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OPINION ARTICLE

Lymphadenectomy After a Positive Sentinel Lymph Node Biopsy in Melanoma: A Paradigm Shift☆

Linfadenectomía tras una biopsia positiva del ganglio centinela en el melanoma: un cambio de paradigma

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In Spain today, physicians recommend completion lymph node dissection (CLND) to almost all patients with melanoma who have a positive sentinel lymph node biopsy (SLNB) result. This has been my own practice since the SLNB technique was introduced, although I have always had reservations about the therapeutic value of CLND.[1–3] Moreover, I have always tried to ensure that both my patients and my colleagues understand that while CLND may facilitate better control of local and regional disease, it would probably not influence the likelihood of systemic spread, which to a large extent is the determining factor in the survival of these patients.

The most recent update of the guidelines published by the Multidisciplinary Spanish Melanoma Group[4] and by the Spanish Society of Medical Oncology[5] in 2015 considers the performance of CLND in patients with a positive SLNB result to be standard practice in patients with melanoma. By contrast, the most recent updates of other recommendations, such as the guidelines published by the British National Institute for Health and Care Excellence (NICE, 2015),[6] the European Society for Medical Oncology (ESMO, 2015),[7] the US National Comprehensive Cancer Network (NCCN),[8] and the French guidelines published in 2017,[9] all make it clear that no survival benefit has been demonstrated for CLND following a positive SLNB result and that the advantages and disadvantages of the intervention should be discussed with the patient before any decision is taken on CLND. Given the most recent evidence, which I will discuss below, I believe that the moment has come to openly acknowledge that CLND does not improve survival in sentinel node-positive patients with melanoma. I believe that all patients should be informed of this fact before they take any decision on whether or not to undergo CLND, and I also believe that the moment has come to abandon CLND as standard practice in this setting. Some authors in Spain have recently made statements supporting such a change in standard practice in this country.[10,11]

The belief that early surgical intervention on the regional lymph basin could increase survival in patients with melanoma has, to a large degree, been based on the existence of a clinical reality clearly reflected in the literature: the appearance of metastasis in regional lymph nodes before the appearance of distant metastasis.[12,13] This common pattern led many authors to propose a stepwise model of progression for melanoma, which holds that in many patients melanoma spreads initially through the lymph system to the regional lymph nodes, from whence, following a variable period of latency, it would start to spread systemically. In earlier papers, I have discussed the question of melanoma progression in depth.[1–3] Despite the obvious popularity of the theory, there is no clinical or biological evidence to support the stepwise progression model for the spread of melanoma. On the basis of this model, elective or prophylactic regional lymph node dissection was proposed in the belief that such early surgical intervention would confer a greater survival benefit than therapeutic or

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deferred regional lymphadenectomy. However, none of the prospective randomized clinical trials carried out during the closing 3 decades of the last century demonstrated any such survival benefit.[14] The stepwise spread model for melanoma progression was mortally wounded, although many people were unable to see that at the time.

The SLNB technique offered solutions to 2 important problems related to prophylactic regional lymph node dissection. In the first place, it facilitated direct surgical intervention on the regional lymph basin affected (sometimes more than one), a particularly important advantage in melanomas of the head, neck, and trunk. In the second place, it made it possible to avoid the unnecessary sequelae of CLND in around 80% of patients—those who had negative sentinel node biopsy results and did not require the intervention. On both counts, SLNB offers undeniable advantages over prophylactic regional lymph node dissection.[1–3] However, was it logical to expect that SLNB would have a beneficial impact on the survival of patients with melanoma? And is it logical to expect that regional lymphadenectomy following a positive SLNB will confer a survival benefit in this setting? I have always believed that the answer to both these questions was no, an opinion I have expressed in previous articles[1,2] even before we learned the results of the 2 most important prospective randomized clinical trials undertaken to study those questions: the Multicenter Selective Lymphadenectomy Trials (MSLT) I and II.[15,16] The findings of those 2 trials have now clearly shown that those of us who have held the opinion for the last 20 years that no survival benefit would be observed were, in fact, right.

The primary objective of MSLT-1[15] was to study the differences in long-term survival between patients randomly assigned to either nodal observation or SLNB. No significant differences were found between the 2 groups. The final results were published much later than originally planned. The statistical study used and the authors' interpretation of the results gave rise to some controversy.[3,17–19] It was clearly difficult for the authors of MSLT-I to accept the lack of evidence for the model of stepwise spread in melanoma (in fact, they did not discuss that issue in their article) and the lack of a survival benefit associated with SLNB. The primary objective of MSLT-2[16] was to study the difference in melanoma-specific survival between patients with sentinel node-positive melanomas who underwent CLND and those assigned to nodal observation. Probably because the results of the second study were even more conclusive than those of MSLT-I, they were published earlier than expected and there was no controversy about the results observed or the authors' interpretation in this case. Melanoma-specific survival at 3 years was similar in both groups.[16] On the basis of this evidence, I will also assert that the hypothesis that melanoma progresses in a stepwise manner (spreading first to the regional lymph nodes and from there to the viscera and other regions via the bloodstream) is necessarily incorrect.

