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Diagnostic biopsy of cutaneous melanoma, sentinel lymph node biopsy and indications for lymphadenectomy

Pavlidis ET *et al.* Diagnostic biopsy of cutaneous melanoma

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Abstract

The incidence of cutaneous melanoma appears to be increasing worldwide, and this is attributed to solar radiation exposure. Early diagnosis is a challenging task. Any clinically suspected lesion must be assessed by complete diagnostic excision biopsy (margins 1-2 mm); however, there are other biopsy techniques that are less commonly used. Melanomas are characterized by Breslow thickness as thin (< 1 mm), intermediate (1-4 mm) and thick (> 4 mm). This thickness determines their biological behavior, therapy, prognosis and survival. If the biopsy is positive, a wide local excision (margins 1-2 cm) is finally performed. However, metastasis to regional lymph nodes is the most accurate prognostic determinant. Therefore, sentinel lymph node biopsy for diagnosed melanoma plays a pivotal role in the management strategy. Complete lymph node clearance has undoubted advantages and is recommended in all cases of positive SLN biopsy. A PET-CT (positron emission tomography-computed tomography) scan is necessary for staging and follow-up after treatment. Novel targeted therapies and immunotherapies have shown improved outcomes in advanced cases.

Key Words: Surgical oncology; Malignant melanoma; Skin cancer; Cutaneous melanoma; Sentinel lymph node biopsy; Complete lymph node dissection

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Core Tip: The value of excision biopsy for the initial diagnosis of melanoma in every suspected cutaneous lesion is important. In positive cases, the roles of sentinel node biopsy and subsequent complete lymph node dissection, along with adequate margin excision of the primary lesion site, are evaluated to improve the prognosis. Novel biological agents and molecular factors will open new horizons for future management policy.

⁹
TO THE EDITOR

We read with great interest the recent paper by Koumaki *et al*^[1] and we would like to congratulate the authors for their excellent trial on melanoma and atypical mole syndrome, which impressed us. This study is meticulous and arduous work that describes, for the first time, many details about the demographic and clinical characteristics of 121 patients. We absolutely agree with the authors that photoprotection education is required to prevent skin cancer development. Taking this opportunity, this paper presents some thoughts and observations from a surgical point of view on the latest developments in biopsy for the diagnosis of suspected primary lesions and the role of sentinel lymph node biopsy and the subsequent prophylactic or therapeutic lymphadenectomy.

¹ The incidence of cutaneous melanoma has steadily increased over the past years. It has been estimated that this increase in the United States has reached up to 3% per year. However, most cases with early-stage disease (I and II) usually have a favorable prognosis^[2]. The eighth edition of the American Joint Committee on Cancer (AJCC) staging system is the most widely used standard for the staging and classification of melanoma^[2-4]. Cutaneous lesions with macroscopic features that raise the suspicion of melanoma can be used as an alternative for changes in color, outline, bleeding, rapid increase in size, nodular growth, and ulceration.

Biopsy and histological examination will initially confirm the diagnosis and determine the stage of the disease, the extent of surgical resection and the management of the sentinel lymph node (SLN). The types of biopsy might be excisional, incisional,

shave biopsy (superficial or deep scallop) or punch biopsies^[5]. The most preferred excisional biopsy is reliable for defining the T stage in TNM staging. It resects the lesion beyond its margins to an extent of 1-3 mm according to NCCN (National Comprehensive Cancer Network) guidelines or 1-2 mm according to AJCC guidelines. This limit is crucial, given that avoiding lymphatic destruction ensures feasible detection of sentinel lymph nodes^[6-8]. The other types of biopsy can potentially lead to misdiagnosis and inaccurate staging. The incisional biopsy removes a small part of the lesion for cosmetic reasons. It is indicated for large lesions of more than 2 cm in diameter that are mainly located on the face.

In a positive biopsy of the initial evaluation of the suspected skin lesion, ³sentinel lymph node biopsy (SLNB) follows. This ¹⁵is because ²the involvement of regional lymph nodes is considered an important prognostic factor for survival. SLNB is indicated by the current ²data, and 15% to 20% of patients have regional node metastasis^[9]. In addition, ²the presence or absence of nodal micrometastases is the most important prognostic factor early-stage melanoma, particularly in intermediate thickness melanoma^[10]. Thus, SLNB is considered the standard of care and has high diagnostic value. It is a minimally invasive procedure ¹with a low complication rate^[9,11]. The ¹detection of sentinel lymph nodes is performed either 24 h preoperatively by Tc-99 administration and the use of a gamma probe or intraoperatively by methylene blue administration. Moreover, their combination can be used. A positive SLNB results in completion lymph node dissection (CLND). This process provides adequate regional disease control and has an indication for adjuvant chemotherapy^[11]. A negative SLNB has a minimal likelihood of metastasis. The final CLND biopsy ensures accurate staging and prognosis. ¹⁶Furthermore, CT (computed tomography) and PET (positron emission tomography) scans contribute to staging by defining the M (distant metastasis)^[12]. ⁴However, the prognosis is influenced by disease progression^[13].

