

Is 0.75mm Breslow thickness the correct cut-off point for performing sentinel node biopsy in patients with melanoma?

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Abstract

Currently, in patients with malignant melanoma there is no clear cut-off point of Breslow thickness in order to avoid unnecessary lymph node excision surgery, without missing metastatic nodes. *We retrospectively studied* a cohort of 64 patients, with pathologically proven malignant melanoma, who underwent lymph node scintigraphy and surgical resection of the sentinel node, during the last two years. The patients were divided into 5 groups: Group 1: Ten patients, mean age 46±6 years (range 40-55 years), with Breslow thickness of the lesion 0.51-0.75mm. Group 2: Eleven patients, mean age 41±9 years (range 31-61 years), with Breslow thickness 0.76-1mm. Group 3: Twelve patients, mean age 59±12 (41-76 years), with Breslow thickness 1.01-1.25mm. Group 4: Fourteen patients, mean age 61±8 (38-74 years), with Breslow thickness 1.26-1.5mm. Group 5: Seventeen patients, mean age 56±10 (32-71 years), with Breslow thickness >1.5mm. *We found* only seven infiltrated sentinel lymph nodes. From these, 3 patients belonged to the 5th group (Breslow>1.5mm), two patients to the 4th group (Breslow 1.26-1.5mm), one patient in the 3rd group (Breslow 1.01-1.25mm) and one patient to the 2nd group (Breslow 0.76-1mm). Since there was no positive sentinel lymph node in any patient with Breslow thickness less than < 0.75mm, *we conclude* that sentinel lymph node biopsy in patients with Breslow thickness less than < 0.75mm may not be useful and might not be carried out, except in high risk cases such as melanomas with ulceration, high mitotic rate and vertical growth phase.

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Introduction

Cutaneous malignant melanoma (MM) is a malignant transformation of melanocytes which is responsible for almost 7500 deaths in the United States each year [1]. Annually, 40,000 new cases are diagnosed and MM represents 5% of all new cancer cases [2]. Primary MM of the head and neck represents 25% to 40% of the total MM count, despite the fact that the head and the neck represent just 9% of the whole body surface [3]. Nowadays, Breslow classification and Clark level are used for tumor staging, by estimating tumor thickness (Breslow) and dermal invasion (Clark) [4]. Alexander Breslow was the first who suggested the measurement of the thickness of a lesion from the skin surface to the deepest point of invasion as a prognostic factor in cutaneous MM [5]. Clark level has a significant correlation with certain categories of thickness and adds prognostic information especially for thin MM [6].

It is well known that patients with thin lesions (<1mm) almost always have only localized disease, whereas patients with thick lesions (>4mm) have 60% risk for regional metastases and 80% risk for distant metastases within 3 years [7]. In another study using sentinel node (SN) biopsy, positive sentinel nodes were found in 1% of MM <1mm and in 5% of MM between 1 and 2mm [8].

Lymphoscintigraphy was introduced in 1953 by Sherman and Puggosian [9] and has proven quite reliable in predicting cutaneous lymphatic flow. In 1992 Morton et al [1] validated the sentinel node concept in MM patients, using intradermal injection of blue dye. In 1993 Alex et al [10] performed lymphoscintigraphy with technetium-99m sulfur colloid, in order to identify lymphatic routes and sentinel nodes for surgical localization. Today, sentinel node lymphoscintigraphy (SNL) remains the procedure of choice for detecting lymph node involvement by cutaneous MM. The use of positron emission tomography (PET) using ¹⁸F-FDG proved to be inadequate in identifying microscopic nodal metastases and metabolic imaging is not recommended as a first-line imaging strategy for staging regional lymph nodes in patients with stage I or II MM [11].

The aim of this study was to identify if 0.75mm Breslow thickness is the correct cut-off point for performing sentinel node biopsy in patients with melanoma.

Subjects and methods

We retrospectively studied a cohort of 64 patients, with MM, who underwent SLN biopsy in our Department of Nuclear Medicine and surgical resection (SR) of the SLN in the Department of Plastic Surgery, during the last three and a half years from 01/2006 to 07/2009. The patients were divided into 5 groups: Group 1: Ten patients, with mean age 46±6 years (range 40-55 years old), with Breslow thickness of the lesion 0.51-0.75mm. Group 2: Eleven patients, with mean age 41±9 years (range 31-61 years old), with Breslow thickness 0.76-1mm. Group 3: Twelve patients, with mean age 59±12 (41-76 years old), with Breslow thickness 1.01-1.25mm. Group 4: Fourteen patients, with mean age 61±8 (38-74 years old), with Breslow thickness 1.26- 1.5mm. Group 5: Seventeen patients, with mean age 56±10 (32-71 years old), with Breslow thickness >1.51mm.

