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Peculiarities of Lymphatic Drainage in Cutaneous Malignant Melanoma: Clinical Experience in 75 Cases

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Rezumat

Particularități ale drenajului limfatic în melanoamele maligne cutanate: experiența clinică în 75 cazuri

În ultimii ani identificarea și biopsia ganglionului santinelă a devenit standard în tratamentul melanomului malign cutanat (MMC). Pentru aplicarea corectă a tehnicii și reducerea riscului de rezultate fals negative este obligatorie vizualizarea drenajului limfatic al tumorii primare cu evidențierea tuturor ganglionilor santinelă, indiferent de localizarea acestora.
Metodă: În Institutul Oncologic București, în decursul ultimilor 3 ani, s-a practicat limfadenectomie selectivă la 75 de pacienți cu melanom malign cutanat stadiul I și II (AJCC). Localizarea tumorii primare a fost la nivelul membrelor în 39 de cazuri și trunchiului în 36 de cazuri. La toți pacienții s-a practicat limfoscintigrafie prin injectare intradermică de Nanocoll, cu urmărirea în dinamica a migrării radiotrasorului pentru a putea surprinde eventualele localizări neobișnuite ale ganglionului santinelă.
Rezultate: Ganglionii santinelă au fost identificați în 100 % din cazuri. La 63 de pacienți din lotul studiat, tumora primară a drenat într-un singur bazin limfatic, iar la restul 12 a drenat în 2 sau mai multe bazine. Melanoamele maligne de la nivelul trunchiului au avut un comportament particular, prezentând drenaj multiplu într-o proporție mult mai mare de cazuri decât cele de la nivelul membrelor.
Concluzii: Melanoamele maligne ale trunchiului, mai ales cele situate în apropierea liniei mediane, dar nu numai, au tendința să dreneze în mai multe bazine limfatice. Existența ganglionilor intermediari și a drenajului limfatic atipic, în bazine minore, trebuie evidențiat preoperator pentru a putea biopsia toți ganglionii santinelă și a lua o decizie terapeutică corectă.

Cuvinte cheie: melanom malign cutanat, ganglion santinelă, limfoscintigrafie dinamică, drenaj limfatic multiplu

Abstract

In the recent years, the identification and biopsy of the sentinel lymph node (SLN) has become standard in the treatment of cutaneous malignant melanoma (CMM). In order to correctly apply the technique and to decrease the risk of false negatives, it is compulsory to track the lymphatic drainage of the primary tumor and to detect all SLN, regardless of their site.
Method: At the Bucharest Oncologic Institute, over the last three years, selective lymphadenectomy was performed in 75 patients with CMM, stages I and II (AJCC). In 39 cases, the primary tumor was at the level of the upper and lower limbs and in 36 on the trunk. In all patients, lymphoscintigraphy was performed through intradermal injection of Nanocoll, with dynamic follow up of the radiotracer, with the purpose of finding the possible unusual locations of the SLN.
Results: The sentinel lymph nodes were identified in 100% of the cases. In 63 patients (84%), the primary tumor drained in only one lymphatic field and in the other 12 the drainage was towards 2 or more lymphatic basins. The CMM situated on the trunk had a particular behaviour, presenting more often (33%) with multiple nodal basin drainage.
Conclusions: CMM of the trunk, mostly those situated close

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to the midline, but others as well, tend to drain into several lymphatic areas. The existence of interval lymph nodes and atypical lymphatic drainage, in a minor lymphatic basin, must be determined preoperatively in order to allow the biopsy of all SLN and establish the right therapy.

Key words: cutaneous malignant melanoma, sentinel lymph node, lymphoscintigraphy, multiple nodal basin drainage

Introduction

Malignant melanoma is the cutaneous neoplasm with the greatest mortality, being responsible for more than 73 % of the deaths assigned to skin cancers (1). An alarming increase in the number of new cases of disease had been noticed, with a percentage of 5-7 % annually, value surpassed only by the incidence of the pulmonary cancer in women (2). If the unpredictable evolution of this neoplasia is added to these worrying statistical data, we draw the whole picture of the disease and understand why the treatment of the cutaneous malignant melanoma (CMM) was subject to much controversy and still represents a challenge.

The treatment of CMM has been significantly modified in the past 20 years, passing from elective lymphadenectomy of the regional lymph nodes (considered standard for almost a century) to selective lymphadenectomy, described by Morton et al. in 1992 (3). This almost revolutionary change, which significantly improved the patient's quality of life, was possible due to development of lymphoscintigraphy.

The lymphatic drainage of the skin was intensely studied in the past centuries and minutely described by Sappey, in 1874, in his paper called "Anatomy, physiology and pathology of the lymphatic vessels in man and vertebrates". In the author's vision, the skin's lymphatic drainage is symmetrical and perfectly predictable, if one takes into consideration certain rules. Therefore, at the level of the trunk, the lymph vessels of the skin do not intersect the median vertical line, nor the theoretical horizontal line which passes anterior to the umbilicus and posterior to L2 (4). This presentation was rapidly accepted and applied in the consequent 100 years.

