Why Does Sentinel Lymph Node Biopsy Not Increase Survival in Patients With Melanoma?

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Before trying to answer the question posed by the title of this article, we should perhaps ask another question: why might we expect sentinel lymph node biopsy (SLNB) to increase survival in patients with melanoma at all? If we think of SLNB as an essentially diagnostic technique, we would not expect the technique to provide therapeutic benefit or to directly (as opposed to indirectly) prolong survival in patients with melanoma. SLNB offers prognostic information of undoubted value, as reflected in the extensive review of the subject by Mangas et al published in this same issue of Actas Dermosifiliográficas. The prognostic value of detecting the presence of melanoma micrometastases in sentinel lymph nodes has led to SLNB being incorporated into the most recent tumor staging system published by the American Joint Committee on Cancer. In my personal opinion, this inclusion is fully supported by the available data. It is at this point, however, that I shall place special emphasis on a first observation essential to following the line of argument in this article: positive SLNB is indicative of poor prognosis even though lymph node micrometastases are detected, in theory, at a very early stage in the process of melanoma spread. This poor prognosis associated with positive SLNB is a strong indication in itself that the technique detects a problem at a very early stage but that, in most cases, we are unable to resolve it (or at least, not to a greater extent than when the problem is detected later).

However, a recent study by Essner affirmed that debate about whether SLNB is a diagnostic or therapeutic intervention persists and Ferrándiz and Mangas, in another recent article, concluded that we might indeed expect some direct therapeutic benefit from SLNB in patients with melanoma. Moreover, the design of the Multicenter Selective Lymphadenectomy Trial-I (MSLT-I) was based on the belief that SLNB would improve overall survival in patients with melanoma, and that was also what the trial aimed to demonstrate. The findings of this study—published recently—indicate that this is not the case, since survival in the group of patients who initially underwent SLNB was similar to that of patients who were initially allocated to observation alone. Here, we should emphasize a second point: long-term survival in patients with stage III melanoma is approximately 30%, suggesting that delayed or therapeutic lymphadenectomy can be curative in a significant percentage of these patients. Therefore, when we state that SLNB is of no therapeutic use, we should be clear that we mean that SLNB is of no greater therapeutic use than therapeutic lymphadenectomy in patients with melanoma. Furthermore, its enormous prognostic value (positive findings, remember, are indicative of poor prognosis) is actually derived from its inability to improve survival compared to therapeutic lymphadenectomy or, in other words, from its inability to modify the natural course of the disease in all patients with melanoma in whom, in addition to lymphatic spread, blood-borne spread has also occurred. This statement of course assumes that this spread involves cells of sufficient metastatic potential to cause macroscopic visceral metastases—the only and ultimate cause of death in almost any disseminated melanoma.

If we address the question of the utility of SLNB from a historical perspective, it seems obvious to me that this technique was originally conceived with therapeutic benefit in mind (and this is essentially the rationale behind the MSLT-I), although it was evidently useful from a diagnostic and prognostic point of view. SLNB is in many respects the direct descendent of elective or prophylactic lymphadenectomy, which was never really intended to provide a more accurate prognosis for melanoma patients. The procedure was first proposed as early as 1892 by Herbert Snow, and it continued to be practiced until the last decade of the 20th century in the belief that an early intervention for primary melanoma at the site where regional lymphatic drainage probably takes place would improve survival compared to delaying the intervention until macroscopic lymph node metastases had occurred. This strategy was based in turn on the belief that melanoma follows a stepwise spread in most cases, that is, it first spreads to regional lymph nodes and then, from there, is carried by the bloodstream to other organs. The stepwise spread model for melanoma has been backed even up until very recently.
by authors of undoubted and worthy prestige in melanoma research and management.\textsuperscript{8,10} Morton (one of the strongest defenders) has called this model the \textit{incubator hypothesis}.\textsuperscript{6} Within such a model, SLNB has 2 unquestionable advantages over prophylactic lymphadenectomy: first, it allows a more accurate identification of the lymph nodes into which lymph from the primary melanoma drains; second, it identifies patients who do not have regional lymph node involvement (approximately 80% of the patients who undergo this technique) and so completely avoids the unnecessary sequelae that would result from prophylactic lymphadenectomy.

