Clinical Management of Primary Cutaneous Melanoma

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Sonia Cohen and Kenneth Tanabe

Contents

Abstract

Surgical management continues to provide the mainstay of treatment for patients with early melanoma. In this chapter the authors describe the surgical approach to primary cutaneous melanoma lesions, including sentinel lymph node biopsy. These techniques are not only potentially curative but also provide the prognostic information necessary for subsequent treatment decisions. The current recommendations for the surgical management of early melanoma based on randomized prospective clinical trials, as well as future directions, are reviewed.

Keywords

Surgery · Melanoma · Excision margins · Wide local excision · Sentinel lymph node biopsy

Introduction

The incidence of cutaneous melanoma has steadily increased over recent decades to 21.6 per 100,000 individuals per year and now represents the sixth most common cancer in the United States (http://seer.cancer.gov). It is estimated that there were over 76,000 cases of melanoma diagnosed in 2016, corresponding to 4.5% of new

S. Cohen
Department of Surgery, Massachusetts General Hospital, Boston, MA, USA
e-mail: scohen22@partners.org

K. Tanabe (✉)
Division of Surgical Oncology, Department of Surgery, Massachusetts General Hospital, Boston, MA, USA
e-mail: ktanabe@partners.org

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cancers among males and females of all races, and that 2.1% of the population will be diagnosed with melanoma at some point during their lifetime. At the time of diagnosis, 84% of melanomas show no evidence of regional or distant metastases. The American Joint Commission on Cancer (AJCC) staging system for melanoma identifies several prognostic factors for these early-stage melanomas which aid in predicting survival, all of which are based on biopsy results. These include primary tumor thickness, the presence of ulceration in the primary lesion, the mitotic rate of tumor cells, and the presence of micrometastases identified by analysis of regional lymph nodes. Initial clinical management of most cases of invasive melanoma is guided by biopsy of suspicious lesions for thorough histopathologic assessment. Once the diagnosis of melanoma is confirmed, the patient will undergo surgical resection of the primary lesion, as well as biopsy of regional lymph nodes to detect metastatic disease when indicated. For localized tumors, resection of the primary tumor is potentially curative and provides an excellent prognosis, with 5-year survival rates as high as 98%. For tumors with evidence of regional metastatic disease, resection of the primary lesion and lymphadenectomy for nodal metastases provide further diagnostic and prognostic information, reduce tumor burden, and may extend overall survival. Understanding the data that guide this surgical management of melanoma is essential to providing optimal care for melanoma patients, as well as for designing new strategies to improve future outcomes.

Historical Overview

Melanoma was first described as a disease entity in the English literature in 1820 by W. Norris, who described tumors arising from pigmented lesions in two separate families (Hecht 1989). Over the subsequent century, the management of melanoma evolved as this disease was further characterized. The observation that there was a high local recurrence rate even after excision prompted the recommendation for aggressive, wide excision of the skin and subcutaneous tissues surrounding the primary lesion. The propensity of melanoma to metastasize led to the recommendation for early surgical intervention accompanied by regional lymphadenectomy at the time of initial resection. By the early 1900s, invasive melanoma was treated with surgical resection of the primary lesion with at least 5 cm margins in all directions, based on the observation of atypical melanocytes up to 5 cm from the edge of a primary lesion (Wong 1970). Primary excision was accompanied by complete regional lymph node dissection for all patients. Due to the frequent need for skin grafts for wound closure as well as wound complications and lymphedema arising from complete lymphadenectomy, this aggressive approach resulted in significant morbidity. Over the past several decades, the surgical management of malignant melanoma was refined using outcomes from clinical trials. While today surgery remains the mainstay of treatment of melanoma, current recommendations tailor treatment based on studies that balance efficacy with morbidity.

