Surgical management of melanoma

Erin E Burke, MD, MS1 and Vernon K Sondak, MD1,2

Abstract
Surgery remains one of the key treatment modalities for melanoma, particularly for early-stage disease when surgery alone can be curative. Wide excision of the primary site with sentinel lymph node biopsy for selected patients has been recognized as the standard surgical approach for patients without clinically evident lymph node involvement. However, questions remain about excision margins and when to perform a sentinel lymph node biopsy. Furthermore, how much surgery should be performed in the setting of a positive sentinel lymph node biopsy has become a particularly controversial topic, with the recent publication of 2 studies not showing a survival benefit for completion lymph node dissection. Additionally, surgical management for metastatic disease and recurrence of regional nodal basins is changing as both new local–regional and systemic therapies are changing the role for surgery in patients with recurrent local–regional as well as metastatic disease. In this article, we discuss the current recommendations as well as the topics of debate in the surgical management of melanoma.

Margins of excision
The first step in the surgical management of melanoma is excision of the primary lesion with negative margins. The margins are defined by measuring a specific predetermined distance from the edges of the biopsy site or any remaining pigmentation, radially in all directions. The depth of the excision, the deep margin, is determined to be the investing fascia of the underlying muscle. As such, the vertical thickness of the excision varies based on anatomic location and body habitus.

Invasive melanoma margin recommendations
A number of studies guide the current National Comprehensive Cancer Network (NCCN) recommendations regarding the measured margin that is taken at the time of excision of a primary melanoma.1-6 For a thin (≤1 mm, T1) melanoma, a 1 cm margin is recommended, while for a melanoma >2 mm thick (T3-T4), a 2 cm margin is recommended. For those melanomas >1-2 mm thick (T2), a 1-2 cm margin is recommended. The range of 1-2 cm that is recommended for a 1-2 mm melanoma is a result of the fact that no randomized controlled trial has directly compared a 1 cm versus 2 cm margin for this situation. In this group of patients, the decision to take a 1 cm versus 2 cm margin is often based on location and ability to close the defect primarily. A recent retrospective review looked at both local recurrence rates and disease-free survival in 965 patients with a 1-2 mm thick melanoma who underwent either a 1 cm or 2 cm margin excision. This study showed no difference in either local recurrence or disease-free survival between those patients who had a 1 cm margin versus a 2 cm margin.7 Additionally, this study showed a decreased need for graft or flap reconstruction when a 1 cm margin was used, which was statistically significant in head and neck and extremity primary melanomas.7 There were no statistically significant differences in histopathologic prognostic factors between the 2 groups, but there may have been subtle surgical biases in choosing the wider margin for more aggressive lesions. Given these findings, we recommend a 1 cm margin for melanomas 1-2 mm thick in areas such as the head and neck where it will avoid the need for grafting, particularly in the absence of adverse factors such as ulceration, high mitotic rate, or angiolymphatic invasion (Table).

As previously noted, the deep margin is determined to be the investing fascia of the underlying muscle. Excision of the fascia is indicated should it be grossly involved with disease or to ensure the excision extends to a level deeper than the initial biopsy. However, whether or not to routinely excise this layer of fascia remains controversial. The first retrospective review on this topic was published in 1964.8 This study was a review that looked at 112 patients who underwent wide excision for melanoma and compared the local recurrence rate

1Department of Cutaneous Oncology, Moffitt Cancer Center, Tampa, Florida.
2Departments of Oncologic Sciences and Surgery, University of South Florida Morsani School of Medicine, Tampa, Florida.

