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EDITORIAL – MELANOMAS

MelMART Trial: It's Now or Never

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Local recurrence after resection of cancer can be a result of many factors, including bad tumor biology, inadequate surgical margins, and lack of effective adjuvant treatments. Removing all macroscopic disease remains a basic tenet of surgical oncology. However, the importance of removing additional "normal" tissue beyond the tumor continues to evolve. Careful studies of the *widest* surgical margins, amputation for sarcoma, or mastectomy for breast cancer have failed to completely eliminate the risk of local recurrence or to improve long-term survival when a less radical option was available.

Surgeons have been attempting to define the optimal surgical margins for melanoma since the original observations of Handley in 1907, in which he described the autopsy findings of a patient who died from advanced melanoma. This report documented multiple subcutaneous metastases extending well beyond the primary melanoma site—what we now call satellitosis.[1] For decades, these observations had been used to justify wide local excision with a 5-cm margin. Satellite lesions, as a manifestation of regional intracutaneous and/or subcutaneous lymphatic spread, are uncommon, found in approximately 4% of melanomas, and are associated with poor survival.[2] The purpose of a wide excision, therefore, is to remove both the primary tumor, which can have asymmetric and unpredictable contiguous spread, as well as the rare subclinical extension of the tumor. Local recurrence, as a first event of recurrence, is associated with a poor survival of $< 10\%$.[3]

Data from multiple, prospective, randomized trials have supported backing down from Handley's original 5-cm–wide margin recommendations without significantly compromising either local recurrence or survival. The first Swedish trial demonstrated the safety of 2-cm margins compared with 5 cm for melanomas $\leq$ 2-mm thick.[6] The WHO trial demonstrated the safety of 1-cm compared with 3-cm margin for melanomas $<$ 2-mm thick.[4,5] The Intergroup trial demonstrated the safety of 2-cm compared with 4-cm margins for melanomas 1–4-mm thick.[4–7] More recently, a second Swedish trial comparing a 2-cm margin with a 4-cm margin for melanomas $>$ 2-mm–thick found that, although there was a trend towards increased local recurrence in the narrow margin group (4.3 vs. 1.9%, $P = 0.06$), there was no difference observed in melanoma-specific or overall survival between the two groups.[8] What is remarkable about all of these trials is that the local recurrence rates were consistently less than 5%.

In contrast to these trials showing no association between narrower margins and outcome, follow-up of a more recent United Kingdom trial comparing 1- versus 3-cm margins for melanomas $\geq$ 2-mm thick demonstrated an increased combined local–regional-nodal recurrence and worse melanoma-specific survival (MSS) in the narrow margin group, despite the fact that the local recurrence rate alone was not different between groups.[9,10] It is not clear that the groups were equally balanced for risk, because patients in this trial did not undergo a sentinel lymph node biopsy. However, the implication was that the 1-cm margin missed residual disease that resulted in increased local/regional/nodal relapse and decreased melanoma-specific survival, disease that would have been encompassed by an additional 2-cm margin. Because these patients are already managed with a 2-cm margin, and there has been no trial addressing a 2 versus 3 cm margin for melanomas $\geq$ 2-mm thick, this trial was not practice-changing. The collective results of these trials, most of which support the safety of narrower margin excisions for melanoma, leave us with the final remaining unanswered question: is a 1-cm margin safe for patients with melanomas $\geq$ 2-mm thick and therefore for all primary invasive melanomas?

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The MelMART trial aims to determine the safety of 1- versus 2-cm margins for patients with melanomas ≥ 1-mm thick undergoing sentinel lymph node biopsy, an equivalency trial design, which is estimated to require a sample size of approximately 10,000 patients. Patients are stratified into intermediate- (IB-IIA) and high-risk groups (IIB-IIC) based on initial biopsy microstaging, then randomized 1:1 to 1-cm or 2-cm resection margin. The primary endpoints of the trial are local recurrence and melanoma-specific survival. In this current report, the authors describe the initial feasibility results of the trial.[11]

Over 18 months, the trial has accrued 473 patients worldwide. Although the follow-up is too short to determine the primary endpoints of the trial, short-term surgery-specific outcomes and quality of life (QoL) are reported. Not surprisingly, there was an increased need for reconstruction (defined as a local flap or skin graft) in the 2- versus 1-cm margin groups (34.9% 2 cm vs. 13.9% respectively); this was most pronounced in the patients with head and neck melanoma (68.6 vs. 8.3% respectively). Wound necrosis rate was increased in the 2- versus 1-cm margin groups (3.6 vs. 0.5% respectively). However, despite the increased need for reconstruction and the increased rate of wound necrosis in the 2-cm margin group, there was no increase in the overall surgery adverse event rate in the wide margin group.