Excision of Primary Lesion

The goal of surgical excision of a primary melanoma lesion is durable disease control at the tumor site. This is of particular importance in the large majority of melanoma patients who are free from micrometastases at regional or distant sites. Potential mechanisms of local recurrence include incomplete excision of the primary tumor, incomplete excision of separate nests of melanoma cells (e.g., satellites or in-transit metastases), second primary melanomas, and hematogenous dissemination of cells back to the original excision site. Excision with wider margins may be an effective strategy to combat the first two mechanisms of local recurrence by facilitating complete excision of a primary tumor and any nearby micrometastases. Wider excision could also have a modest impact on the development of second primary melanomas by removal of additional skin affected by an oncogenic field defect. However, large excisions may be prone to poor healing or surgical site infections, require skin grafting for closure, and lead to impaired function and

Table 1 Current recommendations for margins of excision of primary cutaneous melanoma

	Tumor thickness (mm)	Circumferential excision margin (cm)
Thin melanoma	<1	1
Intermediate melanoma	1–2	2[a]
	2–4	2
Thick melanoma	>4	2

[a]1 cm margin may be acceptable if significantly less morbid than 2 cm margin

mobility. Thus, clinical trials have been used to determine the minimum safe excision margins that are sufficient for cancer treatment while minimizing functional and cosmetic impairments. The current recommendations for surgical margins (Table 1) are based on the results of a series of prospective randomized trials.

Margins of Surgical Resection Are Tailored to Melanoma Thickness

Tumor thickness is a prognostic factor for local recurrence. The overall recurrence rate for melanomas <1 mm thick after excision is less than 6% across a number of studies, suggesting that extensive resection might be unnecessary for these thin tumors. As surgical practice shifted toward narrower margins in this context, initial retrospective reviews of patient outcomes in the treatment of thin melanomas found that the rate of local recurrence was not affected. For example, in one series of 936 patients with thin tumors in which 62% underwent excision with margins of 2 cm or less, not a single case of local recurrence was documented over 5 years of observation (Urist et al. 1985). These data suggested that reducing excision margins for low-risk melanomas could be safe. However, the retrospective nature of these studies and the resultant variability in treatment combined with the overall low rate of local recurrence may have obscured any effect of narrow excision margins on oncologic outcomes.

To better address the safety of narrow excision margins for thin melanomas, the World Health Organization (WHO) Melanoma Program conducted a randomized prospective trial comparing 1 cm versus 3 cm clinical margins for primary melanomas less than 2 mm thick (Veronesi et al. 1988). Six hundred twelve patients with localized, biopsy-confirmed thin melanoma were randomly assigned to either wide or narrow excision and then followed for evidence of relapse or death. After a median follow-up of 55 months, there was no difference in overall, disease-free survival, or local recurrence among the two groups. There were three cases of isolated local recurrence, and all occurred in the narrow excision margin group. However, the overall rate of local recurrence remained too low (2.7%) for this difference between groups to be of statistical significance. Interestingly, all three local recurrences occurred in patients with melanomas with greater than 1 mm thickness, suggesting that excision margins of 1 cm are safe for thin melanomas, but should perhaps be limited to tumors less than 1 mm thick. No randomized prospective trial since has readdressed the excision margin for melanomas <1 mm thick. Thus, current guidelines continue to recommend a 1 cm margin of surgical resection for melanomas less than 1 mm thick and are supported by case-control series (MacKenzie Ross et al. 2016). For melanomas between 1 and 2 mm in thickness, some surgeons are reluctant to use a margin of only 1 cm because of the trend toward increased local recurrence observed in the 1 cm margin group in the WHO trial. However, in cases in which a 1 cm margin could be achieved with substantially less morbidity than with a wider margin, the WHO clinical trial data suggest that the use of a 1 cm margin leads to the same overall survival and perhaps only a slight increased risk for local recurrence. Therefore, current guidelines accept a 1 cm margin of excision if this will result in significantly less morbidity than a wider margin, requiring intraoperative judgment to balance the risk and benefit on a case-by-case basis.

