Chapter 19

Cutaneous Melanoma – Surgical Treatment

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Additional information is available at the end of the chapter

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1. Introduction

1.1. Excision margins for primary tumor

Although surgical excision of the primary melanoma is internationally accepted as the treatment of choice, several questions concerning the follow-up schedule are still debated controversially. Incision biopsies should be avoided, except in selected cases (wide lesions or critical anatomic locations). Excision biopsy is preferred to give the dermatopathologist an optimal specimen and to allow evaluation of the excision margins for residual tumor. Since the beginning of the last century, the recommendation has been to excise a primary melanoma with safety margins. In 1907 Handley [1] analyzed the pattern of satellite metastases in melanoma and recommended excision of the primary tumor with a margin of 1 inch (2.54 cm) from the edge of the tumor. In the 1970s and 1980s, safety margins of 5 cm, independent of tumor thickness, were the surgical standard.[2] The World Health Organization Melanoma Group performed the first surgical trial to compare lower safety margins of 1 and 3 cm in primary melanomas with less than 2 mm of tumor thickness.[3] The group found no differences in survival and only slightly increased local recurrence rates in the patients with narrower excision margins. These results led to the recommendation of 1-cm margins in patients with primary melanomas with less than 1 mm tumor thickness. Later comparisons of 5- and 2-cm safety margins in thick primary melanomas revealed no significant advantages for the 5-cm margins.[4] A recent trial, however, comparing 1- and 3-cm safety margins in thick primary melanoma with 2 mm and more tumor thickness showed an increased rate of local recurrence in those with the small safety margins and a simultaneous trend towards decreased survival rates. These findings indicate that the safety margin cannot be reduced to

zero in melanoma.[5] Different national guidelines now give uniform recommendations for the excision of primary melanoma.[6-9]

2. Sentinel lymph node biopsy and lymph node dissection

Metastasis to regional nodes is the most important prognostic factor in patients with early-stage melanoma and has been shown to occur in approximately 20% of patients with intermediate-thickness tumors.[10,11] As such, it is critically important to identify those patients for whom the expected benefits of resecting regional lymph nodes outweigh the risks of surgical morbidity. The technique of lymphatic mapping and sentinel lymph node (SLN) biopsy for melanoma has emerged during the last 2 decades as a minimally invasive approach to evaluate regional lymph node basins in patients with intermediate- and high-risk primary cutaneous melanoma. Goals of SLN biopsy include accurate nodal staging, identification of patients with clinically occult, microscopic lymph node disease who may benefit from further treatment, regional nodal control, and a possible survival benefit.[12,13] Moreover, this approach may also identify a subset of patients for whom further treatment is not indicated, sparing them from unnecessary surgical procedures or systemic therapies.[12,13] In this review, we examine the evolution of SLN biopsy as a technique, the preoperative assessment and operative strategy, the pathologic evaluation of the SLN, the current practice guidelines, the prognostic significance of SLN biopsy findings, and the potential complications of the procedure and address some of the current areas of controversies in the field. Sentinel lymph node (SLN) biopsy is commonly used in melanoma and has been endorsed by the American Joint Committee on Cancer (AJCC) as a valuable staging procedure for patients with melanoma who are at risk of clinically occult nodal metastases. This highly accurate and low-morbidity staging procedure should be used to guide treatment decisions (ie, completion lymph node dissection [CLND] and adjuvant therapy) as well as entry into clinical trials.[14] To develop and formalize guideline recommendations for the use of SLN biopsy in oncology practice, the American Society of Clinical Oncology (ASCO) and Society of Surgical Oncology (SSO) convened a joint Expert Panel in order to better define what are the indications for SLN biopsy as well as what is the role of CLND. SLN biopsy is recommended for patients with intermediate-thickness cutaneous melanomas (Breslow thickness, 1 to 4 mm) of any anatomic site. Routine use of SLN biopsy in this population provides accurate staging. Although there are few studies focusing specifically on patients with thick melanomas (T4; Breslow thickness, > 4 mm), use of SLN biopsy in this population may be recommended for staging purposes and to facilitate regional disease control. There is insufficient evidence to support routine SLN biopsy for patients with thin melanomas (T1; Breslow thickness, < 1 mm), although it may be considered in selected patients with high-risk features when the benefits of pathologic staging may outweigh the potential risks of the procedure. Such risk factors may include ulceration or mitotic rate ≥ 1/mm^2, especially in the subgroup of patients with melanomas 0.75 to 0.99 mm in Breslow thickness. After a positive SLN biopsy, 97.5% of patients underwent CLND, and 20.1% were found to have additional positive lymph nodes. Overall, the recurrence rate in the same nodal basin after a positive