On the day of surgery, 14.8MBq of ^{99m}Tc-albumin nanocolloid (GE Healthcare, Salugia, Italy) was injected intradermally through a 27-gauge needle into four quadrants around the biopsy scar. The injection site was prepared with povidone (Betadine) and alcohol. Each injection volume ranged from 0.1 to 0.8mL.

Planar dynamic images of the area and surrounding lymphatic drainage basins were acquired using a scintillation two head gamma camera (ADAC-Philips Genesys), 30 sec/frame in a 128X128 matrix for a total of one hour. Dynamic imaging began immediately after injection and continued sequentially in real time until all lymph nodes were identified. Transit time of the radiocolloid from the injection site to the lymph nodes was usually 20min after injection. After the termination of the examination, we marked the sentinel nodes using a permanent skin marker and the patients were sent immediately to the operating room for excision and biopsy of the sentinel node as detected by a surgical probe (Fig. 1 and Fig. 2). By means of an ocular micrometer, the maximal thickness of the lesion was measured from the skin surface to the deepest point of invasion, in order to be classified according to the Clark classification. The Breslow thickness was estimated by an experienced pathologist on all the specimens, using a calibrated eyepiece micrometer.

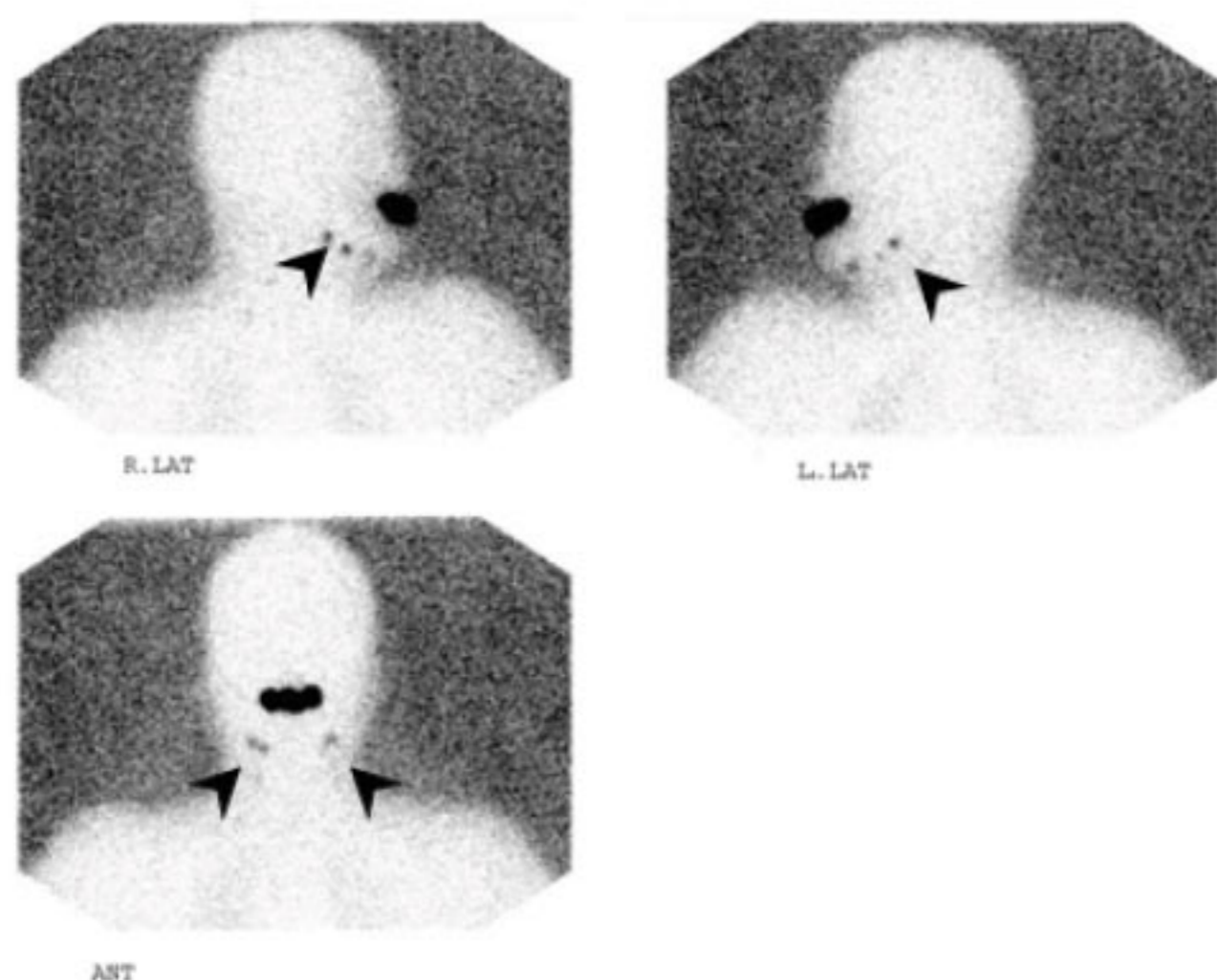


