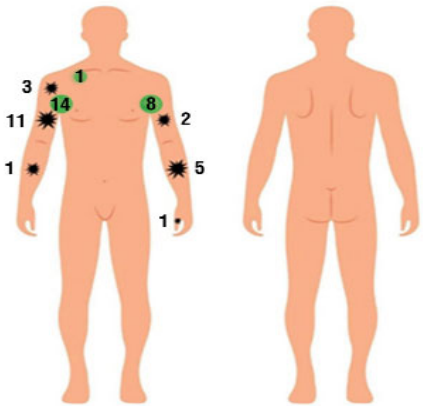
- 18 patients had a primary tumor located in the paravertebral region;
  - 14 had multiple drainage pathways: bilateral axillary – 11; bilateral axillary + right periscapular – 1; right axillary + right inguinal – 1; right axillary + right cervical – 1
  - 4 had single drainage: left axillary – 3; right axillary – 1



- 3 patients had a primary tumor located in the right pectoral region: 2 out of 3 had right axillary drainage, and 1 out of 3 had bilateral axillary drainage
- 1 patient had a primary tumor located in the left pectoral region with single left latero-cervical drainage.

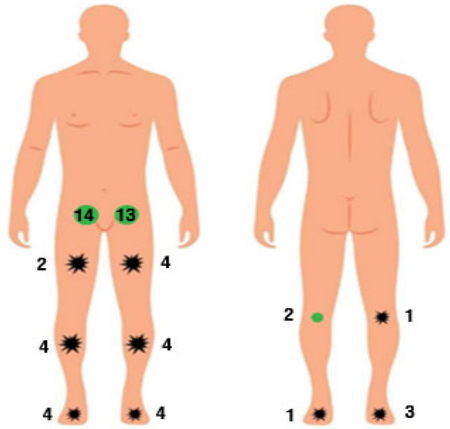


- 10 patients had a primary tumor at the level of the abdomen and pelvis
  - 6 had single drainage: left axillary (2), right axillary (1), left inguinal (2), right inguinal (1).
  - 4 had multiple drainage pathways: left paravertebral + right axillary, right latero-toracic + right axillary, axillary bilateral, and one case had axillary bilateral and inguinal bilateral.

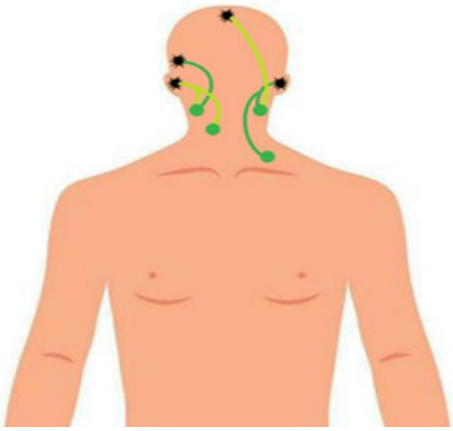


- 23 patients had a primary tumor located at the level of the upper limbs
  - in 22 cases, the drainage was predictable (axillary ipsilateral), except for one case (primary tumor on the right shoulder) with single right subclavicular drainage.

Table 3. **Cont'd**



- 27 patients had the primary tumor located at the level of the lower limbs
  - ➢ in 25 cases the drainage was predictable (inguinal ipsilateral), except for two cases where the drainage was multiple: left inguinal + left popliteal



- 4 patients had a primary tumor located at the level of the head: right temporo-occipital with right cervical drainage, left retroauricular with left cervical and left supraclavicular drainage, at the level of the scalp with left cervical drainage and right retroauricular with right cervical and right submandibular drainage

lymphatic drainage, which was demonstrated in our study and is present with similar results in the literature (*Table 4*).

The SLNB with a radioactive tracer technique has been implemented since 2003 at the Prof. Dr. A. Trestioreanu Oncology Institute in Bucharest and the 100% identification rate is explained by over 20 years of accumulated experience and excellent collaboration between the departments of surgery, nuclear medicine, and pathology (14). A meta-analysis of 66 studies, concluded that the sentinel lymph node identification rate in melanoma was 84% (59-100%) using vital dye, 99% (83-100%) using radioactive tracer, and 98% (98-98%) using the dual method (15). We chose the radioactive tracer method because it offers a high identification rate and is free from allergic reactions that can occur when dyes are used.

