Complete lymphadenectomy following positive sentinel lymph node biopsy in cutaneous melanoma: a critical review*

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Abstract: Cutaneous melanoma is the solid neoplasia with the highest growing incidence among all tumors. It spreads predictably to the lymphatic vessels and sentinel lymph node, and when the latter is affected the prognosis worsens dramatically. Sentinel lymph node biopsy is considered when thickness of the primary tumor exceeds 1mm and/or when there are adverse features in thinner melanomas. When there is nodal metastasis, current evidence in the literature recommends complete lymphadenectomy, although this procedure has its intrinsic risks (i.e., lymphedema and cellulitis), and there are no published clinical trials proving additional overall survival benefits. The current in-depth literature review thus aims to identify patients that will benefit most from the procedure, including those with the highest likelihood of presenting additional affected lymph nodes in the same nodal basin. The authors also discuss techniques for identification of the sentinel lymph node, false-negative rates, and predictive models for lymph node involvement. In conclusion, complete elective lymphadenectomy should always be discussed on a case-by-case basis when metastases are detected in the sentinel lymph node.
Keywords: Lymph node dissection; Lymphatic metastasis; Melanoma; Sentinel lymph node biopsy

INTRODUCTION

Cutaneous melanoma (CM) is associated with high lethality. It is currently the malignant neoplasm with the fastest growing incidence of all the tumors, having increased 15-fold in the last 40 years in the United States alone.[1] Most CMs spread first to the lymphatics, with the sentinel lymph node (SLN) as the first lymph node to receive lymphatic drainage from the skin where the primary lesion is located.

SENTINEL LYMPH NODE BIOPSY

For cases of localized CM – clinical stages I and II (without clinically detectable lymph nodes), sentinel lymph node (SLN) biopsy is the most accurate staging method. The main variables in the primary lesion for risk of SLN metastasis are Breslow thickness, ulceration, and number of mitoses. SLN biopsy should be considered in all patients with Breslow thickness greater than or equal to 1mm, as well as for those with thickness less than 1mm, but greater than 0.75mm, in the presence of the following adverse factors:

1- Positive deep margins;
2- Lymphatic invasion;
3- Age < 40 years;
4- Significant vertical growth phase;
5- High mitotic index;
6- Clark level IV or greater.[2]

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Currently, regression of the primary lesion is no longer considered a predictor of SLN involvement and is thus not used to indicate SLN biopsy.[3,4]

When conventional histopathology fails to identify SLN micrometastases, immunohistochemistry (IHC) is indicated, with the S100, HMB-45, and MART-1/Melan-A proteins as the target antigens. Molecular biology techniques such as RT-PCR (reverse transcription-polymerase chain reaction) and cell culture can identify even smaller amounts of metastatic cells in the sentinel lymph node, but they still lack clinical applicability in this scenario. SLN is the most important prognostic factor for patients with localized CM.[5-8]

SLN biopsy replaced elective lymphadenectomy in patients with clinically localized melanoma at high risk of lymph node metastasis. The current gold standard for patients with negative sentinel lymph node is clinical observation and monitoring of the nodal basin, and ultrasound can be considered in the follow-up.

MANAGEMENT OF THE PATIENT WITH POSITIVE SENTINEL LYMPH NODE

Traditionally, complete lymphadenectomy (CL) has been indicated in patients with positive SLN.[2] When lymphadenectomy is performed, the treatment goal is to remove other lymph nodes with metastases and theoretically interrupt spread of the melanoma to other organs. Metastases to non-sentinel lymph nodes have been observed in some 15 -20% of specimens obtained from CL.[9,10] The therapeutic effect of CL for patients without non-sentinel lymph node metastasis is unknown.

In addition to the possible therapeutic effect of complete lymphadenectomy, the approach stratifies nodal involvement as N1 (one lymph node involved), N2 (two to three lymph nodes involved), and N3 (four or more lymph nodes involved). The eighth edition of the AJCC Staging System adopts the nomenclature "a" (if detected by SLN biopsy), "b" (if detected clinically), or "c" (when in-transit or satellite lesions or microsatellite metastases are detected).[11] Ten-year melanoma-specific survival differs considerably according to the nodal staging: 75% of N1 patients, 68% for N2, and only 47% for N3.[12]

The identification of risk factors for non-sentinel lymph node involvement among the patient's clinical characteristics and those of the primary lesion and sentinel lymph node can be used to select CM patients with SLN lymph node involvement that will not benefit from lymphadenectomy, thus preventing sequelae from the procedure.

Oncologists are currently debating whether or not to perform complete lymphadenectomy in CM patients with positive SLN biopsy, since recent randomized clinical trials results go against the traditionally recommended approach of complete lymph node dissection in the SLN basin.