In an article published in this journal in 2008, I predicted that the results of MSLT-2 would disprove that theory.[2] There was, in my opinion, already sufficient clinical and biological evidence to show that the stepwise spread model was not correct. The model was defended by Donald L. Morton[20] (one of the people largely responsible for the MSLT-I and MSLT-II trials) and was widely accepted by a large section of the medical community involved in the management of patients with melanoma. Morton deserves our sincere recognition and thanks for his enormous contributions to the fight against melanoma, but in this instance he was mistaken. Moreover, several retrospective studies had already provided evidence that survival was similar in patients with positive SLNB who underwent CLND and those assigned to nodal observation.[2] Other retrospective studies have reported similar results in recent years.[21,22] And, finally, the findings of 2 recently published prospective randomized studies, MSLT-2[16] and DeCOG-SLT,[23] have corroborated these results. The authors of both the recent studies mention the possibility that the low tumor load present in the sentinel lymph node of many of the patients included in those trials may have diluted the therapeutic effect of selective lymphadenectomy and led to an underestimation of the benefit of the procedure.[16,23] The authors of the MSLT-2 trial also mention that a lower than expected proportion of patients had tumor involvement in non-sentinel lymph nodes on lymphadenectomy.[16] In any event, the authors of both studies concluded that their results failed to demonstrate that CLND confers any therapeutic benefit in terms of distant metastases or melanoma-specific survival and that their findings did not, therefore, support the routine use of lymphadenectomy in sentinel node-positive patients. A third prospective study dealing with the same issue is currently underway (EORTC 1208 MINITUB). I predict that its results will be very similar to those of the clinical trials mentioned above.

The key to correctly predicting a null effect on survival for lymphadenectomy guided by a positive SLNB result lay in the model for melanoma spread proposed. This is a point I have discussed extensively in previous articles.[1–3] For many years, the debate on the progression of melanoma was between the supporters of a stepwise model and the supporters of a model of simultaneous spread.[1,2,20] Since 2004, I have supported a third option, which in 2006 I called ''the hypothesis of differential spread patterns''. The model is described in my earlier articles.[1–3] Other authors have proposed or discussed models with similar characteristics.[13,24] Wallace H. Clark was especially clear on the subject,[25] and my proposal is very similar and later than his. The basic concept of the model I propose is that, in patients with melanoma, metastasis to regional lymph nodes and systemic metastasis are processes that occur independently. As a result of complex biological interactions between the tumor and the host, patients may develop only metastases affecting regional lymph nodes, only blood-borne systemic metastases, both regional and systemic metastases (although independently), or no metastases whatsoever. Very recent biological and genetic studies in melanoma favor such a model.[26,27] Obviously, no simple model of this type can accommodate the enormous complexity of the process of metastasis formation, and there will always be some patients whose evolution does not fit any model. However, the differential spread model fits what has been observed in most of the patients with melanoma we treat, and can explain the findings of all of the prospective clinical trials on prophylactic regional lymph node dissection and CLND guided by a positive SLNB.

Supporters of the stepwise model have been unable to offer a plausible explanation for the results of all of

the prospective clinical trials involving some form of early lymphadenectomy in patients with melanoma. Why does early lymphadenectomy not reduce the frequency of distant metastases or increase survival in these patients? In my opinion the answer is simple: because the formation of nodal metastases and systemic metastases in melanoma are complex and independent processes. And they occur independently even in patients who present both types of metastasis during the course of the disease, whether consecutively or simultaneously.

Some of the authors who disagree with the stepwise spread model have proposed an alternative model postulating that spread to the regional lymph nodes and distant metastasis are simultaneous processes.[2,11,28] In my opinion, this model is too simplistic and cannot be generalized to all patients with melanoma.[2] A simultaneous spread model does not satisfactorily explain certain phenomena: for example, around one-third of all patients with stage III melanoma never present distant metastasis; sentinel-node positivity is much more common than expected in patients with atypical Spitz tumors and Spitzoid melanomas whereas distant metastasis is infrequent in this group; and some patients with a negative SLNB result do eventually present distant metastases, a circumstance more common in older patients. A positive SLNB result is not an inevitable marker of visceral spread and a negative result does not guarantee that the patient will not develop distant metastases, although it does indicate a lower probability.[1–3] Simultaneous spread is observed in many patients with melanoma, but definitely not in all of them. And, obviously, simultaneous spread does not imply that the metastases in different organs and tissues will occur simultaneously.