The interim results of this trial are important on several levels. First, it affirms that surgeons can recruit and patients will participate in this trial; of the 718 patients meeting inclusion criteria, 473 patients (66%) agreed to be randomized to wide versus narrow margins. This is a high rate for a surgical trial. Second, it demonstrates that surgeons are good at performing wide excisions, even those requiring reconstruction, with a low wound necrosis rate < 4% and an overall surgical adverse event rate of approximately 10%, regardless of the margin. Although there was a significantly higher wound necrosis rate in the 2-cm margin, which likely was associated with more wound care and physician visits, this the study was unable to demonstrate an effect on early difference in quality of life outcomes, again recognizing the high quality supportive care provided to patients. These excellent short-term outcomes support the concept of equipoise in the trial assignment arms.

However, if the short-term surgical results are good in both groups, why should we devote the considerable time and resources necessary to evaluate patient reported outcomes, the financial impact, and the oncological effect of a further reduction in surgical margins? First of all, melanomas > 2-mm thick are currently being excised in areas where a 2-cm margin cannot be obtained; the safety of this practice is unknown. Second, quality of life and cost over the long term may have significant implications not highlighted in this early report. The benefit to the patient who is able to return to work immediately after a 1-cm excision closed primarily in a cosmetically sensitive area, such as the face, will have ramifications over many life years. Furthermore, the cost of an increased reconstruction rate should not be overlooked. While the cost reduction may be marginal per patient, because patients requiring a SLN biopsy will still require a procedure in the operating room, the cost reduction over the entire population could be quite large. If the short-term surgical morbidity and the long-term oncological results are comparable, then an economic model demonstrating the anticipated cost savings of narrower margins would certainly help to justify continuing efforts to complete this trial.

If we believe that the short- and long-term surgical benefits and the potential improvements in quality of life and the cost savings provide sufficient impetus to pursue the question of optimal surgical margins for patients with thicker melanomas, it is imperative to address whether this trial is feasible to complete in its current form, because problems with contemporary relevant endpoints and patient accrual are not trivial. Other margin trials have experienced similar issues. The recent trial of 2- versus 4-cm margins changed from an equivalency to a noninferiority trial design, in large part due to slow accrual. The U.K. trial comparing 1 versus 3 cm for melanoma > 2 mm also expanded the number of patients and modified the initially proposed primary endpoint of local recurrence to a combination of local, regional in-transit, and nodal recurrence because of fewer than expected observed events at interim analysis.

Although not statistically significant, the early reported imbalance in SLNB positivity rate (22.9 vs. 15.2% for 2 vs. 1 cm respectively) is worrisome. While the standard primary tumor factors predicting SLN positivity appeared balanced, the observed difference in SLNB positivity merits close observation and consideration of other criteria for stratification if it continues.

The current target population of the MelMART trial, patients with melanomas > 1-mm thick, may be incorrect. Results from prior prospective, randomized trials already support the safety of a 1-cm margin for melanomas < 2-mm thick; it is not clear that all clinicians would maintain equipoise about randomizing a patient with a 1.1-mm melanoma to a possible 2-cm margin. The important clinical question to be addressed is about the safety of a narrower margin of 1 cm for the ≥ 2-mm thick group. Although focusing on this higher risk group would limit the number of eligible patients, the trial would then directly address the unmet clinical need. If the lower-risk group were removed from the trial, patient target accrual goals would need to be adjusted according to a different set of expected events.

The current primary endpoints of the MelMART trial are local recurrence and melanoma-specific survival (MSS). Local recurrence is the most meaningful primary endpoint, despite the fact that this remains a very uncommon event. In the era of increasingly effective systemic therapies, melanoma-specific survival is no longer as dependent on surgery alone as it has been in the past. It may not be possible to ascertain the role of surgery versus adjuvant treatments on MSS, which will not be consistent amongst patient groups.

All of these issues are compounded by the nearly insurmountable challenge of accrual to a huge equivalency trial. Randomized trials to demonstrate equivalency (or even noninferiority) for an event that happens in less than 5% of patients are nearly impossible to complete. At the current rate of 400 patients per year, it would take more than 20 years to accrue the proposed target of 10,000 patients; even if accrual expands to 1000 patients per year as more centers participate, the timeline for accrual and follow-up seems untenable. With these concerns in mind, the investigators could consider redesigning the trial as a noninferiority trial, while at the same time, providing a realistic timeline for recruiting additional centers and accruing the requisite patient population. These calculations should include a futility analysis whereby if proposed accrual targets are not met, the trial would be abandoned.

This is an important and clinically relevant trial that directly addresses an unmet need in melanoma surgery. It has the potential to impact the care of generations of melanoma patients, while at the same time providing valuable information about the underlying biology of localized melanoma. If the trial demonstrates either equivalency or noninferiority, it has the potential to reap long-term healthcare cost savings far in excess of the cost of the trial itself. If it fails to demonstrate either equivalency or noninferiority, we will know for certain what the minimal safe margins of excision are for invasive melanoma. However, the trial is unlikely to achieve any of its goals unless the worldwide community of melanoma surgeons prioritizes participation and patient accrual. For this melanoma community, the time is now to decide if we should invest the time and resources necessary to complete this trial. If not now, then never.

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