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The role of the surgeon in the management of melanoma

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While multimodality therapy has become the standard for most solid tumors, the mainstay of therapy for melanoma remains surgical. This includes not only early stage disease, but advanced melanoma as well. The surgical approach to melanoma has changed dramatically, with a trend towards less aggressive resection of the primary tumor, and towards a more aggressive approach to regional and metastatic disease. Melanoma surgery has been altered by our knowledge of the biology of the disease, and the results of well-designed, prospective randomized trials. Conversely, new surgical approaches have expanded our understanding of melanoma biology, and new randomized trials are needed to further define the optimal surgical approach. This article will review the evolution of melanoma surgery and the evidence behind today's recommendations.

Key words**: Melanoma - Surgery - Sentinel lymph node - Lymph node biopsy.**

Cancer has evolved over the past century from existing as primarily a surgical disease to one treated in this day by a multidisciplinary approach. Today, few solid tumors, with the exception of the earliest-stage disease, are treated by surgery alone. Melanoma stands out as an exception at all stages. Mainstays in the therapy of most malignancies, chemotherapy and radiation therapy play extremely limited roles in the management of melanoma. Similarly, despite a tremendous interest in their potential for treatment, biologic and immunologic therapies have not to date significantly impacted outcomes in melanoma. Surgery thus remains the primary treatment for both thin, localized malignant melanoma as well as for advanced melanoma.

While the need for surgery has remained constant, the nature of that surgery has changed considerably over that time. It currently targets 3 arms of treatment: the primary tumor, the nodal basin, and when feasible, stage IV disease. Historically, treatment of the primary tumor began with narrow excision. Review of outcomes, and high rates of local and regional recurrence, led next to wide radical excisions, but failure to improve overall survival led to a reversion back to moderate margins. Management of the regional nodal basin has also evolved and continues to be a source of controversy among clinicians. Even further, the role of surgery in stage IV disease is expanding beyond palliation towards curative extirpation.

These changes in the surgical management of melanoma have been the result of both

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TABLE I.—*Randomized trials of wide versus narrow excision for malignant melanoma.*

Trial	Author	No.	Breslow depth	Arms	Follow-up	Outcomes
World Health Organization, Melanoma Program 10	Veronesi [9, 10]	612	≤2 mm	1 cm *vs* 3 cm	8 years	NSD OS, DFS, LRR
Intergroup Melanoma Surgical Trial	Balch [11, 12]	486	1-4 mm	2 cm *vs* 4 cm	10 years	NSD OS, LRR
Swedish Melanoma Group	Ringborg [13, 14]	989	0.8-2 mm	2 cm *vs* 4 cm	11 years	NSD OS, DFS, LRR
United Kingdom Melanoma	Thomas [15]	900	> 2 mm	1 cm *vs* 3 cm	5 years	NSD OS Study Group ? LRR with 1 cm (P=0.05) HR=1.26
French Cooperative Group	Banzet [16]	319	≤2 mm	2 cm *vs* 5 cm	4	NSD OS, DFS

OS: overall survival; DFS: disease-free survival; LRR: local-regional recurrence; NSD: no significant difference; HR: hazard ratio

our increased knowledge of the natural biology of this disease and prospective, randomized trials designed to answer specific questions regarding specific treatment options. This article will review the role of surgery in the management of cutaneous melanoma, the evidence behind our current practice, and the questions that remain.

Surgery and the primary melanoma

Excisional biopsy of melanoma with narrow and negative margins is inadequate treatment, associated with local recurrence rates in the range of 30% to 60%.[1] Since first described by William Norris in 1857, the wide radical excision has remained the mainstay of therapy for localized melanoma.[2] Wide radical excision consists of excising an adequate margin of normal appearing skin down to underlying fascia. Historically, the muscular fascia was excised with the specimen. There existed some belief, however, that removing the fascia might promote the dissemination of tumor cells and increase the recurrence rate.[3] Although this has never been addressed in a prospective trial, a retrospective trial of 202 patients showed no difference in recurrence with the removal of the fascia.[4] Current practice involves dissection down to, but not including the fascia with the resection specimen.

