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OPINION ARTICLES

Sentinel Node Biopsy in Melanoma: An Update[☆]

Estado actual del ganglio centinela en el melanoma

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Sentinel node (SN) biopsy, a procedure based on the identification and histologic examination of the first lymph node on the direct drainage pathway from the tumor, is widely used to stage melanoma and other, non-cutaneous, malignancies, such as breast cancer. The technique was introduced by Morton et al¹ in 1992 as a new standard in the surgical treatment of localized melanoma. Several later studies confirmed that in most cases in which SN biopsy was negative the other nodes in the same drainage basin were also free of metastatic disease, implying that complete lymphadenectomy could be reserved for use only when the SN was found to be tumor-positive.^{2–4} This approach to lymph node excision, based on the state of the SN, is known as selective lymphadenectomy. The same technique is currently being introduced into the management of other types of skin tumors, such as high-risk squamous cell and Merkel cell carcinomas.^{5,6}

However, the use of selective lymphadenectomy in the treatment of melanoma is still controversial. The influence of this procedure on survival rates among melanoma patients was studied in a randomized, prospective, multicenter study by Morton et al⁷ published in 2006. Since both the critics and the advocates of selective lymphadenectomy often refer to the design, results, and interpretation of this study, we consider it useful to review the basic issues involved. In an article published in 2007 in the Evidence-Based Dermatology section of the *Archives of Dermatology*, Urbà González made a case that this study by Morton et al was an example of how the opinion held by a group of researchers concerning the

advantage of one particular intervention over another could influence the way the results of a trial were reported and lead to inadequate analysis of subgroups.⁸

The trial in question enrolled patients with localized melanomas between 1.2 and 3.5 mm in thickness (Breslow), who were then randomly assigned to one of 2 groups as follows: SN biopsy with lymphadenectomy if micrometastases were detected in the biopsy, or observation with therapeutic lymphadenectomy only if nodal metastasis became clinically detectable. The results of the study, based on the analysis of 1269 patients, showed that the presence of metastasis in the SN was the key prognostic factor in the biopsy group. After 5 years, no difference was found in the overall melanoma-specific survival rate between the 2 groups ($87.1\% \pm 1.3\%$ in the SN biopsy group compared to $86.6\% \pm 1.6\%$ in the observation group). There was, however, a small but statistically significant difference in favor of the SN biopsy group in disease-free survival ($78.3\% \pm 1.6\%$ vs $73.1\% \pm 2.1\%$; $P = .009$). In the biopsy group, the incidence of micrometastasis in the SN was 16%, while in the observation group, the rate of nodal recurrence was 15.6%. The mean number of affected lymph nodes in the patients who underwent immediate lymphadenectomy because of a tumor-positive SN was 1.4, while the mean number of affected nodes was 3.3 in the subgroup of patients in the observation group who developed lymph-node metastases ($P < .001$). The authors also compared the survival of the subgroups of patients in both groups who had nodal metastases. Patients in whom micrometastases were detected in the SN biopsy had a 5-year survival benefit over the patients who developed metastases after a period of observation ($72.3\% \pm 4.6\%$ vs $52.4\% \pm 5.9\%$; $P = .004$). Morton et al concluded that the SN biopsy technique improved disease-free survival and local disease control because metastatic nodes were identified earlier and therefore fewer nodes had to be resected, resulting in fewer complications for the patient.

[☆] Please cite this article as: Botella-Estrada R, Nagore E. Estado actual del ganglio centinela en el melanoma. *Actas Dermosifiliogr.* 2011;102:749-753.

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The better survival among patients in whom micrometastases were identified in the SN compared to those in whom metastases were detected clinically during the course of the disease would appear to suggest that the lack of any difference in overall survival between the 2 groups (SN biopsy vs observation) was only due to the fact that the group that benefited from the biopsy procedure represented such a small percentage of the total number of patients in the study (16%) that the statistical advantage was diluted.