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Correspondence: Vernon K Sondak, MD; Vernon.Sondak@moffitt.org

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Surgical management of melanoma for those patients who had fascia excised versus those who did not. This study showed no difference in local recurrence rates. As a result of this publication, routine excision of the fascia was no longer performed at University of Texas MD Anderson Cancer Center starting in 1969. This institution performed a retrospective review of the patients who had had fascia excised prior to 1969 and those who had not because they underwent excision after 1969. Results of this study showed no significant difference between the 2 groups with regards to local or regional recurrence. More recently, a number of studies have again looked at this question. In a retrospective study by Grotz et al that included 964 patients, there was no difference in local recurrence between patients who had fascia excised versus those who did not. However, there was an increased recurrence rate in the major nodal basin in those patients who had both sentinel lymph node biopsy and excision of fascia, resulting in the authors stating that, in fact, preservation of the fascia is recommended. Another study, by Hunger et al, reviewed patients with melanoma ≥2 mm thick and also found no difference in disease-free and overall survival between patients who had fascia routinely excised and those who did not. While prospective data continue to be lacking, retrospective data suggest that routine excision of the investing muscle fascia does not improve outcomes.

Melanoma in situ margin recommendations
Melanoma in situ should be resected to negative margins whenever possible because it has the ability to progress to invasive melanoma if not completely removed. The NCCN recommends a 0.5-1 cm margin at time of excision of melanoma in situ. Of note, unlike for invasive melanoma, the margin recommendations for melanoma in situ come only from retrospective studies because no prospective randomized controlled trial has been completed comparing margins for melanoma in situ. Therefore, when choosing a margin for melanoma in situ (Table), one should take into account not only the anatomic location of the lesion and ability to close the defect primarily but also other factors such as residual pigmentation, which could potentially represent the presence of an unrecognized invasive component that would merit a wider excision margin.

Areas of controversy regarding margin recommendations
Despite the above recommendations, there are a number of areas where the optimal margin size remains unclear. For example, when treating lentigo maligna (a form of melanoma in situ in heavily sun-exposed skin), it has been shown that >0.5 cm margin is often needed to clear the lesion, particularly if located on the head or neck. In these cases, it may be prudent to use an excision technique known as staged contoured marginal excision, in which full-thickness strips of skin are removed 0.5 cm or more beyond the area of pigmentation, essentially creating a picture frame around the lesion. These strips are sent for permanent pathology review. Should these strips be without evidence of disease, the central portion of skin inside the frame, or the “picture,” is then excised, and the area can be closed primarily or with a graft or flap as needed. Another option is to take punch biopsies around the lesion to help map out the subclinical extent of the tumor, to help ensure negative margins are achieved.

Another example of an area of controversy with regards to margin width is related to melanoma in children. All of the data for margin widths come from trials that excluded those less than 18 years of age. Therefore, it is unclear whether these recommendations truly apply to children with melanoma, for whom wide margins of excision can lead to increased deformity and local recurrence rates may be inherently lower than in adults. Our current practice is to excise to a margin of 1 cm in all children less than 14 years of age regardless of lesion thickness and for all atypical Spitz tumors in patients of any age. For older children with invasive melanoma, excision margins are based on melanoma thickness as they are for

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<th>TABLE Summary of recommendations for surgical management of the primary tumor and regional lymph nodes in early-stage melanoma</th>
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<td><strong>Melanoma in situ thickness</strong></td>
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Abbreviation: SLNB, sentinel lymph node biopsy
adults, as outlined by the NCCN guidelines reviewed above.\textsuperscript{14} With this approach, the local recurrence rate in our children with invasive melanoma and atypical Spitz tumors has been extremely low.\textsuperscript{15} However, prospective data to back our approach are currently lacking.

A final example of an area of controversy regarding margin size is desmoplastic melanoma. Desmoplastic melanoma is a rare subtype of melanoma that has been reported to have a higher local recurrence rate after wide excision in a number of series.\textsuperscript{14,16} In a study published in 2010, 1 cm and 2 cm margins were compared in patients with pure and mixed desmoplastic melanoma, and this study showed more local recurrence in those patients undergoing excision with a 1 cm margin.\textsuperscript{17} Therefore, when considering margins for desmoplastic melanoma, a low threshold for a wider margin may be appropriate. On the other hand, when dealing with desmoplastic melanoma, one should also consider the use of adjuvant radiation. Support from this comes from a retrospective series that evaluated 277 patients with desmoplastic melanoma, who underwent either wide excision alone or wide excision plus adjuvant radiation.\textsuperscript{17} In this study, adjuvant radiation was found to be associated with improved local control on multivariate analysis. Furthermore, radiation significantly reduced the local recurrence rate for those patients with positive margins and those with high-risk features, including thickness >4 mm and head or neck location.\textsuperscript{17} What remains unknown, however, is whether the ability to decrease local recurrence risk with radiation justifies routine use of a narrower (1 cm) excision margin.