The definition of an adequate margin for wide radical excision has changed over time. In 1907, Handley recommended a margin of 1 inch. This was based both on the failure of the present approaches to cure the disease and on microscopic examination of strips of adjacent tissue from autopsy studies.[5, 6] In the later half of the 20th century, the recommended margins increased to 4 or 5cm based on the discovery of melanocytes and microsatellites beyond the excision site.[7, 8] In some cases, this involved a radical *en bloc* resection of the regional nodal basins.

This radical excision, despite the morbidity involved, remained the treatment for melanoma until an interest in gathering scientific data to support these recommendations *via* clinical trials emerged. Five randomized trials demonstrated no difference in survival between conservative margins and wide margins (Table I [9-16]). However, the studies differed greatly in both the entry criteria and the margins of excision. Three trials compared 2 cm margins to either 4 cm or 5 cm margins, while 2 trials compared 1 cm margins with 3 cm margins. Our present recommendations are based on the data from these randomized trials, with the margin of excision based on the Breslow thickness of the primary tumor.

Resection margins for thin (<1 mm) melanoma

The World Health Organization (WHO) Melanoma Group prospectively randomized 612 patients with melanomas less than 2 mm thick to receive excision with either 1 cm (narrow) or 3 cm (wide) margins.[9, 10] In the group of patients who had melanoma <1 mm (356 patients), there were no local recurrences whether they had 1 cm or 3 cm margins of excision. There was no difference between the 2 groups in the disease-free and overall survival rates after 15 years.[17] The WHO Melanoma Group trial clearly demonstrated that a 1 cm margin provides excellent control for melanomas 1 mm and less.

Resection margins for melanoma >2 mm

Most of the trials included thicker melanomas. A multi-institutional prospective randomized trial from France demonstrated no difference in either local recurrence rate or survival between patients who had a 5 cm margin or a 2 cm margin.[16, 17] This trial included 319 patients with melanomas 2 mm or greater in thickness.

The Intergroup Melanoma Committee conducted a randomized prospective study evaluating 2 cm *versus* 4 cm margins in 468 patients with intermediate thickness melanomas (1-4 mm).[11, 12] There was a statistically significant difference in the need for skin grafts between the groups, with 46% of the 4 cm group requiring skin grafts *versus* 11% of the 2 cm group. With a ten-year median follow-up, there was no significant difference in recurrence between the groups.

The Swedish Melanoma Study Group compared 2 cm *versus* 5 cm margins of excision in 989 patients with melanomas between 0.8 and 2 mm thick. There were local recurrences in 1% of patients, equally distributed between the 2 study arms, and no differences in recurrence-free or overall survival.[13]

Cumulatively, these studies all demonstrate that a 2 cm margin for intermediate-thickness melanomas (1-4 mm) is appropriate to significantly minimize the risks of both recurrence and the need for skin grafting. These studies do not, however, answer the question of whether 1 cm margins may also be adequate for intermediate thickness melanoma.

Thomas *et al.* [15] reported the result of a trial of 900 patients with melanoma >2 mm randomized between 1 and 3 cm margins performed by the UK Melanoma Study Group, the British Association of Plastic Surgeons, the Institute of Cancer Research and the Scottish Cancer Therapy Network. Although there was no statistically significant difference in overall survival, there was an increase in locoregional recurrences with 1 cm margins, with a hazard ratio of 1.26 (95% confidence interval, 1 to 1.59; P=0.05). There was also a trend towards decreased melanoma-specific survival, with a hazard ratio of 1.24 (95% CI, 0.96 to 1.61; P=0.1). This trial demonstrated that there is an increased risk of locoregional recurrence with 1 cm margins. It also suggested that this margin may be associated with increased mortality. Based on these results, the trial concluded that a margin of 1 cm is inadequate for melanomas greater than 2 mm in Breslow thickness. Notably, though, the increased recurrence rate was primarily restricted to regional recurrences in the draining nodal basin. It is unclear whether this risk would still exist today with the routine application of lymphatic mapping and sentinel lymph node biopsy (SLNB).

The margins of excision necessary for melanomas greater than 4 mm remains controversial, as this population was not represented in the randomized trials. While a more aggressive surgical resection may be warranted given the known biologic aggressiveness of thick melanomas, this must be tempered against the higher propensity of these lesions to have already metastasized, minimizing the impact of local control on overall survival. The optimum approach for this group has yet to be well determined, but the present recommendations are margins of at least 2 cm.

