

Sentinel node biopsy should not be recommended for patients with thick melanoma

A biópsia de linfonodo sentinela não deve ser recomendada para pacientes portadores de melanoma espesso

RENATO SANTOS DE OLIVEIRA FILHO, TCBC-SP¹; ALLISSON MONTEIRO DA SILVA²; DANIEL ARCUSCHIN DE OLIVEIRA³; GUSTAVO GIANOTTO OLIVEIRA³; FABIO XERFAN NAHAS, TCBC-SP⁴

A B S T R A C T

Objective: To ascertain whether there is any relationship between the state of the sentinel lymph node histopathology, recurrence and mortality from thick melanoma in patients undergoing SLNB over a long follow-up. **Methods:** Eighty-six patients with thick melanoma undergoing SLNB were selected from a prospective database. Lymphoscintigraphy, lymphatic mapping and intraoperative gamma probe detection were performed in all patients. The sentinel lymph node (SLN) was analyzed by HE and immunohistochemistry. Complete lymphadenectomy was indicated for patients with positive sentinel node. The histopathological SLN status was related to the rate of recurrence and mortality from melanoma. **Results:** One hundred and sixty-six SLNs were taken from the 86 patients. Ages ranged from 18 to 73 years. There were 47 women and 39 men. Micrometastases were found in 44 patients. Forty-two patients underwent complete lymphadenectomy. Seven other patients had positive lymph node. Among the 44 patients with positive sentinel node, there were 20 recurrences and 15 deaths. There were 18 recurrences and 12 deaths in the group with negative SLN. The Breslow thickness was not correlated with the histopathological SLN status. The histopathological SLN status did not affect the rates of recurrence and mortality (Fisher test, $p = 1.00$). The median follow-up was 69 months. **Conclusion:** Considering the lack of evidence of benefit, SLNB should not be indicated for patients with thick melanoma outside of clinical studies.

Key words: Melanoma. Neoplasms micrometastasis. Recurrence. Mortality. Sentinel lymph node biopsy.

INTRODUCTION

Worldwide incidence of cutaneous melanoma has increased and its high lethality is notorious. Sentinel lymph node biopsy (SLNB) is a necessary procedure to establish the microstaging of melanoma clinical stages I and II, according to the guidelines of the AJCC-2009¹. The presence or absence of lymph node metastases is the most important prognostic factor for survival and recurrence in patients with cutaneous melanoma.

The SLNB procedure in thick melanomas has been questioned due to the perception of poor prognosis in this subgroup of patients, who have a high risk of presenting systemic disease. Currently, all patients with positive sentinel lymph node should undergo complete lymphadenectomy. The benefit for melanoma patients who had positive sentinel lymph node after a removal of the lymph node may be limited to patients whose lesions have intermediate degree in Breslow thickness (1 to 4mm)². Randomized screening showed no benefit for patients with thick melanoma (> 4 mm) undergoing SLNB.

This study aimed to verify whether there is any relationship between the status of the sentinel lymph node

histopathology, recurrence and mortality from thick melanoma in patients undergoing SLNB over a significant follow-up.

METHODS

Data from patients with thick melanoma (Breslow thickness > 4 mm) undergoing SLNB between August 1994 and July 2010 were reviewed.

Preoperative lymphoscintigraphy was performed in all patients with Tc99 plus 500 Dextran or sodium phytate.

In order to perform SLNB, lymphatic mapping with V patent blue and intraoperative gamma probe detection with the Neoprobe 1500 were carried out to find the sentinel lymph node.

SLNB was performed two to 24 hours after lymphoscintigraphy. The lymph nodes were analyzed for micrometastasis by conventional histological examination (hematoxylin and eosin) and immunohistochemical staining for markers HMB45, S-100 protein and Melan-A.

Lymphadenectomy was indicated for patients with positive sentinel lymph node (with micrometastasis).

Work performed at the Center for Cancer Prevention "Prof. Dr. Renato Santos Clinic" - São Paulo - SP, Brazil.

1. Oncologic Surgeon; PhD, São Paulo State University; 2. Head and Neck Surgeon; MSc; 3. Medical School Graduate, Anhenbi-Morumbi Faculty of Medicine, São Paulo; 4. Plastic Surgeon; Lecturer Professor, São Paulo Federal University.

Patients with negative sentinel nodes were not submitted to lymphadenectomy.

Follow-up was done for all patients every three months in the first three years, every six months in the fourth and fifth year and annually from the sixth year on.

The same surgical team operated and followed all patients.

The Breslow thickness of the primary lesion was used to check whether there was any relationship between the sentinel lymph node micrometastases.

Rates of recurrence and mortality of melanoma were analyzed to verify the impact of a positive sentinel lymph node.

Statistical analyzes were performed using relative risk, odds ratio and Fisher's exact test, considering $p < 0.05$ significant.

RESULTS

We reviewed the charts of 86 patients with thick melanoma and 166 removed sentinel nodes. Forty-seven were women and 39 men, aged 18-73 years, median 58.

The Breslow Index varied from 4.1 to 9.9 mm (median 5.4 mm).

Micrometastases in sentinel lymph nodes were found in 44 patients (51%). A total of 42 patients underwent lymphadenectomy. One patient refused resection and another, adjuvant radiotherapy. Seven patients who underwent lymphadenectomy had micrometastases in other lymph nodes. The other 42 patients who had negative sentinel lymph node were not subjected to complementary lymphadenectomy.