If the stepwise spread model were correct, we would indeed expect that SLNB and the subsequent regional lymphadenectomy in the event of a positive biopsy result would improve survival in patients with melanoma, as in many cases, the problem of future visceral dissemination would be detected and resolved. In many patients, we would be practicing an effective intervention at an early stage on a lymph node station that would be acting as a bridgehead for metastatic dissemination of melanoma.\textsuperscript{11} However, my opinion on the matter is clear and I have expressed it previously, and of course before the results of the MSLT-I study were published: the stepwise spread model or the incubator hypothesis is completely erroneous, and the now-published unsatisfactory results of the MSLT-I were therefore readily foreseeable.\textsuperscript{8,12} Although SLNB does not directly contribute to improved survival in patients with melanoma, this does not rule out a clear therapeutic benefit, as I will discuss later.

There are main 2 reasons why the stepwise spread model should be considered erroneous. First, I am not aware of any biological property of tumor cells that requires them to pass through a lymph node before initiating—with a certain time delay—their blood-borne spread. Although I am not unfamiliar with research into the mechanisms of tumor invasiveness and the formation of metastasis,\textsuperscript{13-16} I have never come across a biological mechanism that directly supports stepwise spread as the main means for melanoma progression (or indeed for prognosis of any other type of solid tumor). I do not want to imply that a tumor cell cannot travel from the primary tumor to a lymph node and, from there, spread in the bloodstream to any organ; of course, that can happen. What I do not believe though is that this route is necessary for progression of tumor spread in most patients. It is much more likely that if a tumor cell is able to reach the blood vessels from a lymph node, many other cells will have done so directly from the primary tumor. There is a second reason why the hypothesis of stepwise spread might be considered erroneous, in this case based on available evidence from clinical and experimental data and not on theoretical hypotheses. None of the 4 prospective randomized trials from the last few years of the 20th century that compared survival in melanoma patients who underwent prophylactic lymphadenectomy with survival in those who were allocated to observation and therapeutic lymphadenectomy in the event of macroscopic lymph node metastases showed a significant benefit for prophylactic lymphadenectomy in terms of overall survival.\textsuperscript{7,17} However, both early and late lymphadenectomy cure approximately a third of patients with stage III melanoma for the simple reason that these fortunate patients only have tumor cells with the potential to spread and form lymphatic metastasis in regional lymph nodes. Most of these patients are therefore cured after any type of appropriately performed lymphadenectomy.

At this point in the article, we should dwell on certain basic concepts of the processes of tumor progression and spread that finally lead to the appearance of macroscopic visceral metastases and the death of the patient. During tumor progression, it is very likely that many cells spread both through the lymphatic system and in the bloodstream, but it is safe to say that very few will end up forming clinically relevant macroscopic metastases.\textsuperscript{18,19} It is of little relevance to the final outcome whether spread starts through the lymphatic system, the bloodstream, or both. What is actually important is that this process is initiated by subpopulations of tumor cells with biological potential to successfully culminate each of the many stages of tumor spread, including the final step from microscopic to macroscopic metastasis in certain organs and specific tissues. In some patients, microscopic metastases could remain in a state of tumor dormancy, probably as a result of as yet poorly understood phenomena of tumor quiescence or senescence,\textsuperscript{20} and while this situation prevails the patient will remain in clinical remission and we can consider him or her apparently cured. When, during the course of this article, I affirm, for simplicity, that there are patients whose melanoma only spreads by the lymphatic route or can only produce lymph node metastases, it should be clear that this does not rule out the possibility of concurrent blood-borne spread or of some cells passing from the lymph node to the bloodstream. The implication of such an affirmation is that, in these patients, the cells that reach the bloodstream lack the metastatic potential necessary to culminate the process in organs or tissues other than the regional lymph nodes. The vast majority of patients are therefore cured after lymphadenectomy, whether early or delayed.