The Intergroup Melanoma Surgical Trial was the first randomized prospective trial to address the safety of narrow excision margins for intermediate-thickness melanomas (1–4 mm

thickness). Four hundred eighty-six patients with intermediate-thickness lesions were randomized to undergo excision with either 2 cm or 4 cm margins. After a median follow-up of 72 months, no significant difference in recurrence rate or survival was observed between the two arms (Balch et al. 1993). Increasing tumor thickness, the presence of ulceration, and truncal location of the tumor did correlate with decreased survival, but the margin of excision did not, even after adjusting for these other prognostic factors. Importantly, there was a statistically significant decrease in the rate of skin grafting required to close the excision site in patients who underwent surgical resection with narrow margins (11% vs. 46% in patients with 4 cm excision margins). Lower rates of skin grafting led to significantly lower rates of wound infection and shorter hospital stays. Even after 10 years of follow-up, there remained no statistically significant difference in local recurrence, 10-year disease-specific survival, and overall survival (Balch et al. 2000), supporting the long-term safety of narrow excision margins. Moreover, the short-term decrease in morbidity associated with wider excision suggested an overall advantage to treatment of intermediate melanomas with narrow margins.

Subsequent large, randomized, prospective studies specifically addressed the safety of narrow margins in subsets of these intermediate-thickness melanomas. The Swedish Melanoma Study Group trial examined cutaneous melanoma between 0.8 and 2 mm in thickness (Ringborg et al. 1996). One subgroup of patients with clinically suspected melanoma underwent initial excision with a 2 cm margin – following this initial excision and analysis of tumor depth, patients with tumors between 0.8 and 2 mm thick were then randomized to either undergo subsequent wide excision of the scar with 3 cm margins (for a total of 5 cm) or no further intervention. These data were combined with those from patients where the initial diagnosis of melanoma was made via excisional biopsy, and patients with tumors of the appropriate depth were then randomized to surgical resection of the scar with either 2 or 5 cm margins. All surgical interventions were completed within 6 weeks of the initial diagnostic procedure. A total of 989 patients ultimately participated with a median follow-up of 11 years (Cohn-Cedermark et al. 2000). The observed rates of local and distant melanoma recurrence, as well as disease-free and overall survival, were not significantly different between those randomized to 2 cm rather than 5 cm margins. A similar prospective study by the French Melanoma Group which randomized 337 patients with melanomas less than 2.1 mm thick to excision with 2 cm or 5 cm margins confirmed no differences in rates of recurrence or disease-free or overall survival after a median follow-up of 16 years (Khayat et al. 2003). These studies are consistent with the Intergroup Trial results demonstrating that a 2 cm margin is adequate for all intermediate-thickness melanomas.

Two trials have focused on the safety of narrow margin excisions in cutaneous melanoma 2 mm or greater in thickness. As reviewed above, the Intergroup Melanoma Surgical Trial concluded that 2 cm margins of excision should be safe for all tumors less than 4 mm thick. However, to specifically address recommendations for tumors thicker than 2 mm, Gillgren et al. analyzed 2 cm versus 4 cm excision margins in this patient group (Gillgren et al. 2011). Nine hundred thirty-six patients with tumors of the trunk or extremity were included. There was no difference observed in the overall or disease-free survival between the 2 cm and 4 cm excision groups. The authors did find a trend toward an increase in local recurrence in the 2 cm margin group, although this did not reach statistical significance ($p = 0.06$). In a second study, 900 patients were randomized to excision of melanomas greater than 2 mm thick with 1 cm or 3 cm margins (Thomas et al. 2004). In this study, locoregional relapses were redefined at interim analyses to be inclusive of local recurrence, satellite, in-transit, and regional lymph node metastases. With this new definition including lymph node metastases, the observed increase in the rate of locoregional recurrence identified in the population treated with 1 cm margins of excision (37% vs. 32% in those treated with a 3 cm excision margin) reached statistical significance at a median follow-up of 60 months. By a median follow-up of 106 months, this had translated into a