**Reconstruction options**

Closure of the primary defect after excision of melanoma can be accomplished in a number of ways. Primary closure is the most straightforward and preferred method of closure should the defect be amenable to re-approximation without excessive tension. However, this may not be possible in certain locations, and other options for closure must be considered. One such option is closure with rotational or advancement flaps. Another option is skin grafting, either full thickness or partial thickness, to the excision site. Both techniques have been shown to provide good coverage of the excision site. Consideration of a full-thickness graft with the donor tissue being excised from the sentinel node biopsy site offers some unique advantages. For one, it eliminates the third wound that needs to heal if skin is taken from another donor site. Additionally, a retrospective study comparing this approach to standard split-thickness grafting showed a slight improvement in graft take rate for the full-thickness grafts without any difference in perigraft recurrence.\textsuperscript{18}

Timing of reconstruction can also be critical. Delayed reconstruction should be considered in certain situations in which there is a need for complicated coverage of the resultant defect. Delayed reconstruction in this setting allows time for permanent pathological examination of margins to ensure the margins are in fact negative before tissue is rearranged for closure. A number of biological dressings have been shown to be a good substitute for autologous coverage while awaiting definitive reconstruction. One such option for temporary closure is the use of AlloDerm, which is an acellular dermal matrix. In a series in which 67 patients underwent AlloDerm closure, overall results were good, with 85% of patients showing healthy incorporation of AlloDerm at their first post-op evaluation.\textsuperscript{19} Furthermore, 60% of patients healed their wound after AlloDerm placement without any other type of reconstructive surgery.\textsuperscript{19}

**Sentinel lymph node biopsy**

Another critical aspect of the surgical management of melanoma is assessment of the regional nodal basins for metastasis, because the presence or absence of melanoma in the regional nodes remains one of the most important prognostic factors in patients with localized intermediate thickness or thick melanoma.\textsuperscript{20–22} Surgical staging of the clinically negative (cN0) nodal basin, when indicated, is accomplished by sentinel lymph node biopsy.

A sentinel lymph node biopsy is performed by injecting either or both a radiocolloid and vital blue dye intradermally at the site of the primary melanoma.\textsuperscript{23} The radiocolloid is injected preoperatively so that a planar or computed tomographic lymphoscintigraphy can be performed, which allows for the identification of the general location and number of the sentinel lymph nodes. The vital blue dye is then injected after induction of general anesthesia. The sentinel nodes are identified intraoperatively using both a handheld gamma probe to identify radioactive nodes as well as visual inspection for lymph nodes that are stained blue. The “hot” and/or blue nodes are then excised and sent to pathology for evaluation for histologic evidence of metastasis.\textsuperscript{23}

Melanoma most commonly maps to the major nodal basins, which include the cervical, axillary, and ilioinguinal nodal basins.\textsuperscript{24} However, melanoma may metastasize to lymph nodes anywhere between the primary melanoma and the draining major basin. An interval node has been defined as any node that is identified “on workup with lymphoscintigraphy or incidentally at surgery or clinically based on involvement that [is] not located in either a major or minor nodal basin” (eg, epitrochlear or popliteal nodal basins).\textsuperscript{25} An in transit node has been defined as any node located between the primary melanoma and the draining major nodal basin and as such would include nodes in minor nodal basins.\textsuperscript{25} These lymph nodes will be found on the preoperative lymphoscintigraphy anywhere from 2.1% to 9.8% of the time.\textsuperscript{26,27} Analysis of the Sunbelt Melanoma Trial database, which included 2,332 patients who underwent sentinel lymph node biopsy, revealed that 3.1% of patients had in transit nodes identified as a sentinel node, and of those, 21% (13 patients) were positive for metastatic dis-
These studies suggest that in transit sentinel nodes should be biopsied when present because they provide important prognostic information that may be missed if only the sentinel nodes in the main basins are removed. However, how the regional nodal basin should be managed in light of a positive in transit sentinel lymph node biopsy remains less clear, though this may be of less controversy given recent changes in indications for completion lymph node dissection discussed below.