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SLN biopsy was 7.5%, despite CLND in nearly all patients.[15] Overall, the SLN biopsy procedure is well tolerated and associated with low complication rates.[16] Although clinical variables such as older age have been variably reported as lower risk factors,[17-19] there are no specific variables that can reliably identify patients with intermediate-thickness melanomas at low risk for metastases. The definition of intermediate-thickness melanoma varied by study. Nevertheless, it is clinically consistent with contemporary staging systems to define intermediate-thickness melanomas as those measuring 1 to 4 mm.[20] Clinical judgment must be used when considering SLN biopsy in patients with comorbid medical conditions. The individual risks and benefits of the procedure should be weighed against the operative and anesthetic risks as well as potential competing causes of mortality. Complications after SLN biopsy are uncommon. The overall complication rate reported in the Multicenter Selective Lymphadenectomy Trial I (MSLT I) was 10.1% after SLN biopsy compared with 32.7% after CLND.[21] The most common complications after SLN removal documented in MSLT I included seroma (5.5%), infection (4.6%), and wound separation (1.2%). The Sunbelt Melanoma Trial similarly showed a low overall rate of complications from SLN biopsy (4.6%) compared with CLND (23.2%).[16,17] Most complications were noted to be short-term issues that resolved over time with wound care and selective use of antibiotics. Accurate identification of patients with node-negative (stage I or II) or node-positive (stage III) disease improves staging and may facilitate regional disease control and decision making for treatment with adjuvant therapy.[14,22] With substantive changes in the melanoma staging guidelines in 2002, the AJCC staging system effectively linked disease stage and prognosis.[23,24] At that time, the number of nodal metastases and whether nodal disease was occult or clinically apparent (ie, how the N category was defined with regard to burden of disease) were noted to be the most significant independent predictors of survival in patients with stage III melanomas. With later iterations of the last AJCC staging system,[10] additional refinements were made in the N category based on the prognostic value of distinguishing micrometastases (as would be diagnosed after SLN biopsy) from macrometastases.[25,26] A melanoma macrometastasis is detected by clinical examination (not by size criteria) and confirmed pathologically, whereas a melanoma micrometastasis is a clinically occult nodal metastasis that is detected by a pathologist on microscopic examination of lymph nodes, with or without immunohistochemistry, and is not limited by any minimum or maximum size threshold. Recognizing the value of examining SLNs to detect low volumes of metastatic disease (aggregates of only a few cells), the current staging system[10,27] incorporates the use of immunohistochemistry and eliminates any minimum size threshold for defining nodal metastases. Molecular diagnostics, such as reverse transcriptase-polymerase chain reaction, have unproven prognostic significance, and these results are not used to define positive nodes. As a result, more refined definitions of the N category are now used for classification. Distinct differences in classifications have validated prognostic significance. For example, 5-year survival ranges from 70% for patients with one SLN positive with micrometastatic disease to 39% for patients with > four involved nodes or with nodes that are extensively involved (eg, matted nodes).[1] Although SLN biopsy has been widely accepted for the pathologic staging of patients with intermediate-thickness melanomas, somewhat more controversy exists regarding the value of this procedure for patients with thick primary tumors