It is true that there is a clinical observation that apparently supports the hypothesis of stepwise spread. In most patients with disseminated melanoma, macroscopic lymph node metastases precede the macroscopic visceral metastases.\textsuperscript{4} However, it is currently well established that the microenvironment where the tumor cells settle can exercise a notable influence on their proliferative capacity.\textsuperscript{18-20} The fact that the metastases appear earlier or grow faster in one organ compared to another does not mean that the tumor cells reached the first organ before the second. Moreover,
some recent studies have evaluated the timing of the appearance of different types of metastasis in patients with melanoma.\textsuperscript{21,22} The appearance of visceral metastases often takes place around 2 years after excision of the primary melanoma, and this time interval is independent of the prior presence of satellitosis, in-transit lesions, and lymph node metastases. Although many patients present regional and systemic lymph node metastases during the course of their disease, these observations may indicate that the 2 processes occur independently.

Another observation that might intuitively lead us to support the hypothesis of stepwise spread is the finding that the prognosis in patients with stage III melanoma worsens with increasing number of regional metastatic lymph nodes.\textsuperscript{2} This might lead us to think that tumor cells which have been spreading for a longer period throughout the regional lymph node chain have a greater chance of metastasizing to other organs. Assuming then that spread from the lymph nodes to the viscera is a question of time, an early intervention targeting the lymph nodes should reduce the cases of systemic dissemination and improve survival. However, we know now that this is not the case from the findings of the MSLT-I and earlier studies on the utility of prophylactic lymphadenectomy.\textsuperscript{5,17} In my opinion, the number of lymph nodes with metastasis is of prognostic value merely because it is associated with more biologically aggressive tumors, just as greater Breslow depth or the presence of ulceration in the primary tumor may also be indicative of more aggressive tumors. Clearly, a small ulcerated nodular melanoma that has appeared recently and that is several millimeters deep has a much worse prognosis than a superficial-spreading melanoma present for several years with a greater diameter but less than 1 mm deep. I do not contend that duration should be neglected in studying the natural history of any melanoma, but the intrinsic biological aggressiveness and the interaction of the tumor with other host genetic and immunologic factors are doubtlessly much more important. The same line of reasoning can, I think, be applied to what happens during tumor spread via regional lymph nodes. A faster lymphatic progression probably reflects greater biological aggressiveness and a greater tendency to systemic spread, but it is not the source of that spread. The observation of Tejera-Vaquero et al\textsuperscript{3} that lymph node metastases tend to appear first in patients who later develop systemic spread is therefore interesting. However, if the hypothesis of stepwise spread were correct and the success of our intervention on regional lymph nodes were a question of timing, prophylactic lymphadenectomy would have generated many unnecessary sequelae (mainly lymphedema) in patients without regional lymph node metastases, but it would also have saved many lives compared to therapeutic lymphadenectomy or delayed lymphadenectomy. We know that the first consequence is true but not the second.

There is one final observation clutched at by those who defend the potential utility of early lymphadenectomy as a way of improving survival in patients with melanoma, whether in the form of prophylactic lymphadenectomy or, currently, in the form of lymphadenectomy guided by a positive finding in the SLNB. In the World Health Organization (WHO) Clinical Trial-14, Cascinelli et al\textsuperscript{23} found that the overall survival of patients undergoing prophylactic lymphadenectomy was similar to that of patients undergoing observation and therapeutic lymphadenectomy in the event of macroscopic lymph node metastases. However, comparison of survival in the subgroup of patients submitted to prophylactic lymphadenectomy with microscopic metastases with that in the subgroup of patients undergoing observation who developed macroscopic metastases shows that survival was significantly longer in those undergoing prophylactic lymphadenectomy. In the MSLT-I study, Morton et al\textsuperscript{5} conducted a similar analysis of the data. If overall survival in the group of patients undergoing initial SLNB is compared with that of the group of patients undergoing observation (the comparison for which the study was originally designed), it is seen that there is no significant difference in terms of overall survival. However, if survival in the subgroup of patients with a positive SLNB who underwent regional lymphadenectomy is compared with that of the subgroup of patients with macroscopic metastases who underwent therapeutic lymphadenectomy, we find that survival in the first subgroup is better than in the second. Both Morton et al\textsuperscript{5} and Cascinelli et al\textsuperscript{23} interpreted these data as evidence that early lymphadenectomy in patients with microscopic lymph node metastases improves survival, an observation which would continue to support the stepwise spread model for melanoma. The truth is that the subgroups of patients on which that affirmation was based are not comparable, from either a clinical or a biological point of view, and therefore, any conclusion drawn from such a comparison is invalid. Other authors have recently published similar opinions on the matter.\textsuperscript{24-26}

