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Hot Topic

Contemporary controversies and perspectives in the staging and treatment of patients with lymph node metastasis from melanoma, especially with regards positive sentinel lymph node biopsy

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ABSTRACT

The management of melanoma lymph node metastasis particularly when detected by sentinel lymph node biopsy (SLNB) is still controversial. Results of the only randomized trial conducted to assess the therapeutic value of SLNB, the Multicenter Selective Lymphadenectomy Trial (MSLT-1), have not conclusively proven the effectiveness of this procedure but are interpreted by the authors and guidelines as indicating SLNB is standard of care. After surgery, interferon alpha had a small survival benefit and radiotherapy has limited effectiveness for patient at high-risk of regional recurrence. New drugs, including immune modulating agents and targeted therapies, already shown to be effective in patients with distant metastasis, are being evaluated in the adjuvant setting. In this regard, ensuring high quality of surgery through the identification of reliable quality assurance indicators and improving the homogeneity of prognostic stratification of patients entered onto clinical trials is paramount. Here, we review the controversial issues regarding the staging and treatment of melanoma patients with lymph node metastasis, present a summary of important and potentially practice changing ongoing research and provide a commentary on what it all means at this point in time.

Introduction

Melanoma is one of the deadliest types of skin cancer. The incidence of skin melanoma has been increasing over the past 30 years worldwide at a pace greater than any other malignancy, which makes its management a key issue for national health care systems [1].

Melanoma is usually cured in the early stages with simple surgical removal of the primary tumor [2,3]. Conversely, when melanoma has spread such that there are lymph node (LN) metastasis it becomes a management challenge for surgical, medical, and radiation oncologists [4]. Performing sentinel LN biopsy (SLNB) and completion LN dissection (CLND) for SLNB-positive patients are both still debated, although the results of the Multicenter Selective Lymphadenectomy Trial (MSLT-1) suggests therapeutic value in patients with LN metastasis from intermediate thickness melanoma by earlier removal of the involved nodes [5–7]. After surgery, the survival benefit associated with the only approved adjuvant treatment, interferon alpha, is considered dubious by many medical oncologists [8], as is the effectiveness of radiation therapy for bulky nodal disease because it only adds benefit for regional control with no overall survival advantage [9]. Important adjuvant therapy clinical trials of immune modulating drugs and targeted therapies are currently under way or due to report soon [10]. In this regard, the heterogeneous survival observed in patients with LN metastasis (13–90% after 5 years [11,12]) exemplifies the challenge of accurately stratifying AJCC stage III patients for these clinical trials. This review will pinpoint controversial issues regarding the staging and treatment of melanoma patients with LN metastasis, particularly those with sentinel LN (SLN) metastasis, present a summary of important and potentially practice changing ongoing research and provide a commentary on what it all means at this point in time.

Search strategy and selection criteria

References for this review were identified through searches of PubMed with the search terms "melanoma", "lymph node",

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"sentinel lymph node", "metastasis", "adjuvant" and "post-operative" and through searches of the authors' own files. Only papers published in English were reviewed. The final reference list was generated on the basis of originality and relevance to the broad scope of this review.

Sentinel lymph node biopsy and completion lymphadenectomy

The MSLT-1

The therapeutic effectiveness of SLNB has not been fully proven. Recently, the final results from the only randomized trial that has compared SLNB and nodal observation, the MSLT-1, have been published [6]. The interim analysis, published in 2006, reported on 1296 patients (2001 were enrolled) with intermediate thickness melanoma (defined as 1.2–3.5 mm thick primary) and showed that patients treated with SLNB had a better disease-free survival but similar overall survival compared to patients who underwent nodal observation [5]. That interim report assessed survival differences in patients with LN metastasis (either detected immediately by SLNB or having a recurrence in the regional LN field at a later date) and demonstrated that performance of an early CLND was associated with a better survival compared to a delayed therapeutic lymphadenectomy for a regional LN recurrence. The significance of these results have been widely debated and the effectiveness of SLNB for improving patient survival has been questioned on the basis of the main result of the trial, which is the lack of therapeutic value of SLNB in the whole group of intermediate thickness melanoma patients [7].

The final analysis of the trial was expected to report on all the enrolled patients followed-up for a longer time, but it reported on 1661 patients with intermediate and thick melanomas and excluded participants who had primary tumors <1.2 mm [6]. Overall, the results corroborated the findings of the previous analysis. SLNB was associated with a significantly longer disease-free interval in both patients with intermediate (absolute ten-year benefit: 7%) and thick (absolute ten-year benefit: 10%) primaries. Overall SLNB did not lead to a better prognosis for patients who had it, however, when the analyses was performed only in the LN-positive participants, patients with intermediate thickness melanoma who have had a SLNB had a 21% better ten-year melanoma-specific survival rate (62.1% versus 41.5%), while no significant difference was detected among LN-positive participants with a thick primary.