However, both the inclusion criteria and the conclusions of this study have been criticized by several authors. Some of these criticisms appear to us to be of particular importance and continuing relevance. In the first place, the trial enrolled patients who had tumors with a Breslow thickness of between 1.2 and 3.5 mm. This range does not coincide with the parameters used to select candidates for selective lymphadenectomy in 2006 (1–4 mm) or those currently used by most hospitals today (> 1 mm). Both the upper and lower cutoff values used appear to be artificial, and the reasons adduced by the authors for changing the lower limit—initially established at 1 mm—to 1.2 mm are not clear. Most guidelines recommend the inclusion of tumors with a thickness greater than 1 mm and most specialized melanoma treatment centers use this criteria as specified in the most recent American Joint Committee on Cancer (AJCC) classification. Since the correlation between a tumor's thickness and its behavior is not stratified, it is difficult to justify the inclusion of patients on the basis of criteria not related to any melanoma classification,⁹ making the use of such criteria appear to be a way of obtaining the desired results by including only patients likely to benefit from the intervention.

Other authors have pointed to problems in the comparison carried out in the study between the survival of patients with clinically detected macroscopic metastatic nodes and that of patients with microscopic metastasis detected on selective lymphadenectomy.^{10,11} Their criticism of the comparison is based on the fact that it is highly probable that a percentage of the microscopic metastatic deposits would have disappeared due to the action of the patient's immune response or, at least, would have remained dormant for many years or during the patient's entire lifetime. In the study by Morton et al, if we take into account the subgroup of patients in whom the SN biopsy was negative but who later developed metastatic nodes in the same lymphatic drainage region (the 26 false negatives, 3.4%), the percentage of patients with metastatic nodes in the SN biopsy group (16% + 3.4% = 19.4%) was higher than that of the group treated with therapeutic lymphadenectomy during subsequent monitoring (15.6%). Since the risk factors were comparable in both groups and the percentage of metastatic nodes could be expected to be very similar, the only explanation for the discrepancy between these 2 percentages (19.4% vs 15.6%) is that a certain percentage of the patients who had a tumor-positive SN biopsy would not have eventually developed clinically detectable metastasis or, at least, would not have done so for a long time. However, in response to these criticisms expressed in several letters to the journal that published the original article, the authors of the study made the point that when the follow-up period was extended from the 5 years reported in the original article to 10 years, the incidence of node metastasis in the observation

group increased to equal that of the SN group (taking into account both the microscopic metastasis detected on biopsy and the false negatives).¹² This finding argues against the existence of metastatic deposits that did not develop into clinical metastasis.

It should likewise be remembered that the patients in the study were randomized to 2 treatment groups: SN biopsy and observation. The subsequent comparison of 2 non-randomized subgroups, namely, patients with micrometastases in the SN group and patients with palpable metastases in the observation group is inappropriate because of the possibility that the treatment received by only one of these groups (sentinel node excision) may have influenced outcomes.¹³ In any case, there is no objective evidence to support the hypothesis that the 2 groups compared were comparable; why were the 26 patients in the SN biopsy group who had false negative results not included in the comparison? By excluding the data from this subgroup from the analysis, the authors compared the patients from the observation group who had developed clinically detectable metastases within the follow-up period with patients from the SN biopsy group who had micrometastases, but failed to take into account the 24% of patients in the biopsy group who subsequently developed metastases. It is even probable that a subgroup existed in which metastases would never have developed. In other words, even if we assume that all patients with micrometastases will eventually develop clinically detectable metastases and that both groups in the end had the same percentage of patients with nodal metastases, the comparison as reported in the trial includes the patients from the observation group in whom nodal metastases developed earlier and who probably had a more aggressive melanoma with a worse prognosis.

Thus, the current evidence casts into doubt the therapeutic utility of selective lymphadenectomy, at least with respect to overall survival. However, both the present authors and most of the scientific community support the performance of this procedure on the basis of the benefit it confers with respect to local disease control and its usefulness for correctly staging the disease and determining prognosis.¹⁴ The recently published recommendations of an international panel of well-known melanoma experts established that SN biopsy should be considered standard treatment in patients whose melanoma meets a series of inclusion criteria.¹⁵

Another aspect that remains controversial is the selection of candidates for selective lymphadenectomy. Originally, it was thought that this procedure would most benefit patients with tumors having a Breslow thickness of between 1.01 and 4.00 mm, and those with a tumor thickness of 1 mm or less in the presence of additional risk factors that increased the probability of a tumor-positive SN, such as ulceration or a Clark level of IV or V.^{16,17} The indication for selective lymphadenectomy has progressively been extended, and now includes patients with a tumor thickness greater than 4 mm.¹⁸ However, in view of the high frequency of distant metastases in patients in this group, the individual clinical characteristics of each case must be carefully taken into account.