significantly higher risk of death from melanoma in the 1 cm margin group as compared to the 3 cm group (HR 1.24, 95% CI 1.01–1.53, $p = 0.041$) (Hayes et al. 2016). Notably individuals with tumors greater than 2 mm thick would typically undergo sentinel node biopsy (see below), but patients in this study were treated without sentinel node biopsy. Thus, many of the locoregional recurrences potentially could have been prevented with sentinel node biopsy. This is supported by the finding that the statistical significance of the observed difference in locoregional recurrences between the 1 cm and 3 cm groups is lost when nodal events are taken out of the analysis. Overall these trial results are consistent with the WHO Melanoma Program trial results, summarized above, which suggested that excision with only 1 cm margins is insufficient for tumors greater than 1 mm thick due to a trend toward an increase in the rate of local recurrence (Veronesi et al. 1988). It is therefore not surprising that a 1 cm margin of excision would also be insufficient for tumors greater than 2 mm thick. And for melanomas >2 mm in thickness, the Intergroup Trial results demonstrate that a 4 cm margin is no better than a 2 cm margin, resulting in the current recommendation of 2 cm excision margins for melanoma between 2 and 4 mm thick (Table 1).

Inclusion of all tumors greater than 2 mm in a clinical trial may be too broad a cohort to detect significant differences between excision margin groups. It is possible that melanomas greater than 4 mm in thickness could require more aggressive excision margins than those closer to 2 mm in thickness. Several studies have found that the thickness of tumor (along with the presence of ulceration) correlates with the risk of locoregional recurrence of primary cutaneous melanoma (Urist et al. 1984; Balch et al. 1993; Karakousis et al. 1996), so inclusion of all tumors greater than 2 mm in a single cohort may prevent investigators from identifying significant differences within treatment arms. It seems reasonable to entertain the idea that the thickest tumors may require wider margins of excision. Most melanomas are less than 2 mm thick at the time of diagnosis; thus, the number of very thick primary cutaneous melanomas without clinical evidence of metastatic disease at the time of diagnosis is relatively small. No randomized prospective trial has examined resection margins in only thick melanomas. One retrospective study examining resection of tumors greater than 4 mm thick with margins of excision either less than or greater than 2 cm found no significant difference in locoregional recurrence or survival (Heaton et al. 1998). However, in another retrospective analysis, Pasquali et al. found that patients with melanomas greater than 4 mm thick with a pathologically determined margin of less than 1.6 cm (corresponding to a fresh tissue margin of about 2 cm) had a significantly increased risk of local recurrence compared to patients whose pathologically determined margin was greater than 1.6 cm ($p = 0.01$, with a hazard ration of 2.41 and confidence interval of 1.23–4.73) (Pasquali et al. 2013). Thus, 2 cm margins of surgical resection may be safe for any cutaneous melanoma with a Breslow thickness greater than 2 mm, but further investigation using specific thickness subgroups in a prospective randomized trial is needed to definitively tailor recommendations.

Given the potential difficulty in detecting differences in outcomes between narrow and wide excision margins due to low rates of local recurrence in thin melanomas and relatively few cases of thick melanomas, a number of meta-analyses have been undertaken of the studies reviewed above (Haigh et al. 2003; Sladden et al. 2009; Mocellin et al. 2011; Wheatley et al. 2016). These analyses have the advantage of increased statistical power based on larger combined sample sizes, but the disadvantage of combining heterogenous datasets. The most recent meta-analysis which had access to all the trials reviewed found no significantly increased risk of locoregional recurrence or overall survival between narrow margin and wider margin groups. Importantly, however, this conclusion was based on the grouping of both 1 cm and 2 cm margins as "narrow" excisions. When trials with identical arms were combined for analysis, only overall survival was reported, despite the suggestion that locoregional recurrence may be the most affected outcome. Moreover, there was no attempt to analyze the data by specific subgroup of tumor thickness. As

discussed above, this heterogeneity in the comparison groups makes it difficult to interpret the conclusions reached by this and previous meta-analyses, supporting a need for further investigation. Additionally, thicker tumors have higher rates of regional metastases at the time of diagnosis (Morton et al. 2014), suggesting that locoregional recurrence is dependent on control of these metastases in addition to excision of the primary lesion (reviewed below). Analysis of locoregional recurrence in patients with thicker melanomas without accounting for this difference in tumor stage likely confounds the results.

To summarize, current recommendations based on the data reviewed above are the use of a 1 cm margin for melanomas <1 mm in thickness and 2 cm margin for melanomas >2 mm in thickness. For melanomas with thickness between 1 and 2 mm, ideally a 2 cm margin would be used. However, in instances in which this margin is associated with significantly greater morbidity compared to the use of 1 cm margin, then the use of a 1 cm margin is appropriate (Table 1).