Along with the development of lymphoscintigraphy in the '50s, some of Sappey's affirmations were questioned. Thompson and Uren demonstrated that respecting Sappey's rules would lead to the incorrect appreciation of the lymphatic drainage in 30% of the patients with CMM (5). Lymphatic drainage of the skin is symmetrical and can be approximated with high probability only for the upper and lower limbs (6). Instead, the trunk, head and neck have a complex lymphatic net and a variable drainage, fact which requires the routine use of lymphoscintigraphy, that helps to determine the regional lymphatic basin (7).

After publishing the data from MSLT1 (8), the identification and biopsy of the sentinel lymph node (SLN) became a standard in the treatment of stage I and II CMM (9,10). Subsequent studies showed that the SLN status is the prognostic factor with the strongest impact on the survival of these patients, together with: the Breslow thickness, the number of mitoses/mm^2 and the ulceration of the primary tumor (11).

The definition of the SLN went through several phases, which paralleled the improvement of the procedure and the accumulation of experience in the field:

- the first lymph node that receives the lymph from the primary tumor (3);
- the closest lymph node to the primary tumor (12);
- any lymph node which directly receives an afferent vessel from the primary tumor (3,13);
- the lymph node which presents maximum radioactivity on the static images or after the measurement with the gamma probe – the hottest node (12);
- the first lymph node seen on the lymphoscintigraphic images (12,14);
- the blue-stained lymph node if the method implies vital blue dyes (14).

And the list may go on, which suggests that none of the above mentioned affirmations is complete and all allow interpretation. And then, how do we identify the SLN? Which of the above variants reflect with more accuracy the location of the SLN? Hard to tell because each definition contains traps.

A SLN is not necessarily the nearest lymph node to the primary tumor (15) and it is not always localized in the nearest lymph node basin (16), because the afferent lymph vessel may overpass several lymph nodes before entering the SLN. (15).

SLN is indeed the first lymph node visualised on the images taken dynamically, but it is not necessarily the only one. More distinct lymphatic channels may leave from the primary tumor and each of them may have different rate of lymph flow. Therefore, several SLN situated in the same area of lymphatic drainage or in different areas, may lately appear on lymphoscintigraphy, as the radiocolloidal solution arrives at their level.

There are situations in which the real SLN does not have the maximum radioactivity, or, even more weirdly, it is not radioactive at all. The more intriguing the affirmation, the simpler the explanation: the obstruction of the lymph vessels with tumor thrombi stops the migration of the radiocolloid on that lymphatic path (17). On the other hand, a massively tumor involved SLN loses its function of clear up and doesn't have the capacity to pick up the radiotracer any more. When only few normal macrophages remain in the SLN, this can not be visualized by lymphoscintigraphy (17).

Currently, the following definition of the SLN is accepted: the first lymph node (one or more) directly linked to the primary tumor through a lymph vessel, regardless of its site, radioactivity or the time elapsed until its identification through lymphoscintigraphy (13,17). This definition underlined the importance of the dynamic follow up of the tracer's migration from the place of injection, in order for all the afferent lymphatic collectors to be identified and consequently all SLN. Morton et al. consider that the number of afferent lymph vessels should equal the number of SLN (13), but one cannot

exclude the situation in which two different pathways end in the same lymph node.

In this paper we intend to present the cases of CMM with peculiar lymphatic drainage from our records, which represented a surprising and sometimes unpleasant discovery at lymphoscintigraphy.

Patients and Method

Between January 2009 - January 2012 in the Surgical Oncology Clinic no. 2 of Bucharest Oncologic Institute (IOB), 75 patients with CMM stages I and II were managed with lymphatic mapping (LM) and SLN biopsy (SLNB). In all cases the diagnosis was established through excisional biopsy of the skin tumor followed by its histopathological analysis. In 73 patients, the surgical procedure was performed in other hospitals, the patients being redirected to IOB in order to evaluate them and establish the appropriate treatment. In only two patients the excision of the primary tumor and SLNB were done during the same operative procedure, the remaining 73 being submitted to two consecutive interventions. For this latter patient group, the time elapsed between the excisional diagnostic biopsy and SLNB varied between 10 days and 4 months, with one exception, in which the technique was applied 7 months after the extirpation of the primary tumor.

Taking into account that in the majority of patients the SLNB was not done simultaneously with the wide excision of the primary tumor, an important detail for the accuracy of the procedure was represented by the modality of closing the surgical defect after the excisional biopsy and the dimensions of the postoperative scar. None of the patients required skin grafts or rotated flaps , the closure of the wound being possible per primam in all situations and the maximum scar length was 10 cm.