The aforementioned subgroup analysis performed by Cascinelli et al\textsuperscript{23} and Morton et al\textsuperscript{5} does not take into account 2 biases of great importance in oncology: bias due to early diagnosis and bias due to disease duration. Clearly, if a patient is going to die of subsequent visceral dissemination of the disease, he or she will take longer to do so if we start the clock when the metastases are in the microscopic phase than if we do so when macroscopic metastases have been detected. The bias that arises from bringing forward the time of diagnosis would disappear if the moment of excision of the primary tumor was taken as the reference date. More important in this case is the bias arising from disease duration. It is well known that not all tumor cells have the same tumorigenicity (even though they may have similar invasiveness) and that
neoplastic disease does not progress equally quickly in all patients. With prophylactic lymphadenectomy and even more so with SLNB, we detect most of the patients with microscopic lymph node metastases, and some of these patients will have highly tumorigenic metastatic lesions and rapid disease progression, at both the lymphatic and systemic level. Obviously, the ultimate cause of death will be visceral macrometastases, which, in the case of patients with rapid progression, will probably appear during the study period. In other patients with positive SLNB, disseminated neoplastic cells may have a low tumorigenicity and, therefore, the disease will progress more slowly. Some may die during the study period whereas others will die later. Finally, some patients with microscopic metastases, whether to lymph nodes or the viscera, may remain in complete and lasting remission, even for life, due to tumor quiescence and senescence phenomena. The initial SLNB study includes all these patients in the positive SLNB subgroup. However, the subgroup of patients initially undergoing observation who present macroscopic lymph node metastases during the course of the study—however long that might be—will only include those patients whose neoplastic cells have greater tumorigenicity, giving rise to macroscopic metastases at an earlier time. The disease would obviously progress more quickly in these patients, both in the lymphatic system and the viscera, if concurrent systemic dissemination had occurred. This subgroup will clearly have a worse overall survival than the previous one, although it does not mean that early lymphadenectomy is modifying the course of the disease at a systemic level or prolonging survival. These subgroups are not comparable and the WHO Clinical Trial-I,23 and MSL-I5 were not originally designed to make this comparison. The only valid comparison, both from a clinical and biological perspective, is that of the group of patients who underwent prophylactic lymphadenectomy (WHO Clinical Trial-I) or SLNB (MSL-I) with those allocated initially to observation, and the result is very clear in both studies: there is no significant benefit in terms of overall survival, that is, the hypothesis of stepwise spread is necessarily erroneous. Furthermore, the assumption that there are patients with micrometastasis with slow or even nonexistent potential for progression and knowledge of the biological mechanisms implicated in this phenomenon could help find some of the keys to treating melanoma more effectively. Considering the sentinel lymph node as a marker of systemic dissemination had occurred. Morton has called the model the “marker hypothesis,”6 in which a positive SLNB would indicate that spread to the viscera has also occurred. Morton has certainly been right to defend his incubator hypothesis when a model such as the marker hypothesis—so readily susceptible to criticism—is put forward.

If we examine very long-term survival in patients with stage III melanoma, we find that around 30% do actually survive. As mentioned earlier, this suggests that these patients are cured after an appropriate regional lymphadenectomy regardless of whether the procedure was prophylactic, guided by positive SLNB, or after a delayed therapeutic lymphadenectomy. And if these patients are cured, it is because clinically relevant systemic spread of the melanoma did not occur. Could this spread have started at sometime during the melanoma disease course in some of these patients? It might be so, but we should consider the process of metastatic development in its entirety; metastasis is only effective when culminated by the formation of macroscopic metastases. Certainly, the hypothesis of simultaneous spread is in operation and correct for the remaining 70% of the patients with stage III melanoma who finally die from visceral dissemination of the tumor.2 Considering the sentinel lymph node as a marker of systemic dissemination of melanoma suffers from another obvious failure—negative SLNB does not guarantee future lack of visceral metastases although it admittedly makes them less probable.