Excision Technique

The importance of obtaining an adequate biopsy in the diagnosis of melanoma cannot be overemphasized. Tissue samples are examined by a pathologist for the presence of malignant-appearing cells, which can be confirmed using immunohistochemistry to detect the presence of cellular markers of melanoma. As discussed previously, the thickness of the melanoma itself, in addition to the mitotic rate of the melanoma cells, and the presence of ulceration within the biopsied lesion are all characteristics of the tumor which provide important prognostic information that drive subsequent treatment decisions. Mutational analysis can also be performed from the tissue obtained to help determine the need and utility of systemic therapies in cases of high-risk or late-stage melanoma. Suspicious lesions are most often identified and biopsied in an office setting by a dermatologist or general practitioner, and it is critical that the appropriate technique is used for the initial biopsy to ensure that the tissue sample can be thoroughly characterized. Shave biopsies which take a tangential biopsy of the lesion are often insufficient as they may not sample the complete thickness of the lesion. Shave biopsies should therefore be performed only if the suspicion for and risk of melanoma are very low or the shave is very deep. In contrast, punch or excisional biopsies remove a full-thickness sample of the skin and are the preferred method for sampling any suspected melanoma as they can provide more accurate assessment of tumor thickness.

Once a melanoma has been identified by biopsy, the patient will undergo wide local excision to ensure that the lesion has been completely removed with adequate margins (Fig. 1). Wide local excision is often performed under local anesthesia or regional anesthesia in cases where sentinel node biopsy or lymphadenectomy is not planned; otherwise, general anesthesia is used. Recommended excision margins (Table 1) are clinically determined margins measured from the edge of the lesion or prior biopsy scar and do not refer to the width of the margin assessed by the pathologist. By convention the muscle fascia serves as the deep margin, though there are not data to provide guidance on this matter. Excision of the muscular fascia itself is recommended only in cases of fascial involvement by tumor. Specimens are then submitted for permanent pathology as frozen analysis has not proven reliable for melanoma.

A number of techniques are used to close the wound primarily after excision, including the use of an elliptical incision to prevent “dog ears” and raising skin flaps if needed to reduce tension during closure. The excision site (or “wound edge”) is then closed in layers to reduce the potential space and prevent seroma formation. In the case of excision of a lesion with significant tension or in a difficult anatomical area (e.g., the head or neck), the use of skin grafts or local flaps may