Malignant melanoma (MM) was localized on the trunk in 36 patients (48%), on the lower extremities in 23 patients (30.6%) and on the upper extremities, in 16 patients (21.3%). The Breslow index was greater than 1 mm in 72 patients, with a mean value of 2.8 mm and a maximum of 13 mm. In the 3 patients whose tumors had a thickness under 1 mm (0.4 / 0.46 / 0.9 mm), the procedure was nevertheless justified by a mitotic index $> 1/mm^2$.

All patients were staged according to AJCC 2002 criteria, and 2009, respectively (11). The clinical examination and the compulsory minimal investigations excluded the presence of distant metastases (chest radiography, abdominal ultrasound). According to the site of the MM, ultrasound of the lymph node basins (LNB), empirically considered to be involved, was performed in all patients. The decision to perform LM/SLNB was limited to the cases in which imaging did not raise a suspicion of malignancy.

The technique of SLNB at IOB

At the IOB, in order to identify and harvest the correct SLN, the two-steps technique is practiced: we start with preoperative lymphoscintigraphy, that helps us determine the lymphatic basin drainage, followed by the intraoperative search of the radioactive node with a handheld gamma rays detector (18). We didn't use vital blue dyes in any of the 75 patients (not having an authorized product on the market). In Romania, same as in the rest of Europe, we use Nanocoll which contains colloidal human albumin marked with Tc^{99}. The radiocolloids consisting of small size particles, between 5-50 nm, are preferred because they allow a better display of the lymphatic vessels and a satisfying capture at the level of the SLN (17). Nanocoll is composed of particles with variable dimensions, between 5 and 80 nm, which provide a median migration interval until the SLN of only 10 minutes and a half-life activity at the level of the lymph node of 7.5 hours (17).

In 70 patients, the LM was done in the afternoon of the day before the surgery with a maximum of 20 hours preoperatively. For the rest of 5 patients the radioactive substance was injected in the morning of the surgery day, minimum 6 hours beforehand.

The radiocolloid was injected intradermally at a distance of 0.5-1 cm from the postoperative scar. According to the size and site of the surgical scar, the established amount of radioactive substance was injected in minimally 2 points and maximum 6. For all MM situated at the level of the trunk, at least 4 stings were necessary, usually at the ends of the scar and in the middle of it, on one side and the other. Dynamic lymphoscintigraphy is compulsory to differentiate the SLN from the second echelon or third echelon nodes. Therefore in the first 20 minutes after injection we strongly recommend the tracking of the radiocolloid migration pathways with the emphasis of all afferent vessels and the corresponding lymph nodes. The procedure continues by acquiring static images every 15 -20 minutes in the first two hours from the injection. In the end we mark on the skin all SLN.

Results

The rate of SLN identification was 100%. In the majority of cases, at least 1 SLN was pointed out in the first minute after the intradermal injection of the radioactive substance, with the visualisation of other SLN on distinct pathways, in 3 min (2 cases), 5 min (2 cases), 15 min (1 case), 20 min (1 case) and 1 hour (1 case). There were situations in which the bilateral drainage was obvious from the first minute after injection (2 cases) – *Fig. 1*.

In 63 patients (84 %) the radiotracer migrated to only one lymphatic basin, in 10 patients in 2 lymphatic basin drainage (13.3%) and in 2 patients in 3 fields of lymphatic drainage (2.6%). MM situated on the extremities drained in a predictable way, in only one group of lymph nodes, ipsilateral axilla or groin, respectively. With regard to the tumors situated on the trunk, in only 2/3 of cases the afferent vessels were oriented towards only one regional lymphatic basin, suggested more or less by the site of the primary tumor. In the other 12 patients with MM situated near the body midline, the radiotracer migrated to more SLN from several LNB (2-3), some of which were unexpected and hard to anticipate (*Table 1*). With the exception of the intraabdominal ones, all other SLN were biopsied and analysed histopathologically.