There are currently 3 important areas of uncertainty concerning the indication for SN biopsy. The most important of these involves the change implied by consideration of the

mitotic rate of the primary tumor as an important prognostic factor, to the extent that this rate is now used to divide thin melanomas (≤ 1 mm) into 2 groups in the most recent AJCC classification published in 2009.¹⁹ According to this classification, stage IA includes thin melanomas (≤ 1 mm) with no ulceration or mitosis, while stage IB includes thin melanomas with ulceration or 1 or more mitoses per mm^2 . This change in the AJCC classification is based on a multifactorial analysis of 10 233 patients with clinically localized melanoma that showed mitotic rate to be the second most powerful predictor of survival after Breslow thickness.¹⁹ In the discussion section of the article in the *Journal of Clinical Oncology* in which the new AJCC classification was published, the authors mention the possible desirability of extending the indication for selective lymphadenectomy to patients having melanomas with a Breslow thickness of between 0.75 and 1 mm and a mitotic rate of at least $1/\text{mm}^2$.¹⁹ They based this suggestion on preliminary evidence from large studies on T1 melanomas with a Breslow thickness of at least 0.76 mm and a mitotic rate of at least $1/\text{mm}^2$, which were associated with a 10% rate of metastasis in the SN (J. Gershenwald, personal communication, 2009). Melanomas of 0.75 mm or less with mitoses currently comprise a group for which no evidence exists to support the best approach with respect to selective lymphadenectomy. In 2005, Kesmodel et al²⁰ published a study of 181 patients with thin melanomas (≤ 1 mm) in whom selective lymphadenectomy had been carried out on the basis of earlier results that indicated a higher risk of metastasis in thin melanomas in a vertical growth phase.²¹ Metastases were detected in 9 of the 181 patients (5%). Despite the low number of patients with metastases, the authors identified 3 risk groups: a) patients in whose tumors no dermal mitoses were detected (none of the patients in this group had metastasis to the SN); b) patients with some dermal mitoses and a Breslow thickness of less than 0.76 mm, (2.6% of these had metastases in the SN); and c) patients with some dermal mitoses and a Breslow thickness of 0.76 mm or more (12.3% of these had metastases in the SN). Mitoses were found in about 5% of patients with thin melanomas (≤ 1 mm) in several series.²² An international panel of specialists in melanoma and the SN biopsy technique have indicated that a risk of occult nodal metastases of 10% or more is sufficient to justify using the procedure.¹⁵ Even when this threshold is lowered to 5%, there are currently no studies that justify the performance of selective lymphadenectomy on all patients with thin melanomas (≤ 1 mm) and a mitotic rate of at least $1/\text{mm}^2$. In thin melanomas, the decision should be taken on a case-by-case basis by a committee and in consultation with the patient. However, following the publication of the most recent AJCC classification in 2009, many hospitals are performing selective lymphadenectomy in all cases of thin melanomas with mitoses. Therefore data will soon be available that could serve as a guide to the best course of action in this group of patients. The importance of the presence of even 1 mitosis and its implications for the treatment of melanoma places the pathologist in a key role. The histopathologic report should report dermal mitoses and the hot-spot method should be used to assess the mitotic rate. This involves identifying the area with the greatest concentration of mitoses and then counting the mitoses in adjacent fields until the 1 mm^2 area has been assessed (equivalent

to 4 high-power fields [$\times 400$ magnification]).²³ We reviewed all the thin melanomas (≤ 1 mm) recorded in the database of our hospital between 2006 and 2010. The histologic report of 43.7% of these reflected the presence of 1 or more mitoses; when we restricted the criteria to tumors less than 0.75 mm thick, 34.5% of cases had a mitotic rate of 1 or more. Thus, the decision concerning whether or not to perform selective lymphadenectomy in all melanomas under 1 mm with mitoses is important because the group of T1 melanomas (≤ 1 mm), in addition to being proportionally large (representing 60% to 70% of new melanomas diagnosed in large centers^{20,24}), has been the most rapidly growing group in recent years.^{25,26}