Current NCCN guidelines recommend that sentinel lymph node biopsy be performed for all patients with melanoma ≥1 mm in thickness without clinical evidence of nodal disease. For those patients with melanoma 0.8-1 mm in thickness and for those <0.8 mm in thickness with ulceration, the NCCN guidelines recommend “considering” sentinel lymph node biopsy.1

A recent publication of the American Society of Clinical Oncology (ASCO) and Society of Surgical Oncology (SSO) updates prior recommendations (Table) and states that sentinel lymph node biopsy should be performed for all patients with a melanoma 1-4 mm thick without clinical evidence of nodal disease. It recommends sentinel lymph node biopsy be “considered” for those patients with a melanoma ≤0.8 mm thick that is ulcerated and for those with a melanoma 0.8-1 mm thick. Additionally, it advises that sentinel lymph node biopsy can be recommended for melanoma >4 mm thick but only after a “thorough discussion of the risks and benefits.”20 These recommendations have changed from previously published guidelines by ASCO and SSO, which had also included mitotic rate as a high-risk feature to suggest sentinel lymph node biopsy be considered in thin melanomas. Some of these changes are in response to the new American Joint Committee on Cancer staging system, which now requires that the thickness of melanoma be reported to a 10th, not 100th, of a mm (one decimal place) as well as removes mitotic index from the staging system, given new data that suggest that it is not a key predictor of survival.29,30

As already noted, the prognostic benefit of the evaluation of lymph node basins with sentinel lymph node biopsy has been well established, particularly by the Multicenter Selective Lymphadenectomy Trial 1 (MSLT-I).20,31 In the MSLT-I, 1,347 patients were randomly assigned to undergo either wide excision with observation of the nodal basin versus wide excision with sentinel lymph node biopsy and subsequent completion lymph node dissection if there was a positive sentinel lymph node. This study showed a significant 10-year melanoma-specific survival impact for those patients who had a negative sentinel lymph node biopsy compared to those who had a positive sentinel lymph node biopsy (85.1% versus 62.1%) and, as such, confirmed the importance of sentinel lymph node biopsy for prognosis.21

However, the role of sentinel lymph node biopsy in improving survival remains a topic of debate. Final analysis of the MSLT-I data demonstrated no difference in melanoma-specific survival at 10 years between the sentinel lymph node biopsy group and the observation group.21 However, there was a significant 10-year disease-free survival benefit for those patients who had a sentinel node biopsy versus those who underwent observation (71.3% versus 64.7%).21 Additionally, this study also showed a significantly improved 5-year melanoma-specific survival for the subgroup of patients who had a positive sentinel node and underwent completion lymph node dissection compared to the group who underwent observation, developed nodal disease, and then underwent therapeutic lymph node dissection at time of disease development (72.3% versus 52.4%).21 It is this analysis that has driven the recommendation for completion lymph node dissection after positive sentinel lymph node biopsy up until very recently, which is discussed below.