⁴The incidence of nodal metastases clearly depends on the thickness of the primary melanoma. Lesions more than 1 mm in thickness ⁴are more likely to have metastases in the sentinel node, and lesions between 1 mm and 2 mm only have metastases in the

sentinel node. However, lesions more than 2 mm in thickness have metastases in additional lymph nodes and distant metastases^[9]. According to the excision biopsy, when the depth of invasion (Breslow thickness) is less than 1 mm, or from others, less than 0.75 mm, then the positive SLNB will be less than 5%. An exception to this rule is the mitotic index (≥ 1 mitoses/mm²), especially in cases with a Breslow thickness between 0.75 mm and 0.99 mm. The rate of false-negative SLNB reached 1.5% to 4.1%^[11].

In the case of early-stage (pT1b, pT2a) melanoma with sentinel node micrometastases, when the deposits are less than 0.3 mm in maximum diameter, no adjuvant treatment will be necessary. Otherwise, when they are equal to or more than 0.3 mm, adjuvant systemic therapy could be beneficial^[14].

The final differential diagnosis between melanoma and dysplastic nevus is made by histopathology. A molecular assay would be of value for early-stage lesions, but thus far, there is no such test^[15].

PET-CT has the greatest diagnostic accuracy both for staging and follow-up. However, for the latter, the currently used immunotherapy can create various organ side effects; thus, radiologists should be aware of this^[12].

The dataset of dermoscopic images is a useful tool for the early detection of skin cancer^[16]. Ultrasound-guided fine needle aspiration cytology (FNAC) and core needle biopsy (CNB) can be used for the detection of subcutaneous or lymph node metastases^[17]. Melanomas can be diagnosed in early stages (50%). They are more commonly located on the extremities in women and on the back in men. On the lower limbs, they can be more invasive and are without sex differences^[18].

Current recommendations indicate complete excision biopsy to avoid residual disease in the complementary resection after partial excision biopsy. However, this treatment does not influence survival^[19]. A recent large, retrospective study found that SLNB was more likely to be indicated for a Breslow depth >1 mm or mitotic rate ≥ 1 /mm². It was less likely to be indicated in patients of older age (> 75 years old) and those without an extremity location^[20].

The prognostic value of complete lymph node dissection (CLND) after positive SNDB vs observation and therapeutic lymph node dissection (TLND) has been evaluated^[21], despite the initial aspect of a nonsignificant difference between them^[22]. A large, retrospective study from Italy including 2086 patients after CLND for lymph node involvement found improved survival. The 3-year survival was 79%, the 5-year survival was 70%, and the 10-year survival was 54%^[23]. The preliminary results indicated that the clinicopathologic information (thickness, mitoses, age, and Breslow thickness 2 mm) and gene expression profiling (CP-GEP) were independent predictive factors for lymphatic metastases^[24]. Similarly, 31-gene expression profiling (i31-GEP-SLNB) has become commercially available^[25]. A vitamin D level < 9.25 ng/mL is another negative independent prognostic factor for survival. It is associated with ulceration formation in melanoma^[26].

A stage-based follow-up scheme has recently been proposed by the European consensus for melanoma^[27].

Tilmanocept, a CD206 receptor-targeted novel radiotracer, has recently been introduced for lymphoscintigraphy to assess nodal mapping^[28].

Adequate margin excision (1-2 cm, depending on the invasion depth) has been the standard therapy, despite the de-escalation of its extent, together with SLNB^[10,29]. Targeted therapy and immunotherapy have further improved the prognosis^[30].

In conclusion, SLNB is indicated for melanoma stage IB (T1b ≤ 1 mm, ulceration, and mitoses >1 mm²) and stage II. In positive cases, CLND is required instead of TLND. SLNB offers staging accuracy and has indications for adjuvant therapy. Thus, it can improve prognosis and survival. New diagnostic modalities and immunotherapies will contribute further to improved outcomes.

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