The second controversial point concerns thin melanomas (≤ 1 mm) with histologic evidence of regression. Many authors consider regression to be a sign of poor prognosis with respect to both survival²⁷⁻³¹ and increased risk of metastasis to the SN.³² For this reason, many hospitals recommend SN biopsy for melanomas of 1 mm or less when histologic signs of regression are present.^{20,22} However, other authors have found no association between the presence of regression and metastasis to the SN.^{33,34} A study published in 2008 analyzed the correlation between the presence of regression in the primary tumor and the status of the SN in 931 patients with melanomas.³⁵ The authors of that study found regression to be a positive prognostic factor in the sense that it was associated with a greater probability of a tumor-negative SN. In a study in our hospital, we established strict histologic criteria for regression and further categorized it as early or late and partial or extensive.³⁶ We then reviewed the histology of 103 melanomas in which selective lymphadenectomy had been performed, applying our criteria for regression. All cases were independently assessed by 2 dermatopathologists. Our results showed that regression did not correlate in any way with the status of the SN (Botella-Estrada R, personal communication, XXXV Meeting of the Spanish Dermopathology Working Group, Pamplona, 2009). Therefore, on the basis of both our own data and that of Morris et al,³⁵ we find no evidence to support the performance of selective lymphadenectomy in melanomas of 1 mm or less with regression.

The third area of doubt affects a smaller number of patients and concerns the cases in which melanoma recurs in the scar of an earlier excision and those in which a single satellite or in-transit metastasis develops. Such recurrences may be due to persistence of the melanoma by virtue of an incomplete excision or can be the result of local metastasis. In most cases, the mechanism can be identified by histologic examination. The implications are of prognostic importance since in the case of persistence the prognosis is the same as that of the original tumor, but when the new tumor is the result of spread within the regional lymph vessels it falls into the same risk category as satellite and in-transit metastases.³⁷ Theoretically, in such situations, a new lymphatic drainage pathway must exist and, consequently, a new SN. The excision of this new SN will provide information about whether or not there is regional lymphatic spread in the zone where the local or regional recurrence of the melanoma is situated. Although this situation is not covered by the inclusion criteria for selective lymphadenectomy candidates, it has been argued that neither is it contemplated by the exclusion criteria.^{15,38} Furthermore, the difference

between having satellite or in-transit metastases without metastatic nodes or with metastatic nodes changes the TNM classification from N2c and N3. This in turn implies a change of stage from IIIB to IIIC if the primary tumor is a T1-4a (because T1-4b N2c and T1-4b N3 are both classed as stage IIIC).¹⁹ This is an important difference, as the change of group represents a considerably worse prognosis for the patient. Most hospitals and authors only recommend SN biopsy in the case of persistence of a primary tumor on an excision scar.³⁹ In a few isolated articles, authors have reported cases in which SN biopsy was performed in patients with a single local melanoma recurrence or isolated in-transit metastasis. In 2003, Yao et al⁴⁰ published the results of a group of 30 patients with these characteristics. The SN was tumor-positive in 47% of cases and the median disease-free survival was 16 months in this group compared to 36 months in the patients with a tumor-negative SN. The authors concluded that identifying the status of the SN and carrying out selective lymphadenectomy was useful in the management of this group of patients. In any case, our criterion is that, while it does not contraindicate SN biopsy, the presence of evidence of nodal spread as found in these situations does constitute a situation in which the utility of performing an SN biopsy must be carefully assessed by a tumor committee, taking into account the individual characteristics of each case.

Although Morton's work only showed an improvement in disease-free survival and in local control of melanomas with a Breslow thickness between 1.2 and 3.5 mm, most hospitals and clinics have extended the indication for selective lymphadenectomy to include all melanomas of 1 mm or more. The inclusion of melanomas of less than 1 mm which have 1 or more mitosis or evidence of regression and also the cases of isolated local recurrence or in-transit metastases has led some dermatologists to consider whether this may not be the road that in the near future will lead us to use this technique in all invasive melanomas, with the possible exception of those in a radial growth phase.

Currently, there appears to be no consensus on a level of probability of finding a tumor-positive SN below which the use of this procedure should not be recommended. However, the opinion of the present authors is that the evidence currently available is insufficient to support routine performance of selective lymphadenectomy in these 3 groups of patients, with the possible exception of cases of tumoral persistence in the scar and melanomas with a Breslow thickness of between 0.75 and 1 mm having 1 or more mitoses. Only the performance of further studies in patients for whom no clearly established criteria exist will provide the data needed to corroborate or modify the current criteria.

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