**Lymph node dissection**

Lymphadenectomy, or lymph node dissection, is defined as en bloc removal of all the lymph node tissue in a nodal basin. Before the development and adoption of sentinel lymph node biopsy as the standard of care, the draining lymph node basin could be managed with either therapeutic lymph node dissection or elective lymph node dissection. Therapeutic lymph node dissection is lymphadenectomy of the draining nodal basin that has been proven to harbor melanoma metastases. Today, this remains the standard approach for management of the draining nodal basin in patients who present with clinically evident lymph node involvement without distant metastases. Elective lymph node dissection is lymphadenectomy of a draining lymph node basin without clinical evidence of melanoma metastases. Elective lymphadenectomy has now been replaced by sentinel lymph node biopsy with completion lymphadenectomy for only those patients with a positive sentinel lymph node biopsy. This approach spares approximately 80% of patients from an unneeded elective lymphadenectomy as only 16%-20% of patients with an intermediate thickness melanoma are expected to have clinically occult nodal metastasis at time of diagnosis.21

As noted, completion lymph node dissection has replaced elective lymphadenectomy as the standard of care for patients without clinical evidence of lymph node disease. This approach was largely driven by the results of the MSLT-I reviewed above. However, this was data from subgroup analysis, and as such, controversy regarding the survival benefits of completion lymph node dissection have been ongoing for some time. Two studies that aimed to address this very question have recently published their initial data on this topic.
The German DeCOG-SLT study included patients with a positive sentinel lymph node biopsy and randomized them to either observation or completion lymph node dissection. A total of 483 patients were randomized. Distant metastasis-free survival at 3 years was not found to be significantly different between the 2 groups (77% for observation group and 74.9% in completion lymph node dissection group). Furthermore, 3-year overall survival was not found to be significantly different between the 2 groups (81.7% for observation and 81.2% for completion lymph node dissection group). The MSLT-II study similarly took patients with positive sentinel lymph node biopsies and randomized them to observation or completion lymph node dissection. The 3-year melanoma-specific survival rate was not found to be significantly different between the 2 groups; it was 86% for both groups.

While these studies are the first to provide randomized data regarding survival for completion lymph node dissection, these data must be interpreted with caution. For one, the DeCOG-SLT study struggled with enrollment and as such was closed early; as a result, it was underpowered with regards to its primary endpoint of distant metastasis-free survival. Second, in the DeCOG-SLT, the rate of positive nonsentinel lymph nodes was only 18%, and in the MSLT-II, it was only 11.5%. This means that any survival benefit would likely be diluted, particularly in the case of the DeCOG-SLT study, which was already underpowered. Additionally, the burden of disease in the sentinel node was relatively low in both studies, raising the question of how this data extrapolates to all patients with sentinel node-positive melanoma. Neither study addresses any differences in morbidity between those patients who underwent completion lymph node dissection versus those who were observed, developed evidence of lymph node disease, and underwent therapeutic lymph node dissection at that time. This is worthwhile information to note because there are good data to suggest that lymph node dissection performed once clinical disease is identified is associated with increased complication rates—particularly lymphedema—and also will have more lymph node involvement, increasing the likelihood for the need for adjuvant radiation therapy.

Finally, the results of these studies are in conflict with the results of the MSLT-I, which clearly showed a survival benefit for undergoing a sentinel lymph node biopsy and, if positive, completion lymph node dissection versus therapeutic lymph node dissection. Is this due to randomization fixing an inherent bias in the MSLT-I, which did not randomize to completion lymph node dissection versus observation? Or is this a result of the low rates of positive nonsentinel lymph nodes diluting the results? Or is it that the survival benefit is itself due to the sentinel lymph node biopsy? These questions remain unanswered.

As a result of these studies, the current NCCN guidelines for patients with sentinel node-positive disease without evidence of distant disease is “either completion lymph node dissection or observation.” The recently published guidelines by ASCO and SSO state that “either completion lymph node dissection or careful observation are options for patients with low-risk micrometastatic disease; for higher risk patients, careful observation may be considered only after a thorough discussion with patients about the potential risks and benefits of foregoing completion lymph node dissection.” Therefore, despite the availability of new data, the question of when to perform a completion lymph node dissection remains one without a clear answer.