PRINCIPAL STUDIES AND RESULTS

The Multicenter Selective Lymphadenectomy Trial (MSLT-I) is the only completed phase III randomized trial that has compared SLN biopsy versus no SLN biopsy in patients with localized CM and that assessed the role of complete lymphadenectomy. The study recruited 2,001 patients. In one arm of this study, patients were submitted to broad excision of the melanoma with SLN biopsy. If the SLN was positive, patients underwent CL. If negative, they were simply observed. In the other arm, patients underwent broad excision alone and were followed. The results failed to show a difference between the two groups in either overall survival or melanoma-specific survival. However, in a *post hoc* analysis, for patients with Breslow thickness from 1.2mm to 3.6mm who had lymph node involvement (either at SLN biopsy or during follow-up), there was a benefit in melanoma-specific survival (MSS) for those submitted to immediate CL following a positive SLN result. Despite controversies concerning the therapeutic benefit of SLN biopsy, this study showed that SLN histopathological status was the most important prognostic factor for the survival of patients with localized CM (with clinically negative lymph nodes) and that SLN biopsy provides better disease-free survival (DFS).[13]

Santos-Juanes *et al.* conducted a meta-analysis of six studies with 8,764 patients that underwent SLN biopsy and 11,054 that underwent only broad excision. Although four studies failed to observe a significant difference in survival, in the overall assessment SLN biopsy demonstrated superior evolution when compared to broad excision alone.[14]

The German study, Dermatologic Cooperative Oncology Group - Sentinel Lymph node Trial (DeCOG-SLT), was the first randomized clinical trial to assess the benefit of CL in melanoma patients with positive SLN biopsy. The trial enrolled 483 patients with cutaneous melanoma on the trunk and limbs, with a median follow-up of 35 months. The majority had micrometastases <1.0mm in the SLN (66% of cases), and no difference was found in metastasis-free survival between the group with "dissected" nodal chain versus the group with spared nodal chain and followed with trimonthly ultrasound. The authors concluded that CL should not be performed in cases in which the SLN presents micrometastasis ≤ 1.0mm.[15] It should be noted that the authors reported difficulty in enrolling patients into a supposedly suboptimal therapy, and there was a clear decrease in statistical power from 80% to 50%, which could not be resolved by increasing the follow-up.

In the wake of DeCOG-SLT, in the MSLT–II study, 1,934 patients with positive sentinel lymph node detected by histopathology or RT-PCR were randomized to receive immediate complete lymphadenectomy or watchful waiting with ultrasound. The primary outcome was melanoma-specific survival and the secondary outcomes were disease-free survival and non-sentinel lymph node involvement. The trial was negative for the primary outcome, essentially showing the same 86% three-year MSS in both study arms, even in the subgroup analysis. However, disease-free survival favored the lymphadenectomy arm by 5%, due mainly to a 69% difference in regional lymph node disease-free survival, but with no change in distant disease-free survival. The authors concluded that complete lymphadenectomy following positive SLN biopsy can be waived, especially to spare patients from lymphedema (24% in CL versus 6% in watchful waiting), since it had no impact on melanoma-specific survival, especially in patients with little nodal deposit in the SLN and who were willing to undergo rigorous ultrasound follow-up. Importantly, however, the study showed lower regional disease control and less precise prognostic stratification.[16]

EORTC 1208 MINITUB, a prospective trial still in progress, will assess whether the amount of tumor in the positive SLN is a valid predictor for sparing the patient from CL. Patients with intermediate Breslow thickness and minimal tumor volume, or SLN with minimal involvement (subcapsular ≤ 0.4mm, intraparenchymal ≤ 0.1mm), are followed to determine whether metastasis-free survival differs between those undergoing CL versus watchful waiting. It is not a randomized study, and patients are treated and followed according to each participating center and with ultrasound of the lymphatic basin draining the melanoma. Recruitment into this trial is scheduled for completion in 2019-2020.[17]

Burke *et al.* drew on concepts from theoretical biology to develop a Markov model to simulate the prognosis of hypothetical cohorts of patients with CM with SLN metastases, in two groups: those undergoing immediate lymphadenectomy and those followed and submitted to late lymphadenectomy in the presence of macroscopic nodal disease. The model assessed overall survival, life expectancy, and quality-adjusted life expectancy. Projected five-year overall survival for patients 50 years or older was 67.2%, compared to 63.1% in the watchful waiting group, and this difference was statistically significant. The gain in life expectancy from immediate CL after positive SLN biopsy varied from 2.19 years for patients 30 to 70 years of age to 0.64 years for patients over 70 years. The gain in quality adjusted life expectancy from immediate CL varied from 1.39 years for patients 30 to 70 years of age to 0.36 years for those over 70 years. Sensitivity analysis was conducted to determine the results' stability in the Markov model, varying the parameters within the plausible variations according to the medical literature. For all the age cohorts, complete lymph node dissection was the best strategy when varying the risk of non-sentinel lymph node metastases from 15 to 30%. For risk less than 7.8%, watchful waiting showed the best result.[18]