(T4; Breslow thickness, > 4 mm). Conventional wisdom asserts that patients with thick melanomas have a high risk of systemic disease at the time of diagnosis and that no survival benefit can be derived from removal of regional lymph nodes. However, among patients without distant disease, it can be argued that those with thick melanomas have indications for SLN biopsy similar to those of patients with intermediate-thickness melanomas and derive the same benefits from SLN biopsy as a pathologic staging procedure. One of the main advantages of SLN biopsy in patients with thick melanomas is better regional disease control, which is especially important in a population with > 30% chance of lymph node involvement.[25,28] Evidence from multiple retrospective studies has demonstrated that SLN biopsy provides important staging and prognostic information for patients with thick melanomas. Seven of eight published studies-each evaluating SLN biopsy in > 100 patients with T4 melanomas-have shown that SLN biopsy is a significant predictor of overall survival.[11,25,26,28-33] The one study that did not show a significant difference in overall survival demonstrated a significant difference in disease-free survival.[29] A majority (70%) of melanomas diagnosed are thin melanomas (T1; Breslow thickness, < 1 mm).[34] In general, the routine use of SLN biopsy in patients with thin melanomas has not been advocated, because the overall risk of nodal involvement is estimated to be only approximately 5.1%,[35] although there are reports of positive SLNs in up to 20% of patients in subsets with thin melanomas (especially those that are 0.75 to 0.99 mm in thickness with ulceration and/or mitotic rate ≥ 1/mm^2).[27] An individualized approach to SLN biopsy for patients with thin melanomas has been advocated in many treatment centers based on risk factors that have been shown to be associated with SLN metastasis. Further investigation is also needed to better identify the subgroups of patients with thin melanomas with a greater risk of nodal metastasis. CLND is recommended for all patients with a positive SLN biopsy. CLND achieves regional disease control, although whether CLND after a positive SLN biopsy improves survival is the subject of the ongoing Multicenter Selective Lymphadenectomy Trial II (MSLT II). Currently, CLND is the standard recommendation for patients with tumor-positive SLNs. The goals of CLND are to improve survival rates, maximize regional disease control, and minimize operative morbidity. Whether CLND improves survival is the subject of the ongoing prospective randomized MSLT II study.[36] The main objective of MSLT II is to determine if there is a therapeutic benefit to removing any non-SLNs in patients who have already had their tumor-positive SLN removed. In MSLT I, patients with demonstrated nodal metastases had a survival advantage with early intervention compared with those who had a delayed lymphadenectomy when they presented with clinically evident nodal metastases.[5] Hence, although two goals of CLND are regional disease control and cure, there is currently insufficient evidence to determine whether omission of CLND is safe. In the two large prospective randomized trials (ie, the Sunbelt Melanoma Trial and MSLT I), the rate of positive non-SLNs among patients who underwent CLND for a tumor-positive SLN was 16%.[17,37] In a retrospective multi-institutional study by Wong et al,[38] which included 134 highly selected patients with positive SLNs who did not undergo CLND, regional nodal metastasis was a component of first recurrence in 15% of these patients. Therefore, it is reasonable to conclude from these data that the risk of developing regional nodal metastasis as a first site of recurrence, if no CLND is performed, is at least 15% to 20%.[39,40] In MSLT I,

the rate of regional nodal recurrence after CLND was 4.2%[5]; in the Sunbelt Melanoma Trial, it was 4.9% (unpublished data). These rates are much lower than the 15% rate of regional nodal recurrence as a site of first metastasis and the 41% overall regional nodal recurrence rate when CLND was not performed, reported in the study by Wong et al.[37] Until final results of MSLT II are available, we will not be able to determine, with higher-level evidence, the impact of CLND on regional disease control. Until that time, the best available evidence suggests that CLND is effective at achieving regional disease control in the majority of patients with positive SLNs. MSLT I showed no benefit of CLND with regard to overall survival, likely because only a minority of patients (16%) had tumor-positive SLNs, and the majority of the patients in the study would not have been helped by removal of regional lymph nodes.[37] However, the 5-year survival rate for patients with tumor-positive SLNs who underwent CLND was 72.3% compared with 52.4% for patients who did not undergo SLN biopsy and developed palpable nodal disease (hazard ratio, 0.51; 95% CI, 0.32 to 0.81; P =.004). CLND should be performed until there is convincing evidence that it does not improve regional disease control or survival. CLND is associated with risks of long-term morbidity, especially lymphedema. However, morbidity with CLND may be considerably worse when it is delayed until there is clinically evident disease. The observed increases in morbidity for patients who have undergone therapeutic lymphadenectomy for palpable disease and the increased morbidity associated with radiation therapy support the continued use of CLND for patients with a positive SLN biopsy rather than delayed CLND for palpable disease. There is a need for future clinical trials to address many unresolved research questions related to the use of SLN biopsy in patients with melanoma. These include: determining precise criteria for selecting which patients should undergo SLN biopsy, determining whether early identification of metastases in the SLN truly improves survival or merely represents lead-time bias, identifying which criteria for individualized risks best inform appropriate risk stratification for patients at high risk for relapse and those for whom CLND and/or adjuvant therapy are suitable, and establishing the role of prognostic markers from the primary melanoma and SLN to help assign appropriate risk stratification. Results from MSLT II, in which patients were randomly assigned to CLND or observation, will help determine whether there is any benefit to CLND after a positive sentinel node in patients with melanoma. Answers to these questions will assist clinicians and patients with making decisions and ultimately help to identify patients who may avoid expensive and intrusive procedures in staging and follow-up.