Among the 44 patients with positive sentinel lymph node, there were 20 recurrences and 15 deaths. Those with negative sentinel lymph node displayed 18 recurrences and 12 deaths.

The chance of a patient with thick melanoma and positive sentinel lymph node to present with recurrence is only 1.17 higher than a patient with thick melanoma and negative sentinel node (OR = 1,17).

The chance of a patient with thick melanoma and positive sentinel lymph node dying is only 1.39 higher than that of individuals with thick melanoma and negative sentinel node (OR = 1,39).

The histopathologic status of the sentinel lymph node did not influence the rates of recurrence and mortality of these patients (Fisher, $p = 1,00$). Mean follow-up was 69 months (eight to 158).

DISCUSSION

Before SLNB, melanoma patients with Breslow thickness greater than 4 mm were followed more closely. They were expected to have an increased risk for distant metastases and deaths from systemic disease³. Therefore,

lymphadenectomy did not apply to them. With the advent of SLNB, different results of survival and recurrence rates were published, but the usefulness of SLNB in patients with thick melanoma is still undefined.

Cherpelis *et al.* studied 201 patients with melanoma thicker than 3.0 mm, and 180 were alive at a median follow-up of 51 months. Of these, 166 were alive without disease. Their results indicated that the status of the sentinel lymph node is predictive of disease-free survival for patients with thick melanoma⁴.

Studying 131 patients with T4 melanoma, Gershenwald *et al.* observed that patients with negative sentinel lymph node and no ulcerations had a rate of three-year overall survival of 86%, while patients with T4 melanoma with positive sentinel lymph node and presence of ulceration had the same rate of 57% ($P < 0.03$)⁵.

Reviewing 126 patients with thick melanoma, Ferrone *et al.* developed a prognostic model based on age 60 years, depth of melanoma > 5.5 mm, ulceration and histological status of the sentinel node. They found that the relative risk of recurrence varied from one in patients from without the presence of adverse factors to 29.4 in the four patients with risk factors. They concluded that the histopathologic status of the sentinel lymph node was the strongest independent predictor of results⁶.

Carlson *et al.* reported survival rates at five years of 47-62%, showing that long-term survival for patients with thick melanoma was not uncommon. They concluded that the histopathological status of the sentinel node is an independent prognostic factor for survival in patients with thick melanoma⁷.

Several authors recommend the SLNB to T4 melanoma patients with clinically negative lymph nodes (N0), which is independent of Breslow thickness⁵⁻⁹. In these studies, the histopathologic status of the sentinel lymph node was, independently, the strongest factor for survival in patients with thick melanoma.

Caraco *et al.* have reviewed 359 patients with Breslow thickness greater than 4mm. Survival curves showed no significant differences between patients with positive and negative sentinel node¹⁰.

According to our results, micrometastases were found in 42 of the 86 patients with thick melanoma (Breslow thickness > 4 mm). Rates of recurrence and mortality in patients with positive and negative sentinel node showed no statistically significant difference.

Many authors consider the histopathologic status of the sentinel lymph node a predictor of disease-free survival in patients with thick melanoma, though without evidence of benefit to overall survival. Our results showed that rates of recurrence and mortality were not affected by the status of the sentinel node when the follow-up is long (median 69 months). The "Multicenter Selective Lymphadenectomy Trial" showed similar data^{11,12}.

Considering the lack of evidence of benefit, it is concluded that sentinel node biopsy should be avoided in patients with thick melanoma outside clinical studies.

R E S U M O

Objetivo: verificar se há alguma relação entre o estado histopatológico do linfonodo sentinela, a recorrência e a mortalidade decorrente do melanoma espesso em pacientes submetidos à BLS ao longo de um seguimento significativa. **Métodos:** Oitenta e seis pacientes portadores de melanoma espesso submetidos à BLS foram selecionados de um banco de dados prospectivo. A linfocintilografia, o mapeamento linfático e a detecção gama intraoperatória foram realizados em todos os pacientes. O linfonodo sentinela (LS) foi analisado por HE e por imunohistoquímica. Linfadenectomia total foi indicada para os pacientes com LS positivo. O estado histopatológico do LS foi relacionado à taxa de recorrência e de mortalidade por melanoma. **Resultados:** Cento e sessenta e seis LS foram retirados dos 86 pacientes. As idades variaram de 18 a 73 anos. Havia 47 mulheres e 39 homens. Micrometástases foram encontradas em 44 pacientes. Quarenta e dois pacientes foram submetidos à linfadenectomia total. Sete pacientes tiveram outro linfonodo positivo. Entre os 44 pacientes com LS positivo houve 20 recorrências e 15 mortes. Houve 18 recidivas e 12 mortes no grupo de LS negativo. A espessura de Breslow não apresentou correlação com o estado histopatológico do LS. O estado histopatológico do LS não interferiu nas taxas de recorrência e de mortalidade (teste de Fisher, $p=1.00$). A mediana de seguimento foi 69 meses. **Conclusão:** Considerando a falta de evidência de benefício, a BLS não deve ser indicada para pacientes com melanoma espesso fora de estudos clínicos.

Descritores: Melanoma. Micrometástase de neoplasia. Recidiva. Mortalidade. Biópsia de linfonodo sentinela.

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Address correspondence to:

Renato Santos de Oliveira Filho

E-mail: renato.prevencao@terra.com.br