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OPINION ARTICLE

Models of Melanoma Spread and Final Results of the Multicenter Selective Lymphadenectomy Trial-I☆

Modelos de diseminación del melanoma y resultado final del *multicenter selective lymphadenectomy trial-I*

Á. Pizarro

Unidad de Prevención y Diagnóstico Precoz de Melanoma, Clínica Dermatológica Internacional, Clínica Ruber, Madrid, Spain

Although sentinel node biopsy (SNB) is currently offered at most hospitals that treat patients with melanoma, the usefulness of the technique in the management of this disease has been a subject of controversy.[1–3] My opinion, which I have held for years, is that the debate about the ability of SNB to increase survival in patients with melanoma is actually a debate about our understanding of how melanoma spreads.[4,5] However, I believe that the diagnostic and prognostic value of SNB is beyond question, despite the fact that, as some authors have noted, what patients most want is not an accurate prediction of how likely they are to die from melanoma but rather for their physicians to reduce that likelihood.[6]

Broadly speaking, there are 3 major theoretical models of melanoma spread, which have been defended by, among others, 3 doctors who have made some of the largest contributions to progress in the fight against melanoma and who, unfortunately, are no longer with us. The first is the stepwise progression model defended by Donald L. Morton,[7] which holds that melanoma first spreads to the regional lymph nodes before spreading systemically. The second is the simultaneous spread model defended by A. Bernard Ackerman.[8] The third is what I call the model of differential spread patterns, which is supported by Wallace H. Clark.[5,9] In earlier articles,[4,5] I outlined the basic characteristics of these models and examined the extent to which the initial results of the Multicenter Selective Lymphadenectomy Trial-I (MSLT-I), published in 2006,[10] supported or refuted the validity of each model. My opinion at the time was that Clark's model was correct.[5] The final results of the MSLT-I,[11] published in 2014—significantly later than expected[12]—have reaffirmed my opinion. Clark[9] considered that some melanomas do not spread or metastasize (as we all know, a greater Breslow thickness increases the likelihood of metastases but is not a guarantee that they will develop). Of those melanomas that do metastasize, Clark argued, some produce only lymphatic metastases in the regional nodes, others metastasize only through the bloodstream, and still others (the majority) spread by both pathways, ultimately producing both lymphatic and visceral metastases (the fact that macroscopic lymphatic metastases often precede macroscopic visceral metastases does not imply that the former are necessarily the source of the latter).

Clark died in 1997, so he did not participate in the subsequent debate between Morton and Ackerman about their respective models of melanoma spread and the implications of each model for the usefulness of SNB. In this debate, both Morton and Ackerman—like many others who have written on this subject—ignored the model proposed by Clark. In my opinion, the available biological and clinical data favor Clark's hypothesis[5,9] and his model is the one we should consider when designing the basic and clinical studies that are

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E-mail address: angelpizarro84@gmail.com

needed in order to speed up progress in the fight against melanoma.

The MSLT-I began in 1994. The theory of stepwise melanoma spread (which Morton called the incubator hypothesis[7]) holds that melanoma first spreads through the lymphatic system to the regional lymph nodes, and that the sentinel node is the first one that the tumor cells can reach. The tumor cells then remain confined in these regional nodes for some time before starting to spread through the bloodstream to visceral sites. The lag time between the 2 types of spread varies among patients. Although the defenders of the stepwise model do not deny that melanoma can spread directly through the bloodstream, they consider this to be the exception rather than the rule.[13] According to the stepwise theory, precise detection and early removal of lymph nodes affected by micrometastases should not only reduce the likelihood of subsequent lymphatic recurrence (which it obviously does) but also prevent blood-borne dissemination in many patients, increasing their survival. This was the initial hypothesis that led to the MSLT-I being subdivided into 2 major treatment arms: *a*) SNB followed by lymphadenectomy if the SNB specimen was positive, and *b*) observation with therapeutic or delayed lymphadenectomy if regional lymphatic metastases developed during observation.[7,10,11]