Resection margins for melanoma between 1 and 2 mm

The randomized trials demonstrate that melanomas less than 1 mm can be safely

TABLE II.—*Recommended margins of excision for primary melanoma.*

Melanoma *in situ*	0.5 cm
Less than or equal to 1 mm	1 cm
1 to 2 mm	1 to 2 cm
2 to 4 mm	2 cm
> 4 mm	at least 2 cm

resected with a 1 cm margin, and that melanomas >2 mm should be resected with a minimum of a 2 cm margin. What about melanoma between 1 and 2 mm? While the studies show that 2 cm margins are appropriate, there is little data to answer whether 1 cm margins would be appropriate. The only study of 1 cm *versus* 3 cm margins that included patients with melanoma between 1 and 2 mm melanoma was the World Health Organization Melanoma Group trial. As described above, this trial included patients melanomas less than 2 mm thick to receive excision with either 1 cm (narrow) or 3 cm (wide) margins.[9, 10] While there were no local recurrences among patients with melanomas <1 mm who underwent either wide or narrow excision, in the subset of patients with melanomas 1.1 to 2 mm thick, there was a 2.7% local recurrence rate in the 1 cm resection margin group. No local recurrences were seen in the same group of patients who received 3 cm margins. There was no difference in survival between the 2 groups. Based on these results, the standard recommendation is to obtain 2 cm margins when possible, but if this would be exceptionally difficult or require a skin graft for closure, narrower margins (no less than 1 cm) would be appropriate (Table II).

Surgery and the regional nodal basin

Lymph node dissection for clinically evident nodal disease

All patients with melanoma should undergo a complete physical examination with particular attention being paid to the regional draining lymph node basins, as approximately 5% of patients will have clinically apparent nodal involvement at the time of diagnosis.[18] Patients who have previously undergone a wide excision may recur with palpable adenopathy evident on exam, and occasional patients present with nodal metastases in the absence of a detectable primary melanoma. Palpable enlarged nodes (generally 1-1.5 cm in maximum diameter), or nodes that are hard or fixed to adjacent structures must be considered suspicious for metastatic involvement. Metastatic nodal involvement should be verified with a fine needle aspiration (FNA) biopsy. Excisional biopsy is reserved for those situations where the lymph node is clinically suspicious but the FNA biopsy results are inconclusive.

Complications of an open biopsy (seroma, infection, scarring) can interfere with the performance of the subsequent lymph node dissection. Previous interventions in the regional basin have also been associated with an increase in melanoma recurrence after radical dissection.[19] For both oncologic and functional reasons, if an excisional biopsy is performed, the incision should be oriented in a way that it can be readily re-excised during the complete lymph node dissection.

Patients with biopsy proven palpable nodal involvement should undergo a complete lymph node dissection in addition to the wide local excision of the primary tumor. This procedure may be curative. Prior to proceeding, however, a work-up must be undertaken for the presence of metastatic disease. This begins with a detailed history and physical examination, including a thorough review of symptoms focusing on symptoms consistent with metastases. At the very least, patients with clinically involved nodes should have a chest radiograph and serum lactate dehydrogenase (LDH) level evaluated. Abnormalities on history, physical, CXR or LDH deserve a further search for metastatic disease.

For the asymptomatic patient, many surgeons advocate routine imaging. This may consist of either a CT scan of the chest, abdomen and pelvis or a whole-body PET scan. Both of these imaging studies have been described to upstage stage III patients to stage IV, thereby altering the choice of surgical therapy.[20-22] Some surgeons feel that

PET scanning is superior to CT scans, while others have suggested the false-positive rates for PET imaging is too high to make it a reliable choice. CT scanning has the additional advantage of providing additional anatomic information that the surgeon may find useful to plan the dissection. One example in particular would be the presence of enlarged pelvic lymph nodes; this finding might well convert an inguinal node dissection to an iliac-inguinal node dissection.