It is interesting to note that the findings of several studies on other kinds of tumors, including colon and breast cancer, indicate a similar pattern. Lymphatic and visceral metastases in patients with colon cancer appear to occur independently in many patients and to be related to biologically different cell populations.[29,30] In my opinion, it is only a question of time before we find similar results in many other tumors if we do the same types of studies in other types of cancer. In breast cancer, 2 prospective clinical trials, ACOSOG Z0011[31] and IBCSG 23-01,[32] have shown that complete axillary lymphadenectomy can be omitted in many sentinel node-positive patients without affecting survival. In that setting, it would appear to be clear that the presence of early subclinical systemic spread determines prognosis in these patients, and that systemic spread is independent of subclinical lymphatic spread. In the case of breast cancer, the efficacy of local adjuvant radiotherapy may lead to a decision not to perform complete axillary lymph node dissection following a positive SLNB result.[33]

What are the practical implications of these findings on the management of patients with melanoma? In view of the evidence that SLNB confers no survival benefit, some authors have suggested that the technique should no longer be included in the routine management of patients with melanoma.[17,34] I do not agree. In my opinion, SLNB should continue to be considered as an option in standard practice in patients in whom there is an appreciable risk of subclinical lymphatic spread. However, the patient should be informed that while the intervention will provide information of prognostic value and will facilitate the management of possible local and regional lymphatic spread of their melanoma, it does not influence possible systemic spread and, therefore, will not benefit their eventual survival.[1–3] Once apprised of these facts, the patient can make an informed decision.

SLNB can provide 2 pieces of information that are undeniably useful in the management of melanoma.[1–3] First, it allows us to identify the regional lymph basins affected by the melanoma and, consequently, to identify the areas most likely to be affected by local or regional lymphatic recurrence. Second, it provides information on the presence or absence of subclinical spread of melanoma cells through the lymph system to the sentinel node. This is valuable prognostic information that can be useful when making a decision about the most appropriate adjuvant treatment. SLNB also allows us to eliminate tumor cells that may have reached the lymph node. This, in itself, represents a therapeutic benefit.[1–3] And all of these benefits are achieved by way of a surgical intervention associated with low morbidity and few sequelae. It is my opinion, therefore, that SLNB should continue to be offered routinely to all patients with melanoma when there is a certain risk of metastasis to the lymphatic system. This includes all cases in which tumor thickness is greater than 1 mm and selected cases in which it is less. Since the eighth edition of the cancer staging manual published by the American Joint Committee on Cancer[35] redefines melanomas measuring between 0.8 and 1 mm thick as category T1b, it is likely that the future trend will be to consider patients to be candidates for SLNB if they have a melanoma with a thickness of at least 0.8 mm (according to the latest edition of the staging manual, melanomas measuring between 0.75 and 0.80 mm thick are defined as being 0.8 mm thick because thickness is recorded with only one decimal point and the measurement is rounded up).[35]

Unlike SLNB, CLND after a positive SLNB involves a surgical intervention associated with greater morbidity and potential sequelae, in particular lymphedema. Around 80% of patients who undergo CLND following a positive SLNB do not have micrometastases in other lymph nodes. In such cases, CLND confers no benefit and is associated with greater morbidity and possibly uncomfortable sequelae. Moreover, as shown by the results of the MSLT-2[16] and DeCOG-SLT[23] clinical trials, CLND provides no therapeutic or survival benefit. What argument can be advanced to defend the thesis that CLND following a positive SLNB should be standard practice in patients with melanoma?

It would appear reasonable to offer all sentinel node-positive patients the kind of clinical and ultrasound follow-up of the regional lymph basins that was done in the clinical trials cited.[16,23] Some 20% of these patients may present subsequent regional lymphatic recurrence. Early detection of recurrence (before the lymph nodes affected are numerous, large, or present extracapsular spread) can be resolved with CLND, which, if follow-up has been correct, should not present much more difficulty or be associated with greater morbidity than the CLND performed after a positive SLNB. In terms of survival, the end result will be the same.[16,23] In the future, adjuvant treatments may be more effective than those currently available and they may not only benefit survival in node-positive patients but could also reduce regional lymphatic recurrence, further reducing the percentage of patients who have to undergo CLND, with important benefits for the patients' quality of life.

As I indicated at the beginning of this article, CLND after a positive SLNB result in patients with melanoma is no longer considered standard practice in many guidelines on the management of melanoma.[6–9] It would appear reasonable to explain to patients the advantages and disadvantages of SLNB, and of CLND versus nodal observation in the case of a positive SLNB result, and that patients should make a decision after being adequately informed and advised by their physician. Lymph node observation should include regular ultrasound checks of the regional lymphatic basin. Physicians should also discuss with their patients the option of receiving one of the available adjuvant therapies (which as yet are not very effective and are associated with not inconsiderable side effects) or, preferably, the option of taking part in a clinical trial of a new therapeutic option. The promising results recently observed with new types of adjuvant treatment in melanoma[36] augur well for an active field of research in the coming years with implications for the management of node-positive patients.

In Spain, decision making would be greatly facilitated if the scientific societies most directly involved in this issue, including the Spanish Multidisciplinary Melanoma Group and the Spanish Society of Medical Oncology, would consider modifying their current recommendations on the management of node-positive patients with melanoma[4,5] to take into account the evidence provided by the most recent clinical trials.[16,23]

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