ACCURACY AND DISADVANTAGES OF SENTINEL LYMPH NODE BIOPSY

The main disadvantage of SLN biopsy is the presence of false-negatives (FN). Assessment of false-negatives depends on the patient's evolution. False-negative SLN is defined as recurrence of the disease after negative SLN biopsy in the same lymph node basin. The FN rate is calculated by dividing the number of FNs by the sum of the true positives and false positives and varies from 8 to 20%.[19-24] There are controversies concerning the overall survival of FN patients. In the MSLT-I study, overall survival of patients with false-negative SLN was similar to that of the watchful waiting group that developed lymph node metastasis but was significantly lower than in patients with positive SLN. Gambichler *et al.* found worse MSS in patients with false-negative SLN when compared to those with positive SLN.[25]

False-negative SLN can result from technical failure in the lymphoscintigraphy or in the surgical procedure. A contributing factor is massive SLN involvement altering the lymphatic drainage, resulting in failure to identify and remove the true SLN, as well as lack of intraoperative combined use of vital dye and gamma detection. Another cause lies in the histological protocol, purportedly missing the metastasis. Thus, one may either be examining a lymph node that is not the true SLN or missing occult micrometastases. Gershenwald *et al.* reassessed the histopathological examination of false-negative SLNs with serial slices of the lymph node and found occult metastases in five of seven patients who had nodal disease as the first site of recurrence.[26] Finally, failure may be due to the presence of occult in-transit metastases that have still not reached the lymph node.

The addition of single photon emission computed tomography (SPECT–CT)to planar lymphoscintigraphy facilitates SLN identification and localization in CM, thereby decreasing the false-negative rate.[27] Fluorescence, using hybrid tracers like indocyanine green and technetium-labelled nanocolloid (99mTc), is a promising method for improving surgical precision in SLN biopsy. It promises to be highly useful for excising sentinel lymph nodes in difficult locations such as head and neck, mediastinum, and retroperitoneum.[28] The addition of activated charcoal to vital dye increases the precision in the identification of the true SLN.[29]

False-positive SLN biopsies are also known to exist. This happens when immunohistochemistry (IHC) identifies niches of cells or single positive cells for melanoma markers, such as the above-mentioned MART-1 and S100, but these are not synonymous with CM metastases to the lymph node. As an example, up to 5.1% of patients with MART-1-positive cells can be false-positives as suggested by a study that found this incidence in SLN biopsies in patients without a history of melanoma.[30] The most plausible explanations are the existence of nodal nevi and melanocytes that gained access to the lymphatics due to prior skin biopsy.[31] To mitigate the FP rate, four accessory criteria can be used in the analysis of the SLN:

1- Existence of IHC-positive cells inside the lymph node: melanocytic cells in the nodal parenchyma are known to be malignant, while subcapsular or trabecular melanocytic cells are considered benign;

2- Cytologic characteristics, especially those related to the cell nucleus, such as nuclear pleomorphism, hyperchromasia, and enlargement, among others;

3- Absence or presence of evidence of proliferation, such as mitotic figures;

4- Positivity for HMB45 marker, which is less sensitive but highly specific for melanoma.[32]

Does a tool exist to increase prognostic accuracy in patients with positive SLN biopsy? The groundbreaking work of Hao *et al.*, although not clinically applicable at present, identified two genes in the positive sentinel lymph node, namely PIGR, already correlated with early recurrence of other tumors, and TFAP2A, one of the genes responsible for acquisition of the malignant phenotype in melanoma. These two genes, together with the patient's clinical and pathological characteristics, were able to differentiate precisely between high-risk and low-risk groups for recurrence in the study cohort (AUC = 0.864).[33]

Positive non-sentinel lymph nodes in the presence of a positive sentinel lymph node

Nagaraja *et al.* conducted a meta-analysis to identify the predictive clinical and pathological variables for metastases in non-sentinel lymph nodes detected during complete lymphadenectomy in patients with positive SLN cutaneous melanoma. The results were analyzed by odds ratios with 95% confidence intervals in a random

effects model. Fifty-four studies were analyzed, with a total of 8,388 patients, with incidence of metastases in non-sentinel lymph nodes varying from 8 to 38%. The variables found in the primary lesion that presented significantly high odds of metastases (in a lymph node other than the sentinel lymph node) were presence of satellitosis, neurotropism, angiolymphatic invasion, and ulceration. In the sentinel lymph node, the variables extranodal extension, capsular involvement, extensive SLN involvement (Dewar), Starz 3, macrometastasis >2mm, and more than one positive sentinel lymph node were statistically significant. Three characteristics were associated with absence of non-sentinel lymph node metastases: subcapsular localization, Rotterdam criterion <0.1mm, and Starz I.[34] The meta-analysis thus provides an additional argument for sparing CL in patients with low metastatic load in the SLN, thereby preventing the morbidity associated with the procedure.