Figure 1. Lymphoscintigraphy of a patient with head MM (lower lip). A cobalt source is located under the patient, to delineate the contour of the body. Three submandibular lymph nodes are localized (arrowheads).

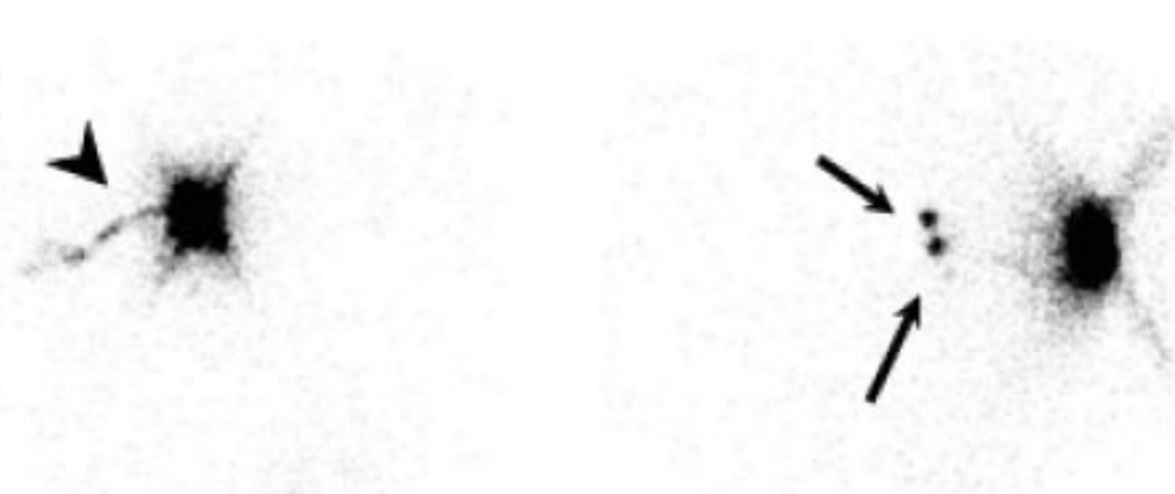


Figure 2. Lymphoscintigraphy of a patient with thigh MM. Two inguinal lymph nodes are localized (arrows), with the adjacent lymph vessels (arrowhead).

Results

Of the 64 cases studied, a positive for MM invasion SLN was identified in 7 cases. From these, three patients belonged in the 5th group (Breslow >1.5mm), two patients to the 4th group (Breslow 1.26-1.5mm), one patient belonged to the 3rd group (Breslow 1.01-1.25mm) and one patient belonged to the 2nd group (Breslow 0.76-1mm). There was no patient with Breslow less than 0.75mm having positive SLN (Table 1).

The results brought some skepticism about the necessity for performing LNS localization in patients with Breslow classification less than 0.75mm.

Table 1. Distribution of patients according to positive SLN and Breslow thickness

Breslow	Patients	Percentage	(+) SN ^a	Percentage
0.51 - 0.75mm	10	15.6%	0	0%
0.76 - 1mm	11	17.3%	1	9%
1.01 - 1.25mm	12	18.7%	1	8,3%
1.26- 1.5mm	14	21.6%	2	14%
>1.5mm	17	26.6%	3	17%
Total	64	100%	7	11%

^a (+) SN: Positive for metastases sentinel node

We note that the patient of the 2nd group, with positive SLN and Breslow thickness 0.96mm, was classified as IV Clark stage.