Table 4. Multiple lymphatic drainage basins data in cutaneous melanoma

Authors	No.of patiens	1 LDB	2 LDB	3 LDB	4 LDB
Uren (2003)	3059	1963 (64%)	803 (26%)	207 (7%)	62 (2%)
Kroon (2007)	561	499 (89%)	61 (11%)	1 (0.2%)	-
IOB (2022-2023)	104	76 (73.08%)	26 (25%)	1 (0.96%)	1 (0.96%)

Authors	No.of patients	1 LBD	>1 LBD
Federico (2008)	2060	1709 (83%)	351 (17%)
Manca (2008)	124	96 (77%)	28 (23 %)

SLNB is a key element in the diagnosis and treatment of cutaneous melanoma, even though false negative rates ranging from 5.6% to 21% were reported (16,17). A cause can be lymph node invasion, which disrupts lymphatic drainage and bypass these lymph nodes, causing the radioactive tracer to migrate through another lymphatic pathway. For this reason, it is important to excise also non-sentinel lymph nodes, enlarged, hard and especially black-gray nodes, a matter that depends on the surgeon's experience. It is important to take into consideration if the patient has tattoos, especially in the areas of skin drained by the lymphatic basin of interest as this could lead to misinterpretation of dyed lymph nodes (18). IHC examination of the lymph nodes is mandatory, and we demonstrated it's importance by the high number of settled cases: 8 with invasion and 2 without, that would be missclassified otherwise.

The fact that most patients required additional re-excision of the scar to obtain oncological resection margins (69.23%) indicates that in most cases, excisional biopsy of the lesion alone is not sufficient. Full depth WLE of primary tumors (with safety margins of 0.5 cm for in situ melanomas, 1 cm for tumors with a thickness of ≤ 2 mm and 2 cm for tumors thicker than 2 mm) is recommended (12). However, this should not suggest an escalation in biopsy size, since thin initial margins allow for a more precise injection for SLNB because it causes less disruption to lymphatic drainage; while in the case of a negative biopsy, unnecessary skin excision is avoided, which is especially important in areas with minimal skin reserves. If the safety margins were not obtained by the excisional biopsy, then we performed a WLE in the same time with SLNB. Diagnosis should be based on a full thickness complete excision with a minimal margin of clinically uninvolved skin, to permit accurate subsequent lymphatic mapping (12).

We had 21 patients with a Breslow index > 4.0 mm. The correlation between Breslow index and the incidence of positive SLN highlights the importance of this parameter as a prognostic factor (19). Among these 21 patients, 9 had positive lymph nodes. This is an important finding, as the previous indication for SLNB was a Breslow index < 4.0 mm and this would have ruled out 20% of the patients from our study. Moreover, 12 of the 21 patients didn't have lymph node invasion, which is a reasonable reason to perform SLNB for every patient diagnosed with cutaneous melanoma > T1b and clinically node negative.

CLND was performed in the same surgery at 5 patients because routine use is not recommended for all positive SLN patients when nodal observation is available (20).

The strengths of the study are that we conducted it in an experienced clinic, with a lot of patients in a short period of time and with a multidisciplinary team involved in treatment of cutaneous melanoma: surgical oncology, nuclear medicine, medical oncology and histopathology departments. The weakness was that we could not use blue dye, as it is not commercially regulated in our country and indocyanine green (ICG) because of the lack of equipment in our clinic at the moment of conducting the study.

For the upcoming period, we aim to implement SLNB using dual method: radioactive tracer (99mTc) and ICG for our patients diagnosed with cutaneous melanoma.

Conclusions

SLNB with a radioactive tracer is particularly useful for melanomas of the trunk, head, or neck due to their unpredictable lymphatic drainage, allowing us to detect the drainage basins. It also proves to have less false negative results for melanomas located at the level of the limbs. In the case of SLNB using just a dye, lymph nodes in the epitrochlear or popliteal regions can be missed. Routine intraoperative examination of lymph nodes is not recommended due to its limitations, the workload on pathology departments and the fact that even if positive nodes are identified, CLND is not always necessary. The excision of non-SLN in our study provided staging and therapeutic advantages. Positive non-SLN were identified even in patients with no

positive SLN. For those, omitting the excision of non-SLN would have resulted in staging failure. In conclusion, SLNB remains an indispensable technique in the context of cutaneous melanoma, offering valuable prognostic information. These benefits translate into selective surgery of the lymph nodes, providing optimized patient management by reducing the morbidity associated with extensive surgical interventions and ensuring a higher quality of life post-treatment.

Conflict of Interest and Source of Funding

The authors have no conflicts of interest to declare. The authors declared that this study has received no financial support.

Ethical Statement

All procedures involving human participants were in accordance with the ethical standards of the 1964 Helsinki Declaration and its later amendments.

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