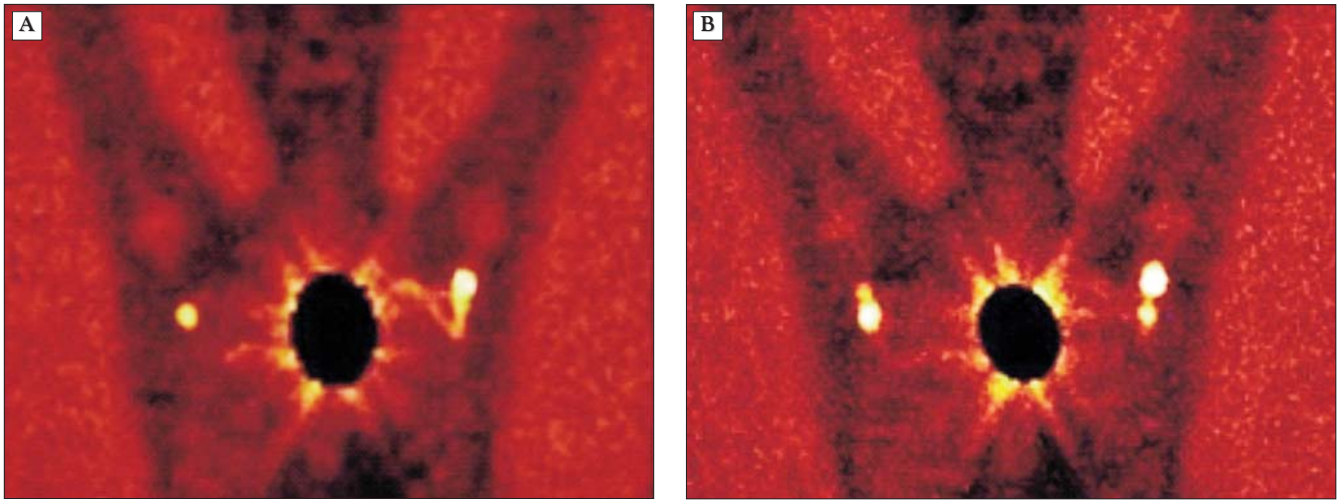


Figure 1. *Presternal MM stage T4b;* ***(A, B)*** *Anterior images: simultaneously bilateral axillary drainage in the first minute from the injection with the identification of one SLN in the left axilla and 2 SLN in the right axilla*

Discussions

Literature review on the theme pointed out that lymphatic drainage to multiple lymph node groups is relatively frequent and varies in according to the percentage of CMM localized on the trunk, head and neck. In *Table 2* we present the experience of some famous centers in the treatment of CMM regarding LM and multiple lymphatic drainage. The results obtained at the IOB are in line with the international ones.

These percentages change significantly if we take into discussion only the CMM localized on the trunk, as we see in *Table 3* (22,23,24,25).

There are certain locations (upper and lower limbs) for which the lymphatic drainage of the primary tumor is highly predictable, the afferent vessels go towards the nearest

Table 1. *The location of SLN in patients with multiple drainage (IOB database)*

Location of the CMM	No patients	Location of the SLN
Presternal	1	Axillary bilateral
Thoraco-dorsal (paramedian)	8	Axillary bilateral
Right Scapular	1	Right axillary, right paravertebral and left laterocervical
Left Scapular	1	Left axillary and left laterocervical
Epigastric (right paramedian)	1	Left intramammary, right interpectoral and left intraabdominal

Table 2. *Types of lymphatic drainage in CMM (15, 19, 20, 21)*

Authors	Patients	1 LNB	2 LNB	3 LNB	4 LNB
Uren et al. – 2003 (15)	3059	64 % (1963)	26 % (803)	7 % (207)	2 % (62)
Kroon et al. – 2007 (18)	561	89 % (499)	11 % (61)	0,2% (1)	---------
Federico et al. – 2008 (19)	2060	83 % (1709)	17 % (351) –to several lymph basins		
Manca et al. – 2008 (20)	124	77 % (96)	23 % (28) – to several lymph basins		
IOB	75	84 % (63)	13.3 % (10)	2.6 % (2)	----------

Table 3. *Lymphatic drainage in CMM of the trunk (22,23,24,25)*

Authors	Patients	1 lymphatic basin	≥ 2 lymphatic basins
Porter et al. – 2000 (21)	295	69 % (209)	31 % (86)
Jacobs et al. – 2003 (22)	120	68 % (81)	32 % (39)
Jimenez et al. – 2005 (23)	266	71 % (190)	29 % (76)
McHugh et al. – 2006 (24)	423	77 % (325)	23 % (98)
IOB	36	67 % (24)	33 % (12)