Just as research has endeavored to predict the involvement of non-sentinel lymph nodes after positive SLN biopsy, tools have also been created to predict the odds of sentinel lymph node involvement. In 2005, Wong *et al*. developed a nomogram based on age, primary site, Breslow thickness, Clark level, and ulceration, showing a negative predictive value of 90% with 0-3% error. Another model was developed by Mocellin *et al.*, who reported a negative predictive value of 93%, with 1-2% error.[35] However, these models have not been validated in phase III trials and are not currently used in clinical practice.

Returning to the topic in the subtitle, there are various scores for the prediction of non-sentinel lymph node involvement, including the Rotterdam system, based on the measurement of the largest diameter of the largest metastatic deposit, dividing the positive SLNs in three groups: <0.1mm; 0.1 to 1.0mm; and >1.0mm, predicting the risk of non-sentinel nodal involvement at 3%, 21%, and 32%, respectively.[36] In the Dewar microanatomical classification of metastatic deposit in the SLN, the odds of additional lymph node involvement vary from 8% for subcapsular localization to 19% for parenchymal localization, reaching 40% in extensive involvement. There are other classifications, such as S, based on the depth of the metastatic deposit, dividing the positive SLNs into <0.3mm (S-I); 0.3mm to 1.0mm (SII); and >1.0mm (S-III); the Hannover-II classification, based on the largest dimension of the largest deposit, depth of the metastasis, and capsular involvement.[37,38] The Non-Sentinel Node Risk Score (N-SNORE) considers gender, regression, proportion of involved SLN, maximum dimension, and perinodal lymphatic invasion.[39] The EORTC melanoma groups adopts a Rotterdam-Dewar combination.[40] Sloan Kettering Memorial Cancer Center bases its approach on the size/ulceration score.[41] The Rotterdam system is currently the most widely used.[42]

Based on these scores, when the patient is spared of CL, lymph node basin ultrasound plays an important role in follow-up. The test allows diagnosing early recurrence, and fine needle aspiration biopsy (FNAB) is performed in the suspicious lymph nodes. However, the technique is operator-dependent, which requires the patient's availability for trimonthly ultrasound in the first year of follow-up, in addition to displaying some loss of sensitivity for lesions measuring less than 10mm.[43]

CONCLUSION

Currently, the change from a standard treatment to another potentially better one should be based on the best possible level of evidence and is worthy of note when there are phase III randomized clinical trials. Offering complete lymphadenectomy only to cutaneous melanoma patients with positive SLN that truly benefit from the procedure has been a highly desired step forward, since the complications from lymphadenectomy, especially lymphedema and cellulitis, significantly comprise the patient's quality of life.[44]

The vast majority of CMs send metastases initially to regional lymph nodes, and the sentinel lymph node is the principal marker for the condition. All stages of this technique need to be improved in order to decrease the false-negative and false-positive SLN rates. Progress is still needed in the stages that involve nuclear medicine, surgical technique, and anatomical pathology.

The results of the MSLT-I phase III randomized trial show that management based on sentinel lymph node biopsy in patients with melanoma of intermediate to high thickness leads to the best disease-free survival. Contrary to this reasoning, however, MSLT-II strongly suggests that complete lymphadenectomy following positive sentinel lymph node biopsy can be waived, since the overall survival and melanoma-specific survival rates were essentially the same.

Meanwhile, Burke *et al.*, in a critical analysis using a Markov model, found that complete lymphadenectomy following positive SLN biopsy was associated with gains in overall survival and quality-adjusted life expectancy, compared to observation and late lymphadenectomy in patients with cutaneous melanoma that developed clinically apparent metastases.

EORTC 1208 – MINITUB will help answer this question. It is still not clear whether minimal SLN involvement (micrometastasis <1mm) can harm prognosis in these patients, despite evidence to the contrary, nor whether it can be used as an exclusion criterion in clinical studies of adjuvant immunotherapy and target therapy with anti-BRAF associated with anti-MEK.[45,46]

Despite the false-negatives, false-positives, and lack of definition as to the value of SLN micrometastases, SLN biopsy is still the best methodology for staging initial melanomas. However, conducting complete lymph node dissection in all patients with positive SLN biopsy is not consistent with the current body of data in the literature, especially in patients with minimal SLN involvement. The procedure should be discussed in detail with the patient, listing the pros and cons of complete lymphadenectomy, considering the risk of regional recurrence, complications from the procedure, and the need to define the prognosis based on the result of the CL, and emphasizing the absence of benefit in overall survival from CL in prospective studies, despite the increase in lymph node recurrence-free survival. ❑

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