Axillary lymph node dissection

For patients with palpable disease in the axilla, the axillary lymph node dissection (ALND) should include levels I, II, and III nodes to provide the best regional control. Some surgeons, however, include level III only when suspicious nodes are present.[23-25] In a thin patient, with adequate mobilization and anterior retraction of the pectoralis major and minor muscles, it may be possible to adequately dissect the level III nodes without dividing the pectoralis minor muscle. This may involve dissection between the pectoralis major and minor muscles to adequately include the level III nodes, which lie medial to the pectoralis minor muscle. In most patients, however, it is necessary to divide the pectoralis minor muscle. The extent of dissection, as measured by the number of nodes removed, has been correlated with improved five-year survival in one retrospective study.[26]

Other variations in technique affect both the regional recurrence rate and the morbidity of axillary dissection. Preservation of the long thoracic and thoracodorsal nerves is considered routine, and injury to these nerves should be extremely rare in experienced hands. The intercostobrachial nerves may also be preserved, however most surgeons routinely resect these when the dissection is being performed for palpable disease. Some authors have advocated a more extensive dissection, including removal of the supraaxillary fat pad, although this greatly increases the morbidity by exposing the brachial plexus. Brachial plexus injuries, although rare, can be devastating complications of this procedure. Because there is no evidence that removal of the fat pad improves survival, this procedure is not routinely recommended.

Lymphedema remains the most common complication of ALND. While many surgeons skeletonize the axillary vein during the dissection, others have suggested that this may increase the rate of lymphedema. Lawton *et al.*[27] proposed preservation of the fascia from the *pectoralis* and *latissimus dorsi* muscles to decrease postoperative lymphedema. Definitive studies addressing variations in technique and their impact on outcome have not been performed. In experienced hands, the lymphedema rate after ALND should be between 5% and 12%.[24, 28, 29]

Groin dissection

Groin dissections are associated with a much higher overall complication rate; 50% to 64% compared to 14% to 17% for axillary lymph node dissection.[30, 31] More than 20% of patients will have chronic lymphedema.[32-34] Wound complications, including skin flap necrosis, wound dehiscense and surgical site infections, are quite common.

For patients with inguinal disease, the extent of lymphadenectomy is more controversial. Whether simply an inguinofemoral dissection (superficial) should be performed (with the inguinal ligament being the superior boundary of dissection) or the iliac nodes should be included is a matter of debate given the higher rate of complications involved with the pelvic dissection. Some surgeons advocate routinely performing the additional iliac dissection (deep) for patients with clinically apparent inguinal disease. Others limit iliac dissection to only patients with a positive Cloquet's node or multiple (3 or more) involved nodes. The drawback of using Cloquet's node as a deciding factor for dissection boundaries is its limited ability to predict the involvement of pelvic lymph nodes.[35] Still others do not perform an iliac dissection unless there is radiographic evidence of pelvic adenopathy.

A retrospective review of 104 patients who underwent superficial *versus* superficial plus deep dissection demonstrated no influence of the deep dissection on locoregional recur-

rence or survival.[36] Another retrospective study of 227 patients who had either superficial or superficial and deep dissections also failed to demonstrated a survival advantage associated with the extent of surgery, prompting the conclusion that pelvic dissection should be limited to patients with clinical evidence of disease.[37] Five-year survival rates of 24% to 35% have been reported for patients with pelvic involvement who undergo superficial and deep dissection.[37, 38]

If an iliac dissection is to be performed with the inguinofemoral dissection, this can be accomplished through one skin incision by obliquely dividing the external and internal oblique muscles to expose the pelvic retroperitoneum, or alternatively by dividing the inguinal ligament. This may be particularly useful in cases of disease low in the pelvis along the distal external iliac vessels. The inguinal ligament may be divided either over the femoral vessels, which is technically simpler, or at the anterior superior iliac spine, which may be associated with better wound healing.

Cervical dissection

The gold standard for treating regional disease in the neck has been the radical neck dissection (RND); removal of levels I-V as well as the sternocleidomastoid muscle, internal jugular vein and spinal accessory nerve. Given the extent of the structures removed, RND can be associated with significant morbidity. A modified radical neck dissection (MRND), also described as a functional neck dissection, includes preservation of any or all of those structures. Several authors have reported no appreciable difference in the risk of regional recurrence with MRND *versus* RND.[39-41] A more selective approach has therefore been advocated, basing the dissection on the location of the involved nodes or primary lesion.[41]

Sentinel lymph node biopsy as a staging procedure

While there is little argument as to the potential benefit of a lymph node dissection for patients with clinically evident disease, the optimal management of patients without clinically evident disease remains controversial. Prior to the advent of SLNB, many advocated the performance of an elective lymph node dissection (ELND) for patients without clinical evidence of nodal metastases in order to assess for microscopic metastatic disease. Although ELND provides important prognostic information, this is only of benefit if there are adjuvant therapies to offer the patient who is found to harbor metastases. Given the high rate of complications associated with ELND, the morbidity of it is hardly justified on the basis of accurate staging alone.