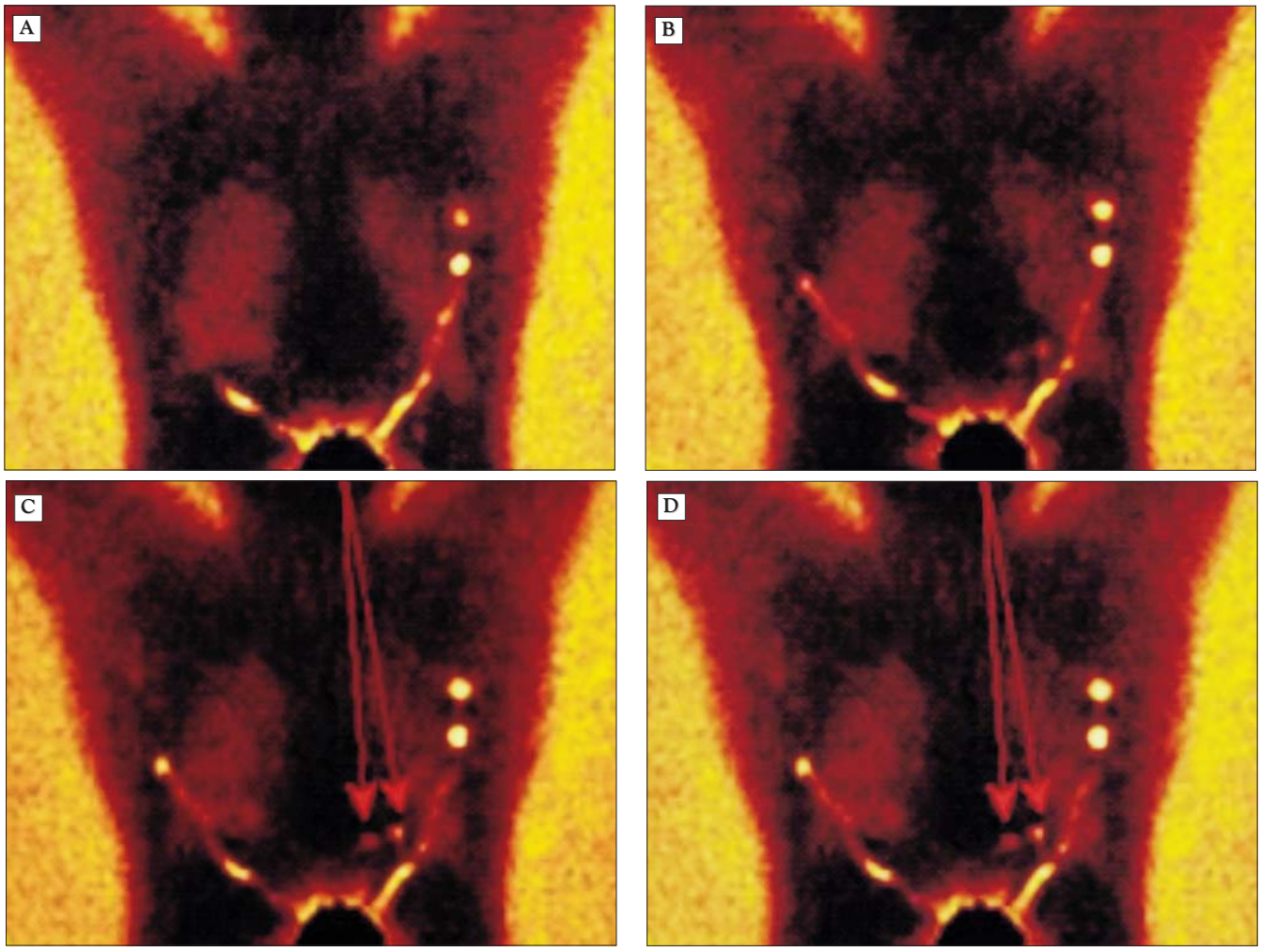


Figure 2. *Epigastric T4b MM:* ***(A)*** *Anterior dynamic image 1 minute after the injection with evidence of the left intramammary SLN;* ***(b)*** *Anterior image 6 minutes postinjection with emphasis of the right interpectoral SLN;* ***(C)*** *Anterior image 15 minutes postinjection with determination of the lymphatic drainage in the left paramedian epigastric region, superior to the scar;* ***(D)*** *Anterior static image 20 minutes later with visualization of the three SLN and other lymph nodes from the second echelon*

ipsilateral lymphatic basin, without draining simultaneously to other lymph fields or to interval lymph nodes (26). This affirmation is not true for MM of the trunk, mostly those situated near the midline.

In our statistic, in one patient with right paramedian epigastric MM, dynamic lymphoscintigraphy pointed out 3 distinct afferent channels, each of which ended at the level of an interval lymph node: left intramammary, right interpectoral and left intraabdominal, superior to the scar. In a preoperative intuitive analysis, none of the described locations was taken into account, assuming that a bilateral axillary drainage would probably appear. But surprise! The scenario didn`t come true. Without lymphoscintigraphy none of the true SLN would have been biopsied (*Fig. 2*).

Another interesting case was that of a patient with a left scapular MM whose lymphatic drainage was expected to be to the left axilla. Dynamic lymphoscintigraphy revealed a simultaneous lymphatic drainage to the left axilla and left paravertebral area (*Fig 3*). The histological analysis of the 2 SLN discovered melanic cells only in the paravertebral lymph node. In the era of elective lymphadenectomy, we would have performed left axillary lymphadenectomy which not only would have been useless, but would have led to a wrong postoperative treatment decision.

We encountered a similar situation in a patient with right scapular MM that drained into three distinct lymphatic basins, all of which were hardly predictable: right axillary, right paravertebral and left laterocervical (*Fig. 4*). And the only invaded lymph node was the paravertebral one!