The fundamental finding of the MSLT-I is very clear: survival was similar for patients in both arms of the study (an outcome already evident from the initial findings published in 2006).[10,11] However, the authors—possibly dissatisfied by its implications for their theoretical model of melanoma spread—failed to reflect this finding in their conclusions. Instead, they analyzed the results by subgroups, highlighting a very questionable comparison between patients with a positive SNB result and patients with macroscopic lymphatic metastases—situations that are neither clinically nor biologically comparable—and thereby introducing considerable bias.[14,15] Moreover, they submitted the data to a particularly complex statistical analysis for which the study probably was not initially designed (and which may have had something to do with the delay in publication).[16] Finally, based on the results of this analysis, the authors concluded that SNB may confer an advantage in overall survival.[11] Both the initial MSLT-I results from 2006[10] and the final results from 2014[11] were published alongside editorials supporting this (probably biased) interpretation. These editorials were authored by individuals who had been closely involved in the introduction and assessment of prophylactic lymphadenectomy and, later, SNB, and who largely shared Morton's view of the stepwise progression of melanoma.[17,18] In both cases, the authors' interpretation of the study's findings was promptly challenged by other melanoma experts, who saw evidence in the MSLT-I results supporting the opposite conclusion. In other words, these experts considered that the MSLT-I results actually supported the conclusion that SNB does not increase overall survival in patients with melanoma.[14,16,19] The latter conclusion, which in my opinion is correct, would imply that the hypothesis of stepwise melanoma spread is necessarily incorrect.

One of the greatest opponents of the introduction of SNB in the routine management of melanoma was A. Bernard Ackerman, a brilliant and intelligent dermatopathologist known for his incisive analysis of the issues he studied. Ackerman argued that the presence of tumor cells in the sentinel node was a marker of both lymphatic and systemic spread of melanoma (what Morton called the marker hypothesis).[7,8] This hypothesis holds true for most patients with melanoma who develop lymphatic and visceral metastases during the course of the disease, but not for many patients who develop only lymphatic metastases and who go into long-term complete remission after any type of lymphadenectomy (prophylactic, SNB-guided, or delayed), nor for patients who develop visceral metastases after a negative SNB result.[5]

In a review[9] of the literature on tumor progression published in 1991, Clark clearly outlined his vision of melanoma spread, a model I call the hypothesis of differential spread patterns. This model[4,5] is compatible with the ''seed and soil'' hypothesis, which was proposed with great foresight by Stephen Paget more than 100 years ago and is based on clinical observation and finely tuned common sense.[20] And it is also compatible with many more recent discoveries that have revealed the enormous complexity of the process leading to metastasis formation.[21] The fact that tumor cells are capable of entering and leaving lymph and blood vessels is important, but there are surely many other factors that help to explain how macroscopic lymphatic and visceral metastases develop. Moreover, the process of metastasis formation generally appears to be very inefficient.[21] Many cells begin the process, but few complete it. In addition, it is clear that many tumor cells, once they reach the target organ, enter a period of dormancy that in some cases can last a very long time.[22,23] Some such micrometastases could be detected with highly sensitive techniques such as SNB (especially if immunohistochemical and molecular detection techniques are used), but this would not necessarily mean that these micrometastases are destined to progress to macrometastases.[15] If they do progress to macrometastases, the speed of progression varies widely depending on the genetic and epigenetic characteristics of the primary tumor and probably also certain host-related factors, among which the antitumor immune response would undoubtedly be important. Certain tumor cells develop more quickly in some organs than in others because their interaction with the microenvironment varies between organs. Thus, it is not necessarily the case that the cells reached the organs where the first metastases developed before they reached other organs where metastases may appear later or, in some cases, never.[5]