Conceptually, the simultaneous spread model or marker hypothesis is only partly wrong, whereas in my opinion the hypothesis of stepwise spread or incubator hypothesis is
completely wrong. On this point, the opinions of Medalie and Ackerman⁶⁰ have, I think, a certain advantage over those of Morton and Cochran⁶ but they also happen to be more dangerous. If we take the hypothesis of simultaneous spread to its ultimate consequences, we may become dangerously skeptical towards therapy as Morton and Cochran⁶ rightly pointed out. The most obvious sign of this extreme skepticism, both from a diagnostic and therapeutic point of view, is to favor abandoning SLNB as Medalie and Ackerman⁶⁰ do. Although SLNB cannot cure more patients than therapeutic lymphadenectomy, at least it cures the same patients as therapeutic lymphadenectomy but with 3 obvious advantages in my opinion:

1. First, it does so at an early stage, almost at the same time as the primary tumor is excised. At least in those patients who are going to present exclusively lymph node metastasis, the problem will be resolved right from the start with a simpler surgical procedure, fewer complications, and a greater chance of success than if we had waited for macroscopic metastases to occur.³²,³³ An obvious and practical example of this is the possibility of metastasis to the Cloquet lymph node in the inguinal region. In this case, the technique used may decide whether a superficial inguinofemoral lymphadenectomy is sufficient or whether a more extensive and deeper procedure is required.³⁴,³⁵ In which situation does the reader believe it will be more likely to find metastatic involvement of the Cloquet lymph node—in the case of an early intervention for a positive inguinal SLNB or after macroscopic inguinal lymph node metastases?

2. Although SLNB does not improve the prognosis of patients with melanoma, it does help to establish prognosis more accurately¹²,⁵,⁶ and I believe that the patient has the right to know, taking into account the current diagnostic accuracy⁷ and the limited side effects of the procedure.

3. With the knowledge available, it is reasonable to consider the findings from the SLNB as an essential piece of information when offering a patient the chance to participate in a clinical trial of some adjuvant melanoma treatment or when discussing available treatment options.

If the stepwise spread model is completely wrong and the simultaneous spread model is only partly right, is there a model that is likely to be a more accurate reflection of reality? In my opinion there is—while conceding of course that no simple model can provide a completely satisfactory explanation of a behavior as complex as any type of cancer. However, the model that I support provides a satisfactory explanation for most of the main events in the natural history and course of melanoma that do not fit into any of the other 2 models. I call this model the hypothesis of differential spread patterns, a term I used for the first time in a presentation at the VI Curso de Avances en Cirugía Dermatológica y Melanoma (Course on Advances in Dermatologic Surgery and Melanoma) (Pamplona, Spain, 2006), although we had been defending such a model for some time.⁷ According to this model, melanomas can be divided into 4 groups depending on their dissemination potential:

1. In the first group are certain melanomas without the biological potential to form metastases (I emphasize, without the biological potential to culminate such a process even though it has been initiated). The existence of this first group would explain why the outcome of thick melanomas is not always death. It would also explain, at least partly, why the percentage of patients in whom we detect melanoma cells in the lymph nodes or peripheral blood using exclusively molecular techniques is very much higher than the percentage of patients who finally develop clinical metastases.

2. The second group contains melanomas with potential to form metastases exclusively in regional lymph nodes. This group would explain why therapeutic lymphadenectomy achieves complete and lasting remission in around 30% of patients with stage III melanoma and why neither prophylactic lymphadenectomy nor lymphadenectomy guided by positive SLNB manages to improve on these outcomes in terms of overall survival. Any type of lymphadenectomy will only be curative in the long term in patients with metastases exclusively affecting the lymph nodes. However, it seems obvious to me that SLNB is of undoubted diagnostic utility in these patients and that it also provides therapeutic benefit (even though it does not cure more patients than therapeutic lymphadenectomy, it cures them earlier and in a more favorable surgical setting, a worthy advantage in my opinion).³²,³³