The management of patients with melanoma changed considerably after SLNB was described by Morton *et al*.[42] There now exists a reliable method for the identification and removal of the primary lymph node draining the site of a cutaneous melanoma, one that accurately determines whether tumor cells have metastasized to that respective lymph node basin.[43-45] Regional recurrence after sentinel node biopsy is infrequent, and has a greatly decreased morbidity as compared to ELND. [46, 47]

SLNB possesses the further advantage of allowing for a more detailed histological examination than ELND. Identification of micrometastases in sentinel nodes is carried out by careful sectioning of the node (step-sectioning) as well as the use of immunohistochemical staining with anti-S-100, anti-MART-1, or HMB-45 (anti-gp100) antibodies.[48] Clinically, even microscopic foci of melanoma detected only by immunohistochemical staining are significant. With this increased sensitivity, sentinel lymph node status is the most important predictor of survival for patients with melanoma. Patients with a negative sentinel node are over 6 times more likely to survive than those with a positive sentinel lymph node (SLN), making the predictive impact of sentinel node status much greater than any other prognostic factor.[49]

SLNB plays a central role in staging the regional lymph nodes and is the standard of care in many major melanoma centers.[44, 50]

Currently, the compelling prognostic value of the nodal status makes SLNB indispensable for accurate staging, and thus obligates it to be a key component of future studies examining adjuvant therapy. Which patients should undergo SLNB? Cascinelli *et al*.[50] reported SLN positivity rates of 16% in lesions thicker than 1 mm. Among the 829 patients in a WHO study, positivity rates of 2% (<1 mm), 7% (1-1.99 mm), 13% (2-2.99 mm), and 31% (>3 mm) were reported. In addition to tumor thickness, other factors such as tumor ulceration, young patient age, and mitotic rate have been shown to be associated with SLN positivity.[49, 51, 52] Based on these data, as well as on additional corroborating studies, the SLNB procedure should be routinely considered for primary melanomas deeper than 1 mm. It may be selectively applied for tumors 1 mm or less, when other worrisome features are present.

The same arguments against ELND may be made against SLNB: the cost and morbidity, albeit lower, are not justified simply to obtain accurate staging information. Since the introduction of SLNB, however, adjuvant therapy in the form of high-dose interferon (HDI) has become available for the treatment of high-risk melanoma. Although the use of HDI is controversial, the available evidence demonstrates an improvement in disease-free survival as well as a likely improvement in overall survival.[53-56] Justification of its use and appropriate patient selection are issues beyond the scope of this article. If the patient is a candidate for adjuvant interferon or participation in a clinical trial for other adjuvant therapies, SLNB is certainly justified in order to identify high-risk individuals. Regardless, the primary argument in favor of SLNB is the potential improvement in long-term outcome associated with the early eradication of microscopic disease.

Lymph node dissection for microscopic disease

Complete lymph node dissection in patients without nodal disease was first advocated by Snow in 1892.[57] The argument favoring ELND theorized that of the patients with occult metastases in the regional basin, some may have no distant disease at diagnosis, but could develop secondary metastases from occult lymph node metastases during the interval between diagnosis of the primary melanoma and progression to clinically evident nodal disease. Eradicating that microscopic disease from the lymph nodes before spread occurs would prevent the development of distant disease and thereby improve survival. The exact impact of lymph node dissection on survival, however, would depend on the size of the target population. If a large percentage of patients with microscopic nodal disease already have concomitant distant disease at diagnosis, or conversely, if only a small percentage of patients with microscopic disease go on to develop secondary metastases, then the impact on survival would be quite small. As only approximately 20% of patients are node positive, the impact of ELND on these subjects would have to be quite large in order to see a survival benefit for the entire group.

The argument for ELND was fueled by retrospective data suggesting a survival benefit existed. Two retrospective reviews compared survival statistics for patients with localized melanomas (stage I and II) who underwent wide excision alone with those who underwent wide excision plus ELND.[58, 59] Both reviews suggested that patients who underwent wide excision plus ELND had a significantly higher survival rate than those who had wide excision alone, even after the analysis was stratified for tumor sites. As with all retrospective research, though, any number of unknown variables may have played a role in the choice between ELND and observation.