The impact of multiple drainage on the survival of patients with CMM is an intensely debated subject without it being possible to draw a conclusion. The existence of multiple drainage vessels towards the same lymphatic basin or towards multiple basins is considered a risk factor for relapse and metastasis because the presence of multiple afferent collectors could ease the metastatic process (22,24,27). This is nevertheless contradicted by other studies in which the identification of several lymph nodes, in distinct lymph areas, didn't change the

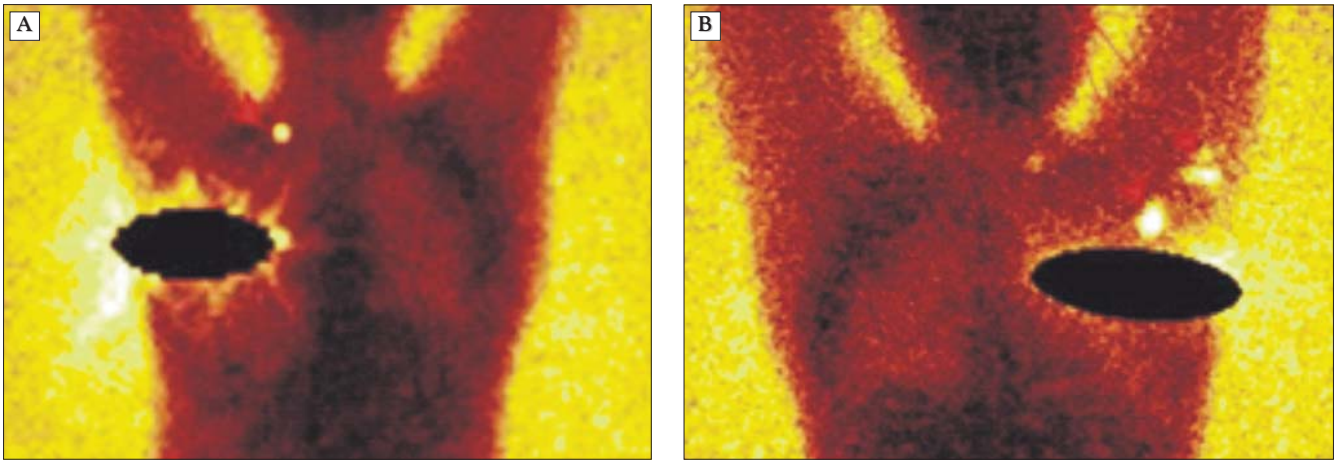


Figure 3. *Left scapular MM T4b:* ***(A)*** *Posterior image which points out the left paravertebral SLN, superior to the primary lesion, 1 minute after the injection;* ***(B)*** *Anterior image 10 minutes after the injection with the visualization of the left axillary lymph node*