These results are not going to completely remove the skepticism around SLNB because the statistically significant difference is seen in a non-randomized subgroups, as it was only able to be detected when comparing the patients with positive LNs, and clearly there was no way of knowing this fact before they either had a SLNB or relapsed [7]. Nevertheless there was almost exactly the same proportion of patients with LN metastasis in both groups suggesting that eventually all retained LNs will develop clinical disease, providing the patient does not die of systemic spread of disease in the interim. The statistical method of accelerated-failure-time latent-subgroup analysis validated the results but this is relatively new and it remains to be seen if it is widely accepted.

It is most likely no co-incidence that previous non-randomized studies have also shown that SLNB can be associated with approximately 20% survival benefit over nodal observation for patients with involved nodes. A meta-analysis of non-randomized studies encompassing 2633 patients showed that SLNB was associated with a better survival and the results suggested that SLNB and CLND might prolong survival in one of five treated patients after five-year [13]. Another compelling source of evidence is a retrospective study which was conducted in a large patient series and showed that patients who had a CLND immediately after a positive SLNB had a better survival plateauing around 60% with very few events after seven or eight years compared to patients who did not have a SLNB and had a delayed lymphadenectomy for clinically positive LNs whose ten year survival was around 45%. This is despite patients in the SLNB group having worse primary tumor prognostic factors than the delayed lymphadenectomy group and having better survival until around 3 years [14]. Again, a consistent quantum of benefit was suggested.

The MSLT-2

The MSLT-1 suggests that if the SLNB is positive CLND dissection is standard of care at least for intermediate thickness melanoma patients. In 2004, well ahead of this evidence, the MSLT-1 investigators started the MSLT-2 [15] to investigate the therapeutic value of SLNB and CLND compared to SLNB and observation with CLND only if regional LN relapse occurs. The MSLT-2 study cohort is not diluted by lower risk patients, in that all of the patients had LN metastases, however there is very little stratification for factors that leads to the wide range of outcome for SLNB positive patients. The study has recently completed accrual and it has long been anticipated that it will provide important information to standardize the treatment of melanoma patients with LN metastasis, however, there are concerns as well as limitations in the study design that may affect the acceptance and applicability of the final results. Many clinicians have questioned the safety of conducting a trial where part of the therapy that led to a survival advantage in MSLT-1 is not given, resulting in anxiety that it may not be safe to avoid lymphadenectomy in SLNB-positive patients, particularly in the cases previously demonstrated to benefit from early CLND such as intermediate thickness primary tumors and also those with high SLN tumor burden. The MSLT-2 investigators would argue that it may be the SLNB alone that provides the survival advantage for node positive patients and not the addition of the lymphadenectomy. A recently published international survey and anecdote suggested that melanoma surgeons were selective with the patients they offered the MSLT-2 [16]. The survey reported on 193 surgeons involved in melanoma treatment, of whom 78 (40.4%) were participating the MSLT-2 [16]. Only 56% of surgeons participating in the MSLT-2 offered virtually all patients randomization, whilst in the whole group of responders, which included non-MSLT-2 investigators, approximately one third thought the criteria for enrollment in MSLT-2 should be modified by considering predictors of non-SLN involvement at CLND and half the responders did not consider it appropriate to enroll patients with multiple positive SLNs in MSLT-2. This selection bias towards lower risk patients will firstly limit the power of the study to detect meaningful differences and secondly if this factor is accurately reported when it comes to publication then the results should only apply to those patients fitting into the characterization of the typical MSLT-2 patient. There is a great similarity with the ACOSOG Z11 study testing the need for completion axillary lymphadenectomy after positive SLNB in breast cancer patients [17]. The Z11 trial was slow to recruit (and indeed never reached accrual target) and mainly involved low risk patients but despite this, at least in some parts of the world, has ended up changing practice for all LN-positive patients [18].

Considering these issues in more detail with regards MSLT-2, it should be noted that patients are not stratified according to the amount of melanoma in the SLN. In the last decade several studies have underlined the predictive and prognostic value of several measurements of melanoma SLN metastasis, such as the diameter of the largest metastasis [19], the location of the metastasis within the SLN [20], the penetrative depth of the metastasis in the SLN [21], the metastatic area [22], the presence of dendritic cells [23] and intra-lymphatic melanoma cells [24]. These parameters correlate not only with patient survival, but also with the probability of