The results of both earlier trials on the usefulness of prophylactic lymphadenectomy in patients with melanoma and the more recent results relating to SNB from the MSLT-I study show that, while both prophylactic and SNB-guided lymphadenectomy have obvious therapeutic utility, the procedure is only curative in patients with metastases that exclusively affect the regional lymph nodes.[5] Therefore, in terms of survival the results obtained following these procedures are similar to those obtained with therapeutic or delayed lymphadenectomy on follow-up. However, given that we do not usually know a priori which patients will have exclusively lymphatic spread and which ones will also have systemic spread, it is reasonable to propose the option of additional adjuvant therapy in all patients (while recognizing that the efficacy of such treatments currently remains very limited). Oncologic surgeons on the other hand recognize that a regional lymphadenectomy guided by a positive

SNB result is usually simpler and more likely to be successful than a delayed lymphadenectomy based on the presence of macroscopic lymphatic metastases, which, moreover, carries the risk of extracapsular spread and greater locoregional extent of disease.[24] Given the value of the diagnostic and prognostic information that SNB provides, it seems very clear to me that SNB should be offered routinely to patients with melanoma in whom the procedure is indicated. On this point, I agree with Morton and many others who defend the clinical utility of SNB.[5] But it is one thing to argue in favor of SNB and another to attribute magical powers to the procedure (although statistical analysis can sometimes yield results that certainly appear magical). Unfortunately, in my opinion some of the conclusions drawn by the authors of the MSLT-I study[10,11] are closer to magic than to the biological and clinical reality of melanoma. As I noted in an earlier paper,[5] I am not aware of any biological property of tumor cells that requires them to pass through a lymph node before reaching any other organ. This progression may occur in some cases, but it is not the rule.

The problem with the biased, uncritical interpretation of the MSLT-I results[10,11] is that it prevents us from understanding which model of melanoma spread is likely to be the most accurate—Clark's model, in my opinion[5,9]—and at the same time spurs on those who openly argue against the routine use of SNB. It is easy to criticize the conclusions of the MSLT-I; unfortunately, it is also easy to conflate such criticism with opposition to the routine use of SNB.

If we consider the differential spread model, we can see right away that it is perfectly compatible with the basic results of the MSLT-I, and that it is the only one of the 3 models that predicted the results that were ultimately observed.[5] Any type of lymphadenectomy will only cure patients with exclusively lymphatic involvement because lymphatic and systemic metastases are essentially independent events, even though in many patients they may occur consecutively or, in some cases, simultaneously.[4,5] The differential spread model also suggests some avenues for research that would certainly help us gain a better understanding of how melanoma progresses and how we can slow its progression. First, we should make an effort to characterize genetic, epigenetic, proteomic, and immunologic signatures, as well as any other kind of signature that would allow us to predict the cases in which melanoma will tend to form exclusively lymphatic metastases, exclusively visceral metastases, or both types. With such a complex problem it is not certain that we will find sufficiently satisfactory answers, but we definitely will not find them if we do not look for them.

Tumor dormancy[22,23] is another very important area for research because it can help us to understand why melanoma progresses more quickly in some patients, and in some organs, than in others. Some researchers believe that, rather than trying to physically eliminate all tumor cells from the body (a formidable goal, considering melanoma's degree of resistance to the available treatments), the most feasible objective in the fight against cancer would be to induce and maintain a very long period of tumor dormancy in the malignant cells. This may be an easier objective to accomplish; in fact, it is one of the goals of adjuvant therapy.[25] But there is a problem. Many adjuvant therapies have been proposed for this purpose because they have been shown to be effective against macroscopic metastases. However, it is becoming increasingly clear that the cells responsible for the growth of macroscopic metastases have very different biological properties from the cells responsible for tumor dormancy and for persistent micrometastases that do not progress for an interval that varies by case.[23] SNB provides a valuable means of deepening our understanding of the differential biological properties of melanoma cells in micrometastases and macrometastases as well as the responses of these cells to different treatments.

The MSLT-I was a necessary clinical trial, and Donald L. Morton made an extraordinary personal contribution to progress in the study and treatment of melanoma. Despite the fact that SNB has not met all of Morton's expectations, the procedure remains extremely useful in the diagnostic, prognostic, and therapeutic management of melanoma. In my opinion, when SNB is indicated, all patients should be offered the procedure and given realistic, honest explanations of the expected benefits.

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