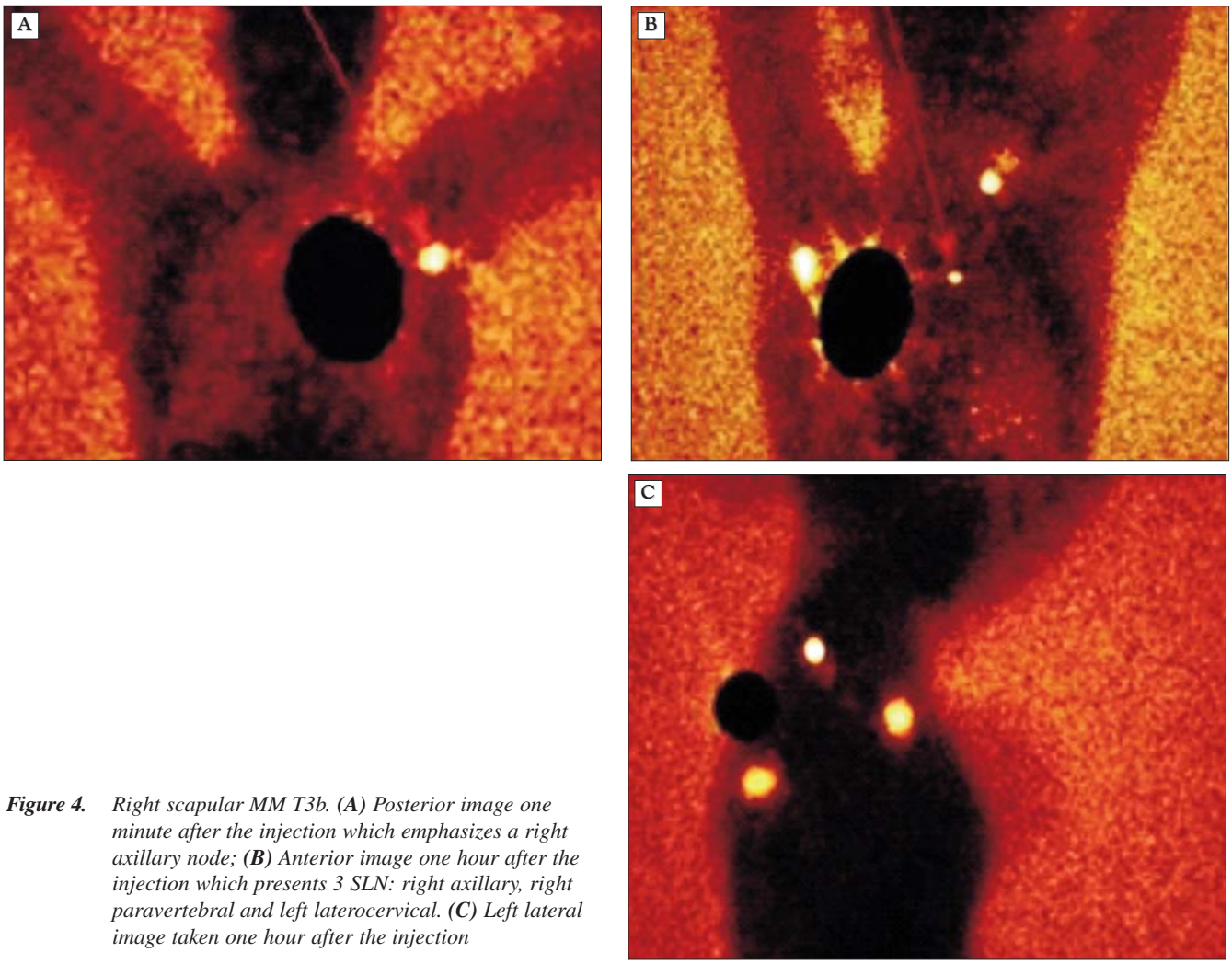


Figure 4. *Right scapular MM T3b.* ***(A)*** *Posterior image one minute after the injection which emphasizes a right axillary node;* ***(B)*** *Anterior image one hour after the injection which presents 3 SLN: right axillary, right paravertebral and left laterocervical.* ***(C)*** *Left lateral image taken one hour after the injection*

overall survival rate, nor the disease free survival (23,25). As in our statistic there is a relatively small number of cases with multiple drainage, we cannot give an opinion in this respect.

Conclusions

The SLNB should be recommended to all patients with clinically stage I and II malignant melanoma, which have an estimated risk of regional lymph nodes metastases of at least 10 % (10,11).

Both the cases presented above and the medical literature lead to an obvious conclusion: lymphatic drainage of the skin is unpredictable and can differ from patient to patient, even for tumors having the same location (15).

The disposition of the lymph vessels may not respect Sappey's classical description in variable percentages, leading to as many as 34% of cases with unexpected paths (26). This is why dynamic lymphoscintigraphy, which allows the visualisation of all afferent vessels and the follow up of their routes, is essential to the correct identification of the SLN (the differentiation of the first lymph node from secondary ones and also the presence of interval lymph nodes). The SLN with unusual locations, less encountered and known, are not to be ignored, because sometimes they can be the only ones invaded by the neoplasm.

The recommendation is to take out and analyse all SLN discovered because the histopathological status of a lymph node from a lymph basin doesn't offer information about the histopathological status of other lymphatic fields in case of a MM with multiple drainage (22,23). On the other hand, the discovery of malignant cells in a SLN with atypical location, distantly from the primary tumor, for instance in the retroperitoneum, although it may seem odd, doesn't mean stage IV, because it represents loco-regional disease, hence stage III.

Knowledge of all these technical details is essential in order to correctly stage the patients with CMM and accurately establish the treatment strategy, the prognosis and the post-treatment follow-up. We consider that dynamic lymphoscintigraphy is a key step in the procedure of the SLNB, because it provides additional information with regard to the lymphatic drainage of the primary tumor, that can not be given by static images, thus permitting the proper identification of the SLN.

Conflict of interest

The authors have no conflict of interest to declare.