Another point worth considering given this new data is the role of sentinel lymph node biopsy in an era in which completion lymph node dissection may no longer be routinely performed. As previously discussed, sentinel lymph node biopsy has predominantly been performed for its staging information. However, as fewer patients with positive sentinel lymph node biopsies undergo completion lymph node dissection, does sentinel lymph node biopsy become not only a procedure done for prognosis but also one done for definitive local–regional control? In other words, if you know you will not be performing a completion lymph node dissection in the setting of a positive sentinel node, do you become more aggressive with your sentinel lymph node biopsy in the hopes of removing all diseased nodes? Moving forward, this may become an important consideration for the surgeon when performing sentinel lymph node biopsies.

Metastasectomy for melanoma
Survival for metastatic melanoma has historically been poor; however, with the development of new systemic therapies, this is beginning to change. With regards to surgical management of metastatic melanoma, there have been a number of studies that have shown a survival benefit when all disease can be resected, but these studies are generally small retrospective reviews. However, newer data from larger studies as well as some prospective studies have also shown data to support metastasectomy in selected patients. First, in a study by Howard et al, the MSLT-I data were analyzed for patients who developed stage IV melanoma and underwent resection (plus or minus systemic therapy) versus systemic therapy alone. The 4-year survival was 20.8% versus 7% (\(P < .0001\)) for those who underwent surgery versus systemic therapy alone. In a phase II prospective trial by the Southwest Oncology Group, 64 patients were included in analysis after undergoing complete resection of metastatic disease. Overall survival at 4 years was 31% in this group. Finally, in a phase III randomized controlled trial looking at survival for patients with metastatic melanoma treated with resection and bacillus Calmette–Guérin (BCG) versus resection, BCG and Canvaxin showed a 5-year overall survival of 44.9% and 39.6%, respectively.

These data, along with other smaller retrospective studies, suggest that in selected patients, meaningful long-term surviv-
al can be achieved. However, which patients are most likely to achieve long-term survival after metastasectomy remains not entirely clear, and therefore indications for metastasectomy remain vague. Furthermore, the development of a number of new and effective systemic therapies for melanoma will likely increase the potential use and success of metastasectomy, and as such, indications are likely to be changing. In a recent publication by Ferguson et al, many of these new treatments are reviewed in the context of their possible impacts on the surgical management of melanoma. For example, new targeted therapies like BRAF inhibitors and immune checkpoint inhibitors like ipilimumab and nivolumab have opened up the opportunity for neoadjuvant therapy in melanoma. Additionally, work is being done that evaluates surgery as another way of modulating the immune system and as such addresses the question of when is the best time for surgery. While work is ongoing, questions about what metastatic lesions should be resected, the timing of this resection, and how to best combine systemic, surgical, and radiation therapies will remain. Therefore, the decision about when to pursue metastasectomy continues to be made best on a case-by-case basis in the setting of a multidisciplinary tumor board.

**Salvage surgery for recurrence**

There are a number of treatment options for locoregional recurrent melanoma. These options include wide excision, isolated limb infusion (ILI), hyperthermic isolated limb perfusion (HILP), intralesional injection, and radiation therapy, as well as systemic therapy with either targeted therapies or immunotherapy. The choice of treatment requires consideration of the location, distribution, and overall burden of disease as well as the morbidity associated with each treatment.

In cases in which the disease is limited to a small area, wide excision with negative margins is preferred and has shown good results. For multiple sites of disease not amenable to wide excision but confined to an extremity, both HILP and ILI can be considered. HILP involves open surgical placement of arterial and venous catheters in the effected limb. The limb is then isolated from systemic circulation by use of a tourniquet. Using an extracorporeal bypass circuit, the extremity is perfused with warmed, oxygenated melphalan. At the same time that the vessels are exposed for cannulation, a lymph node dissection can be performed. In contrast, ILI involves percutaneous placement of arterial and venous catheters. The limb is isolated by use of a tourniquet. The limb is then infused with melphalan and actinomycin D that is also warmed but is infused at a lower flow rate and without oxygenation.