This data prompted 2 large prospective, randomized trials to answer the question of whether ELND provides a survival benefit. The WHO Melanoma Group randomized 2 groups of patients to receive either wide excision plus ELND (n=267) or wide excision with subsequent therapeutic lymphadenectomy if clinically indicated (n=286).[60] Analysis of these data revealed no difference in survival between the 2 groups. With follow-up

now at greater than 20 years, the WHO Trial still shows no statistical improvement in either survival or disease-free interval.[17] The largest trial to examine the issue was the Intergroup Melanoma Surgical Program, which randomized 740 stage I and II melanoma patients to ELND or observation.[61] Overall, there again was no significant difference between the 2 groups. Long-term results confirmed no significant ten-year survival difference between ELND or observation (77% *vs* 73%, P=0.12).[31]

On the surface, this would seem to end the discussion on whether we should be performing ELND, or even SLNB, for melanoma. Further assessment of the data, however, suggests that there are subsets of patients who do benefit from ELND.

In the Intergroup trial, a significant reduction in mortality with ELND was seen for patients with nonulcerated melanomas, tumors between 1 and 2 mm, and limb melanomas. It is possible that these subsets represent patients who are less likely to have distant disease in the presence of regional disease, and thus might benefit from early lymph node dissection. Further evidence is provided from the WHO Program 14 Trial, which compared ELND to observation for patients with truncal melanomas. When the survival of patients in the WHO Program 14 Trial with microscopic disease at ELND was compared with those who had regional recurrences during observation, the survival was significantly improved in the former group (48.2% *vs* 26.6%, P=0.04). [62]

This data suggests, but does not prove, that lymph node dissection may benefit patients with microscopic disease in the lymph nodes, but not all clinically node negative patients. The SLN has provided a selective approach to complete lymph node dissection, sparing node-negative patients the morbidity of the procedure, while offering improved regional control and any potential survival benefit to the node-positive patient.

The Multicenter Selective Lymphadenectomy Trial-I is the only current prospective randomized trial that specifically compares wide excision alone to wide excision plus SLNB, with complete node dissection for patients with a positive SLN. The most recent follow-up data was presented at the American Society of Clinical Oncology (ASCO) meeting in Orlando, Florida in May, 2005.[63] The *interim* results compared only those patients with positive SLN, either those found to be positive on SLNB or those who recurred after wide local excision alone. The seven-year melanoma specific survival for patients who had completion lymph node dissection (CLND) for a positive SLN was 69%, compared to 48% for patients undergoing delayed CLND after nodal relapse (P=0.0034, RR=0.53, 95% CI 0.33,0.84).

The evidence to date suggests that performing SLNB plus CLND for a positive SLN is unlikely to result in a survival advantage when all patients are compared, but will improve survival among the subset of patients with occult lymph node metastases. Whether this approach is worth the added cost will require maturation of the data. When analyzed along with the use of adjuvant interferon, it does appear to be cost-effective. [64]

But is the completion node dissection necessary? It is possible that SLNB alone will identify patients at high risk, and in the subset of patients for whom the SLN is the only node that harbors disease, it in itself is therapeutic. Additional positive non-sentinel lymph nodes (NSN) are found in only 7-33% of patients with a positive sentinel node. Unfortunately, predicting which patients will have residual disease in the NSN has proven difficult.[65-67] Even patients with the most favorable primary melanomas have a substantial risk of additional disease in the basin. The on-going Multicenter Selective Lymphadenectomy Trial-II will help answer this question by randomizing patients with a positive SLN to CLND or observation. Until the final results from these 2 trials are available, CLND for a positive SLN remains the standard approach.

Surgery for stage IV melanoma

The management of metastatic disease from most cancers rarely falls into the domain of the surgeon. Notable exceptions include liver resection for colorectal metastases and

pulmonary resection for sarcoma metastatic to the lung, both of which may be associated with long-term survival. Distant site recurrences of melanoma are unpredictable, though, and can occur in almost every major organ or tissue. While most patients with metastatic melanoma will not be candidates for curative resection, complete surgical resection of melanoma metastases may be associated with an improvement in long-term survival.