3. The third group includes melanomas with potential to form lymph node and visceral metastases, and in this group (but only in this group) the hypothesis of simultaneous spread defended by Medalie and Ackerman⁶⁰ is fully applicable. As I have repeatedly stated throughout this article, the fact that neither prophylactic lymphadenectomy nor SLNB improves survival with respect to therapeutic lymphadenectomy rules out the stepwise model even in this group, which also happens to be the largest group of melanomas with metastatic potential. In this group, no type of lymphadenectomy, whether early or delayed, will be able to cure the patient given that no type of regional lymphadenectomy will stop or eliminate the systemic spread of the process. To stop systemic dissemination, we should try adjuvant treatment. Those who have worried too much about the possible harmful effect of early lymphadenectomy from an immunologic point of view (I myself stated such a point of view some years ago)³¹,³⁶ should remember that while
prophylactic lymphadenectomy or SLNB does not improve survival with respect to therapeutic lymphadenectomy it does not make it worse. The consequences of this seem obvious to me.12

4. A fourth group—a minority one compared to the 2 preceding groups but nevertheless a group with an appreciable number of patients—comprises certain melanomas with a potential to metastasize exclusively to the viscera. These patients will have a negative SLNB but will still succumb to melanoma. These patients would also be candidates for adjuvant treatment, but SLNB does not help us to identify them.

Unfortunately, we still do not have any clinical, histologic, immunohistochemical, or molecular markers that allow us to say exactly which metastatic pattern of spread will be followed in each individual patient. At present, it is possible to evaluate the overall expression of a large number of genes in melanoma samples.37,38 In the future, it may be that some data derived from such studies will help us more accurately predict the outcome in each patient and design therapeutic strategies able to prevent the appearance of the different types of macroscopic metastases more selectively and effectively.

Our proposed understanding of melanoma spread is based on ideas put forward by Stephen Paget at the end of the 19th century (the seed and soil hypothesis).8 Renowned researchers in the field of tumor dissemination such as Isaiah J. Filder39 have supported this model on the basis of both solid theoretical arguments and robust experimental evidence. The most recent advances in the understanding of the biology of the process of metastasis formation40 fit much better in a model like ours than in the stepwise spread model (the incubator hypothesis) or simultaneous spread model (the marker hypothesis). In any case, we are not the first to propose this idea. More than 15 years ago, Wallace H. Clark41 proposed a model of melanoma dissemination very similar to ours. I find it surprising that his proposal was forgotten and excluded from the debate between those in favor of stepwise spread and those in favor of simultaneous spread.

Any theoretical model that we propose should fit the known observations rather than oblige us to fit the observations to the model. Furthermore, if the model is right, it should accurately predict observations that have not yet been made. In accordance with the differential spread model for melanoma, negative findings in the MSLT-I were foreseeable (that is, SLNB would not improve survival compared to an initial observation approach),5 and this was indeed the case. What will happen with the findings of the MSLT-II? The study is designed to evaluate whether, once positive results have been obtained in the SLNB, there are differences in overall survival when patients undergo observation or complete regional lymphadenectomy.6

According to our model8 there may be differences (but not large ones) in terms of local/regional control of melanoma, but overall survival of the patients should be similar. The MSLT-II is a prospective trial that is still ongoing, but we already have data from another interesting retrospective study that included a series of 134 patients from 16 centers who had positive SLNB but who did not undergo additional lymphadenectomy.42 In that study, survival was compared with another series of patients with similar characteristics and positive SLNB who did undergo lymphadenectomy (the current standard of care). If our model were correct, survival should be similar, as indeed was the case.42 In my opinion, the findings of the MSLT-II are as foreseeable as those of the MSLT-I and will confirm what the aforementioned retrospective study has already shown.42

Does this mean that SLNB is a failure as a diagnostic and therapeutic technique in the management of melanoma? No, it merely reflects the failure of a theoretical model for the dissemination of melanoma, the stepwise model (incubator hypothesis). Is the sentinel lymph node a bridgehead in the systemic dissemination process of melanoma? Certainly not, but study of the sentinel lymph node is a valuable bridgehead towards a better understanding of essential aspects of the biology of tumor spread and could provide us with powerful weapons in the fight against this process in the future. Moreover, even if we were unable to do much to stop systemic spread, it would be an extraordinary advance if we could prevent the formation of lymph node metastases with nonsurgical treatment. The experimental studies that reflect immunologic disorders, increased lymphangiogenesis, and other sentinel lymph node changes, even before it is reached by the tumor cells, open up some interesting possibilities.3,43-45 Should we abandon the technique? No, but we should abandon dogmatic positions on the subject for the good of our patients, both present and future.

Conflicts of Interest
The author declares no conflicts of interest.

References