References

1. Swetter S. Cutaneous Melanoma. Feb 2012; Available from: http://emedicine.medscape.com/article/1100753-overview#a0199(accessed Apr.2012)
2. Tan W. Malignant Melanoma. Apr.2012; Available from: http://emedicine.medscape.com/article/280245-overview#a0156(accessed Apr.2012)
3. Morton DL, Wen DR, Wong JH, Economou JS, Cagle LA, Storm FK, et al. Technical details of intraoperative lymphatic mapping for early stage melanoma. Arch Surg. 1992;127(4): 392-9.
4. Sappey MPC. Anatomie, Physiologie, Pathologie des Vaisseaux Lymphatiques consideres chez L'homme at les Vertebres. Paris: A. Delahaye et E. Lacrosnier; 1874.
5. Thompson JF, Uren RF. Lymphatic mapping in management of patients with primary cutaneous melanoma.
6. Reynolds HM, Walker CG, Dunbar PR, O'Sullivan MJ, Uren RF, Thompson JF, et al. Functional anatomy of the lymphatics draining the skin: a detailed statistical analysis. J Anat. 2010; 216(3):344-55.
7. Amersi F, Morton DL. The role of sentinel lymph node biopsy in the management of melanoma. Adv Surg. 2007;41:241-56.
8. Morton DL, Thompson JF, Essner R, Elashoff R, Stern SL, Nieweg OE, et al. Validation of the accuracy of intraoperative lymphatic mapping and sentinel lymphadenectomy for early-stage melanoma: a multicenter trial. Ann Surg. 1999;230(4):453-63.
9. Bichakjian CK, Halpern AC, Johnson TM, Foote Hood A, Grichnik JM, Swetter SM, et al. Guidelines of care for the management of primary cutaneous melanoma. American Academy of Dermatology. J Am Acad Dermatol. 2011;65(5): 1032-47.
10. NCCN Guidelines Version 3.2012 Melanoma http://www.nccn.org/professionals/physician_gls/pdf/melanoma.pdf (accessed 02.2012)
11. Balch CM, Gershenwald JE, Soong SJ, Thompson JF, Atkins MB, Byrd DR, et al. Final version of 2009 AJCC melanoma staging and classification. J Clin Oncol. 2009;27(36):6199-206.
12. Nieweg OE, Tanis PJ, Kroon BB. The definition of a sentinel node. Ann Surg Oncol. 2001;8(6):538-41.
13. Bagaria SP, Faries MB, Morton DL. Sentinel node biopsy in melanoma: technical considerations of the procedure as performed at the John Wayne Cancer Institute. J Surg Oncol. 2010;101(8):669-76.
14. Morton DL, Bostick PJ. Will the true sentinel node please stand? Ann Surg Oncol. 1999;6(1):12-4.
15. Uren RF, Howman-Giles R, Thompson JF. Patterns of lymphatic drainage from the skin in patients with melanoma. J Nucl Med. 2003;44(4):570-82.
16. Intenzo CM, Kim SM, Patel JI, Lin HC, Kairys JC. Lymphoscintigraphy in cutaneous melanoma: a total body atlas of sentinel node mapping. Radiographics. 2002;22(3): 491-502.
17. Chakera AH, Hesse B, Burak Z, Ballinger JR, Britten A, Caracò C, et al. EANM-EORTC general recommendations for sentinel node diagnostics in melanoma. Eur J Nucl Med Mol Imaging. 2009;36(10):1713-42.
18. Bordea C, Plesca M, Condrea I, Gherghe M, Gociman A, Blidaru A. Occult breast lesion localization and concomitant sentinel lymph node biopsy in early breast cancer (SNOLL). Chirurgia (Bucur). 2012;107(6):722-9.
19. Kroon HM, Lowe L, Wong S, Fullen D, Su L, Cimmino V, et al. What is a sentinel node? Re-evaluating the 10% rule for sentinel lymph node biopsy in melanoma. J Surg Oncol. 2007; 95(8):623-8.
20. Federico AC, Chagpar AB, Ross MI, Martin RC, Noyes RD, Goydos JS, et al. Effect of multiple-nodal basin drainage on cutaneous melanoma. Arch Surg. 2008;143(7):632-7.
21. Manca G, Romanini A, Pellegrino D, Borsò E, Rondini M, Orlandini C, et al. Optimal detection of sentinel lymph node metastases by intraoperative radioactive threshold and molecular analysis in patients with melanoma. J Nucl Med. 2008;49(11): 1769-75.

22. Porter GA, Ross MI, Berman RS, Lee JE, Mansfield PF, Gershenwald JE. Significance of multiple nodal basin drainage in truncal melanoma patients undergoing sentinel lymph node biopsy. Ann Surg Oncol. 2000;7(4):256-61.
23. Jacobs IA, Chang CK, Salti GI. Significance of dual-basin drainage in patients with truncal melanoma undergoing sentinel lymph node biopsy. J Am Acad Dermatol. 2003;49(4):615-9.
24. Jimenez RE, Panageas K, Busam KJ, Brady MS. Prognostic implications of multiple lymphatic basin drainage in patients with truncal melanoma. J Clin Oncol. 2005;23(3):518-24.
25. McHugh JB, Su L, Griffith KA, Schwartz JL, Wong SL, Cimmino V, et al. Significance of multiple lymphatic basin drainage in truncal melanoma patients undergoing sentinel lymph node biopsy. Ann Surg Oncol. 2006;13(9):1216-23.
26. Statius Muller MG, Hennipman FA, van Leeuwen PA, Pijpers R, Vuylsteke RJ, Meijer S. Unpredictability of lymphatic drainage patterns in melanoma patients. Eur J Nucl Med Mol Imaging. 2002;29(2):255-61.
27. Wall JK, Florero M, Accortt NA, Allen R, Kashani-Sabet M, Morita E, et al. Impact of multiple lymphatic channel drainage to a single nodal basin on outcomes in melanoma. Arch Surg. 2007;142(8):753-7.