Selection of patients for curative resection

The five-year survival for patients with stage IV melanoma is approximately 10%. Not all stage IV disease is equivalent in prognosis, however, so careful selection of stage IV melanoma patients for consideration of metastatectomy is imperative. Five-year survival rates as high as 35% have been reported with proper patient selection. Several factors should be weighed into the decision to resect metastatic disease, foremost being the initial site of metastases. The new American Joint Committee on Cancer (AJCC) staging system groups metastatic melanoma into 3 subsets. M1a disease is defined as nonvisceral metastases such as skin, subcutaneous tissue or lymph nodes outside of the draining basins. Patients with M1a disease have a 5 year melanoma specific survival rate of approximately 19%.[68] M1b disease is defined as pulmonary metastases, and M1c disease includes all nonpulmonary visceral metastases. The survival rate for visceral disease is lower than for M1a disease, at approximately 7% for M1b and 9% for M1c disease. All patients with metastatic melanoma should have a serum LDH level drawn, as this correlates with distant disease. If elevated, it leads to a classification of M1c disease regardless of the site of distant disease.

Other factors that deseve consideration include the likelihood of a complete resection, the number of metastatic foci, the initial stage of disease and the interval between primary therapy and distant recurrence. The patient's performance status, co-morbidities and life expectancy are also considered. The patient with the solitary, easily resected lesion who is >2 years out from initial resection is an ideal candidate for resection. The patient with multiple metastases shortly after primary therapy presumed to have more aggressive disease and is very unlikely to benefit from surgical resection; other treatment options should be explored. For patients on the fence, one option is to treat the patient with systemic therapy for 2 to 3 months and then re-evaluate the patient. Patients who have a response or remain stable may then proceed to resection.

Preoperative evaluation begins with a thorough history and physical examination, including a complete review of systems designed to elicit signs and symptoms of additional metastatic disease. Blood count, metabolic profile and serum LDH should be obtained. Although LDH is clearly associated with prognosis, it is unclear whether an elevated LDH in a patient with what appears to be resectable disease should preclude surgery.[68] A thorough search for the extent of metastatic disease must be undertaken. Any symptoms suggestive of metastatic disease should prompt the appropriate additional studies, such as MRI for symptoms consistent with brain metastases. Asymptomatic patients have typically been evaluated with a CT scan of the chest, abdomen and pelvis. However, recent studies have suggested that 18-flourodeoxyglucose positron emission tomography (FDG-PET) should be obtained to detect occult metastatic disease, and would be the imaging study of choice in this situation.[22, 69, 70]

Resection of M1a disease

The most common site of distant metastases are to remote areas of skin and soft tissues, as well as to lymph nodes outside of the draining basins. Patients with a solitary metastasis to dermal or subcutaneous tissue have a reasonable long-term prognosis. There should be no hesitancy to resect these patients if the work-up reveals no additional areas of disease. Patients with more extensive M1a disease must be evaluated on a individualized basis, taking into account both the number and location of metastases and

TABLE III.—*Survival after complete resection of M1a disease.*

Author	Year	No.	Site	5-year survival (%)
Markowitz [71]	1991	72	Lymph nodes	38
Markowitz [71]	1991	60	Soft tissue	49
Gadd [72]	1992	190	All	14
Karakousis [73]	1994	23	Lymph nodes	22
Karakousis [73]	1994	27	Subcutis	33
Meyer [74]	2000	45	Lymph nodes	20
Meyer [74]	2000	30	Skin/subcutis	17.8

TABLE IV.—*Survival after complete resection of M1b disease.*

Author	Year	No.	5-year survival (%)
Wong [75]	1988	38	31
Gorenstein [76]	1991	59	25
Harpole [77]	1992	98	20
Karakousis [73]	1994	39	14
Tafra [78]	1995	106	27
La Hei [79]	1996	83	22
Leo [80]	2000	282	22

the disease-free interval. Several series have reported impressive five-year survivals after resection of M1a disease (Table III [71-74]). Resection of these lesions may also be palliative, so erring on the side of an aggressive surgical approach may be reasonable in the appropriate setting.