3. Treatment of *in transit* metastases

In 5–8% of cases, melanoma patients will develop in-transit metastasis (IT-mets). Standard regional treatment options include surgical resection, isolated limb perfusion (ILP), isolated limb infusion (ILI) and Electrochemotherapy. As regional recurrence often precedes systemic disease, amputative surgery is in general no longer practiced, although old series of radical surgery have demonstrated that some patients with IT-mets confined to the limb can be cured.[42,43] Simple surgical resection may suffice for incidental and low numbers of IT-

mets. In cases of rapid recurrences and multiple IT-mets, other techniques must provide an attractive treatment option that can improve local control markedly and thereby quality of life. ILP, developed by Creech et al., achieves a 20-fold higher concentration of chemotherapeutic drugs when compared with systemic therapy.[44,45] Melphalan-based ILP (M-ILP) has been the standard treatment and has been reported to achieve overall complete response (CR) rates in the range of about 50%.[46]In general large IT-mets showed a poor response and inhomogeneous uptake comparable with locally advanced soft tissue sarcomas (STS). The introduction of tumor necrosis factor-α (TNF) changed this situation dramatically. Large tumors now reacted very well to ILP.[47] This led to a successful multicenter trial in Europe and the approval of TNF-based ILP (TM-ILP) for unresectable extremity soft tissue sarcomas (STS).[48] Similar encouraging results were reported for the use of TNF in ILP for melanoma patients.[49] Preclinical and clinical studies suggested that a reduction of the dose of TNF to 1 mg for the arm and 2 mg for the leg might be as effective as the higher doses.[50-53]Isolated limb infusion (ILI) is a minimally invasive technique for delivering high-dose regional chemotherapy in locally advanced melanoma. It was first described by Thompson et al. in 1994 from the Sydney Melanoma Unit as a simplified alternative to ILP [54,55]. Percutaneous arterial and venous catheters are placed in the affected extremity by interventional radiologists and a tourniquet is placed proximal to the catheter tips to allow isolation of the limb from the systemic circulation. High-dose chemotherapy (e.g. melphalan and actinomycin-D) is infused into a hyperthermic, hypoxic limb via the arterial catheter and blood is withdrawn from the venous catheter to be re-infused into the arterial side. Therefore, it is a quicker, safer, and cheaper procedure with reported response rates comparable to ILP.[56,57] Although the primary indication for this technique is melanoma, it has been successfully applied to other tumors such as soft-tissue sarcomas,[58] Merkel cell tumor,[59] and cutaneous T-cell lymphoma.[60]