HILP has been shown to have complete response rates as high as 40% to 81%. ILI has been shown to have complete response rates ranging from 23% to 43%. In general, HILP has been traditionally reported to have higher response rates, but to date, no randomized controlled trial has ever compared the 2 procedures head to head. However, 2 nonrandomized trials have been done comparing ILI and HILP: one was a retrospective review and the other a prospective review. In the study by Dossett et al, the overall response rate of HILP versus ILI was compared and showed that the objective response rate was higher for HILP (80%) versus ILI (53%). However, the median overall survival was not significantly different (40 months for HILP versus 46 months with ILI; P = .31) despite a higher burden of disease in the ILI group. In the study by Raymond et al, the overall response rate was similarly found to be higher for HILP (81%) versus ILI (43%), but again, overall survival was not different between the 2 groups. Furthermore, when reviewing data across several studies, we have found the rate of limb loss for HILP to be 2% (6 of 294), compared to 0.3% (1 of 313) for ILI. Given the current data, ILI is our favored approach because it provides good disease control, comparable survival outcomes, and less risk of severe complications, as well as an increased ease in repeating the procedure given its percutaneous approach for catheter placement.

Another option for the treatment of recurrent locoregional disease is intralesional therapy. The mechanism of action thought to be behind this type of therapy involves both a cytotoxic effect due to the local injection of the tumor itself as well as an immune-mediated cytotoxic effect due to induction of the immune system against the tumor cells. This systemic activation of the immune system is thought to be the reason behind the so-called “bystander effect,” which is regression of additional or all lesions, not just the injected lesions.

Currently, talimogene laherparepvec (T-VEC) is the only intralesional agent approved by the US Food and Drug Administration for treatment of patients with IIIB, IIC, IVM1a unresectable and injectable metastatic melanoma. T-VEC is a modified herpes simplex type 1 oncolytic virus. It is designed to selectively infect and replicate only in tumor cells, causing lysis of the infected tumor cells, as well as local production of granulocyte macrophage colony-stimulating factor (GM-CSF), which is thought to stimulate an immune response against tumor cells. The efficacy of T-VEC has been shown in a number of trials; however, the key study regarding this medication was the Oncovex (GM-CSF) Pivotal Trial in Melanoma (OPTiM Trial), which was a randomized controlled phase III trial that randomized patients with unresectable stage IIIB to IV melanoma to receive intralesional T-VEC versus subcutaneous GM-CSF. This study showed a significantly higher durable response rate for T-VEC of 16.3% compared to 2.1% for GM-CSF (P < .001). On subgroup analysis of patients staged IIIB, IIC, and IVM1a, there was an even more pronounced difference in outcomes in favor of T-VEC over GM-CSF. While the OPTiM study only showed a trend in improved overall survival for T-VEC over GM-CSF, this same subgroup analysis did in fact show a significant overall survival benefit for treatment with T-VEC in patients with stage IIIB, IIC, and IVM1a disease (hazard ratio 0.57;
95% CI 0.4-0.8). These findings support the use of T-VEC as part of the therapeutic options for recurrent locoregional melanoma.

A number of other agents aside from T-VEC have been previously investigated or are under investigation for use in intralesional therapy in metastatic melanoma. Some of these agents include velimogene aliplasmid, BCG, interleukin 2 (IL-2), and rose Bengal (also known as PV-10). Velimogene aliplasmid initially showed promise in early trials; however, it never met its endpoint in phase III trials. Other agents like BCG and IL-2 have been limited by a number of different factors, which include a high toxicity profile, difficult administration schedule, and cost. Rose Bengal remains under current investigation, and results of ongoing trials with this agent are pending.

Conclusion

Surgery continues to play a critical role in the management of melanoma. Wide excision of the primary melanoma with sentinel lymph node biopsy when indicated remains the standard surgical approach for the treatment of early stage melanoma. However, controversies remain in a number of areas, particularly with regards to surgical management of the draining nodal basins. New modalities such as intralesional therapy and new systemic therapies are also impacting traditional surgical approaches to recurrent local-regional and metastatic disease. Future work will need to continue to direct the best surgical approach for the treatment of melanoma in the setting of a rapidly changing field.

References

30. Burke et al
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