Resection of M1b disease

Fifteen percent to 30% of metastases from malignant melanoma will occur in the lungs, typically asymptomatically, and is detected by either chest radiography or computed tomography (CT). Most will not be candidates for surgical resection because of either multiple lesions or the presence of extrapulmonary disease. The patient with the solitary pulmonary metastasis, in the absence of additional disease discovered on CT or PET scan, should undergo resection. It is important to remember that in the patient with a history of melanoma and the new solitary pulmonary nodule, this may not be a metastases but a new primary lung cancer. When more than one lesion is present, the decision to perform a pulmonary metastatectomy necessitates consideration of the ability to achieve a complete resection. The pulmonary function and comorbidities of the patient as well as the disease-free interval also play a heavy role in this decision. In selected patients, five-year survivals of 15% to 15% may be achievable (Table IV[73, 75-80]).

Resection of M1c disease

Visceral recurrences outside of the lung are less likely to benefit from surgery, but resection may be appropriate for highly selected patients. Although it is one of most common malignancies to metastasize to the gastrointestinal tract, this is in actuality a relatively rare occurrence. Patients with gastrointestinal tract involvement are usually symptomatic, with pain/obstruction, bleeding/anemia and weight loss. Surgery is primarily palliative, but may offer long-term survival (five-year survivals of 5% to 10%).[81-85] One series demonstrated that long-term palliation could be achieved in a majority of patients, and patients who underwent complete resection had a longer median survival than patients who could not.[86] Factors associated with a poor outcome include short disease-free interval or elevated serum LDH.[83] Resection of metastases to the spleen or liver have also been described, although only rare patients are candidates for that surgery. [87, 88]

Brain metastases are common in melanoma patients and are associated with an extremely poor prognosis. Patients may present with headaches, focal neurologic deficits or seizures; if left untreated they will experience rapid deterioration and death. Palliation often involves whole brain irradiation, though surgery or radiosurgery have been used with reasonable results. Not only is palliation achieved in a significant number of patients, but several series describe median survivals of 6 to 18 months, depending on the selection criteria.[89-94] Whether surgical resection should be followed by whole-brain irradiation remains controversial. The criteria used to select patients include the number of lesions and their accessibility. Patients with deep-seated or multifocal lesions, while not good surgical candidates, may be candidates for

stereotactic radiation techniques (gamma knife). These consist of multiple convergent beams that deliver a single high dose of radiation to the lesion(s). [95, 96]

Conclusions

In summary, surgery remains the cornerstone of therapy for the treatment of both primary and metastatic melanoma. It offers a cure for primary melanoma when appropriate resection margins are taken. Surgery also plays a substantial role in the diagnosis and treatment of regional disease, a role that has changed significantly since the advent of SLNB. Even when the spread of disease has exceeded microscopic levels, surgery can not only provide palliation, but prolong survival if metastectomy is applied to an appropriately selected patient population. The future of melanoma therapy is hopeful; it holds promise for adjuvant or neoadjuvant treatments in the form of vaccines, new chemotherapies and biologic agents. The objectives and outcomes of surgical intervention will continue to change dramatically as these other therapies demonstrate their potential. Until those roles are better defined and bear out success, however, surgical therapy remains the foundation of treatment for melanoma.

Riassunto

Il ruolo del chirurgo nella gestione del melanoma

Mentre la terapia multidisciplinare è diventata lo standard per la maggior parte dei tumori solidi, per il melanoma il trattamento è ancora imperniato sull'intervento chirurgico. Questo è vero non solo per le fasi precoci della malattia ma anche per quelle avanzate. L'approccio chirurgico al melanoma è mutato radicalmente, indirizzandosi verso un'asportazione meno aggressiva del tumore primario, accompagnata, però, da un approccio più aggressivo nei confronti delle metastasi. La chirurgia del melanoma è stata influenzata dalla comprensione dei meccanismi biologici della malattia e dai dati emersi dagli studi clinici prospettici e randomizzati appositamente disegnati. Viceversa, i nuovi approcci chirurgici ci hanno consentito di comprendere meglio la biologia del melanoma, ma sono necessari ulteriori studi randomizzati per definire ulteriormente l'approccio chirurgico ottimale. Questo articolo rivede l'evoluzione della chirurgia del melanoma e sottolinea le evidenze che sono alla base delle raccomandazioni attuali.

Parole chiave: Melanoma - Chirurgia - Linfonodo sentinella - Biopsia linfonodale.

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