Electrochemotherapy (ECT) represents an effective therapeutic option for skin tumors that has received experimental and clinical support in recent years.[61-71] The European standard operating procedures for ECT emphasize the technical aspects of the procedure and have established this treatment in clinical practice.[72,73] In recent years, the effectiveness of ECT treatment has been confirmed in several small series of patients with melanoma.[71] At present, ECT is employed routinely with encouraging results not only for superficial tumor control but also to preserve quality of life.[70]Patients with regional or distant skin or subcutaneous metastases, with or without visceral disease, could undergo this technique. Eligibility criteria were the following: melanoma stage IIIC–IV (American Joint Committee on Cancer, 6th edition)[74] lesions no deeper than 3 cm suitable for electrode insertion; no anticancer treatments 4 weeks before and 8 weeks after ECT; age more than 18 years; and an Eastern Cooperative Oncology Group performance status equal to or less than 2. Exclusion criteria included: allergy to Bleomycin; pulmonary, cardiac or liver impairment; epilepsy; life expectancy less than 3 months; active infection; brain metastases; and cardiac pacemaker in patients with chest wall metastases. Bleomycin is administered intravenously (15 000 units/m^2 in a bolus administered over 60 s) and was followed, within 8 min after intravenous injection, by the application of brief electric pulses to each tumor nodule. Electric currents were delivered by means of a 2–3-cm long needle electrode according to lesion size.

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The electrodes were connected to a pulse generator (Cliniporator™; Igea, Modena, Italy). This generator produces high voltages (up to 1000 V), but delivered as a compressed train of eight pulses at a frequency of 5000 Hz and 100 μs duration, and therefore well tolerated by the patient. The software controls and stores the applied voltage and the actual current delivered to each tumor. ECT could be repeated every 8–12 weeks according to local response, the appearance of new lesions and the patient's tolerance of the treatment.

4. Surgical approach for distant metastases

Conventional teaching maintains that resection is not indicated in patients with distant metastases, except for palliation. This dogma stems from the concept that patients with multiple metastases usually also have occult micrometastases and circulating tumor cells. However the results of surgical treatment of stage IV melanoma patients have improved considerably over the past two decades. Recent studies [75] provide further evidence of the beneficial role of surgery for distant metastases of melanoma. Our findings indicate a survival advantage for a surgical approach, even in patients with high-risk visceral metastases or multiple metastases that may require multiple operations for complete resection. At least 55 % of stage IV patients may be eligible to undergo surgery as part of their treatment plan and the surgeon should play an integral role in evaluation and treatment planning for all patients with stage IV recurrence of melanoma. One potential therapeutic advantage of resection is that it may delay disease progression by interrupting the metastatic cascade associated with hematogenous seeding of cells to other sites.[76]In addition, it immediately reduces tumor burden and thereby decreases tumor-induced immune suppression.[77] Finally, metastasectomy may enhance the patient’s endogenous immune defences or response to adjuvant immunotherapy and thus maintain a complete clinical remission. Surgery for distant metastases has been improved by development of more advanced imaging techniques that can detect lesions as small as 5–10 mm.[78] These techniques can differentiate patients with multiple versus limited metastases, allowing surgeons to better judge the extent of disease and plan the operative procedure necessary for complete resection. In addition, modern advances in anaesthesia, surgical techniques and supportive care have reduced operative mortality from multiple metastasectomy with a corresponding reduction in morbidity and finally, shorter postsurgical hospitalizations have decreased the total costs of cancer surgery. Surgical therapy for stage IV disease remains controversial. The development of metastases is a complex process and the rationale for surgical resection of metastatic melanoma is multifactorial. First, reduction of tumor burden through surgical resection limits disease progression by interrupting the metastatic cascade associated with haematogenous seeding of cells to other sites. Unlike chemotherapy, surgery can easily eradicate tumor masses 2 cm or larger. Second, surgery may reverse tumor-induced immunosuppression, restoring immune function and inhibiting metastatic progression. Third, most patients tolerate surgical resection to a much greater extent than they can tolerate adverse effects of systemic therapy and recurrences after initial metastasectomy can also be treated through a secondary resection of metastases. Last, metastasectomy does not preclude systemic therapy;

however, if metastasectomy is delayed, increasing tumor burden may make disease unresectable. In addition the advent of newer and better systemic therapies makes the role of surgical resection more relevant today than ever before. Timing of surgery versus systemic treatment is another important end point. The development of new and effective drugs in the systemic treatment of stage IV melanoma patients have been reported recently, with the BRAF inhibitor Vemurafinib and the monoclonal antibody Ipilimumab; other targeted drugs are being developed, and some are currently being tested in the clinical setting. Thus a therapeutic strategy combining new drugs with aggressive surgery in selected cases of melanoma metastatic disease could be designed in the following years.

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