Discussion

Melanoma has an unpredictable clinical course and the risk of occult nodal metastasis increases in parallel to the thickness of the primary tumor [12]. The Clark level has been used to describe the anatomic involvement of the tumor within the cutaneous and subcutaneous structures [13]. Level I is the intraepidermal growth of MM with intact basement membrane, level II is the invasion of the papillary dermis, level III is tumor involvement filling the papillary dermis and also involvement of the junction between the papillary and reticular dermis, level IV is invasion of tumor cells into the reticular dermis, and level V invasion into the subcutaneous fat. Breslow, on the other hand, combines Clark's criteria with the stage of invasion (depth of invasion in mm) [5]. Today, Clark level is found to be most predictive of survival in thin (<1mm) melanomas and it is part of the staging system only in

patients with such lesions. It is well known that lesions with a thickness less than 1mm carry a metastatic risk of <5%, while the metastatic risk increases by 30% to 50% when the lesions are thicker than 1mm [14]. Sentinel node is the first node that in theory receives drainage from the primary tumor site, even though some exceptions do exist [15, 16].

Sentinel node biopsy can predict lymph node involvement, according to microanatomic location of metastasis into the sentinel node parenchyma [17], while reduces the morbidity associated with extensive surgical intervention and is advantageous over elective lymphadenectomies because the node can be individually excised, at a much lower cost. Others studied 274 melanoma cases with SLN [14]. The percentage of SLN-positive patients varied according to the primary thickness, from 11.8% in patients with Breslow of 2mm or lower, to 34.7% in patients with Breslow from 2 to 4mm, up to 55.9% in patients with Breslow greater than 4 mm ($P<0.001$). Only two patients with Breslow thickness lower than 1mm had positive SLN biopsy. Others investigated 2250 cases of melanoma, with 235 positive nodes [18]. All patients were classified as Clark III and higher, and all appeared with a Breslow thickness >1mm. Others investigated 348 patients with malignant melanoma [19]. In melanomas thinner than 0.90mm, no positive SN was found (95% confidence interval 0-5%).

Finally Solari et al on 2009 [20] studied 88 patients with cutaneous melanoma using SLN lymphoscintigraphy. They found 23 nodes with metastasis and none with a Breslow thickness <1mm. The overall concept, based on the above studies, is that the thinner the lesion is, the smaller the possibility of having metastasis at the sentinel nodes. All previous studies suggest that the cut off for performing sentinel node biopsy may be set on 1mm of Breslow thickness. Only one study, suggests a cut off point of Breslow thickness to 0,7mm [21]. There are studies which can not reliably set the cut off value at the above mentioned 1mm Breslow thickness, in order to avoid SLN scintigraphy and biopsy. On the contrary, others found in 409 patients with cutaneous melanoma less than 1mm in thickness having 20 lymph nodes with micrometastases [22]. In another study, 71 melanoma patients with <1mm lesion thickness revealed four positive for metastasis nodes [23]. Nodal metastases have also been described in melanomas of <0.75mm thickness. Stitzenberg and his colleagues [24] noted 3 patients from a cohort of 146, while Kesmodel [25] found only one positive patient among 91 lesions. Based on the above findings, the Moffit Cancer Center seems to be reluctant for performing sentinel node biopsy in Breslow thickness between 0.75-1.00mm [22]. In all the above mentioned studies, the incidence of positive sentinel nodes within thin (<0.7mm) lesions may exist, but all of them concern patients with high Clark level classification, with regression, or with high mitotic rate >1/mm². In order to refine the criteria for performing SLN scintigraphy and biopsy, others applied the Shields' index in 102 malignant melanoma patients with more than five years follow-up [26]. Others proposed that lymphatic density, Breslow thickness and the presence or absence of lymphatic invasion combined together, can serve as a prognostic index of metastasis [27, 28]. Using the above Shields' index, the authors suggested that sentinel lymph node biopsy could be targeted more towards those patients with thin melanomas.

In our study, only one metastatic node was found, in a patient with Clark level IV disease and with a lesion

thickness of 0.96mm. At the group I, with Breslow thickness less than 0.75mm, all samples proved to be without any tumor invasion and thus we support the hypothesis of setting the cut-off point for performing sentinel node biopsy to 0.75mm. If we consider the statement, mentioned by other investigators [29], who estimated an additional cost for performing sentinel node biopsy in all melanomas patients with <1mm thickness of more than \$900,000 per positive node, one can imagine where this cost would be raised, if the procedure would be carried out in lesions smaller than 0.75mm.

In conclusion, an SLN biopsy in patients with Breslow thickness of less than <0.75mm may not be useful and might not be carried out, except in high risk cases such as melanomas with ulceration, Clark level IV, high mitotic rate and vertical growth phase, or high Shields' index [22, 26, 30-33]. Using the above mentioned criteria, we can achieve a lower health care cost, with minimal nodal metastasis risk. Since there is still no agreement on this issue between the authors, we hope that the forthcoming guidelines will be more precise and helpful at the everyday care of these patients.

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