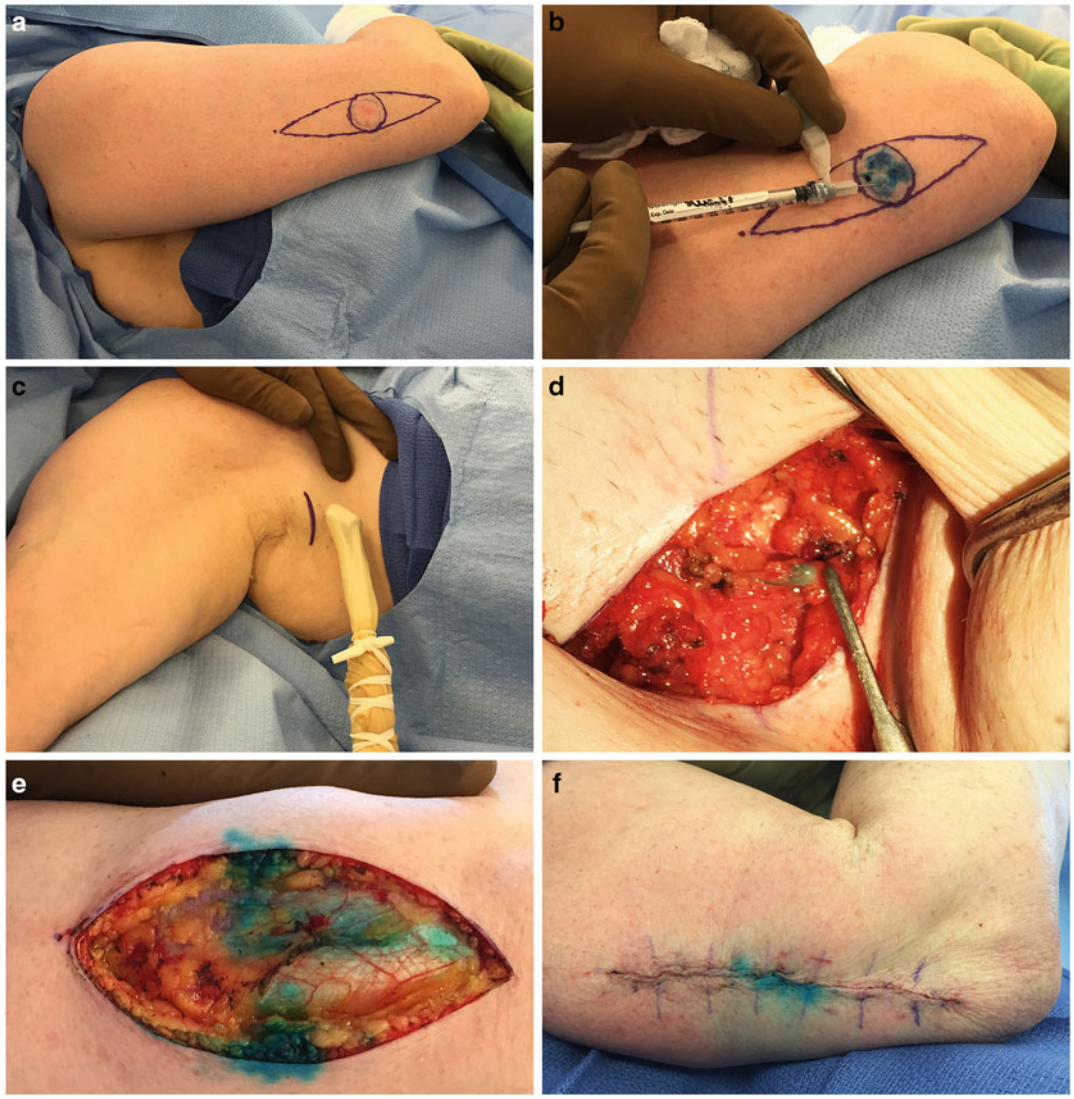

Fig. 1 Wide local excision of right arm melanoma with right axillary sentinel node biopsy. The site of the previously biopsied primary cutaneous melanoma on the right upper extremity has been sterilized and draped. The right axilla has been included in the operative field for planned sentinel node biopsy. The site of the previous biopsy has been marked with a circumferential 1 cm margin (blue circle surrounding scar in **a**) to delineate the planned margin of wide local excision. The incision will be extended into a longitudinal ellipse to reduce the size of "dog ears" on the ends (blue ellipse in **a**). Orienting the excision longitudinally will also help minimize future tissue loss if re-excision is necessary. For sentinel node biopsy, the dermis surrounding the lesion is injected preoperatively with a radioactive tracer, technetium-99 sulfur colloid. This dye is taken up by the dermal lymphatics which label the drainage basin (in this case the right axilla). The nodes are also labeled with intradermal injection of isosulfan blue (**b**) prior to the start of the procedure. The sentinel node biopsy precedes excision of the primary lesion so as not to disrupt the lymphatic drainage from the lesion. A handheld gamma probe is used to guide the initial incision (**c**). Identification of the sentinel node(s) is made by the presence of radioactivity and the blue coloration of the node (**d**). After dissection of the sentinel node is complete, the primary lesion is excised including all subcutaneous tissues down to the muscle fascia (**e**). The elliptical excision site is then closed primarily (**f**)

prove helpful. In some cases where the surgeon is not confident that the excision margin is free of cancer, or where narrow margins are necessitated by anatomy, the wound may be left open. Alternatively, a temporary wound closure device (e.g., a wound vacuum) can be placed until pathology results are available. If the pathological margins prove to be negative, then a skin graft or local flap can be used to close the excision.

A final important consideration for both the initial biopsy (if incisional) and wide local excision is the orientation of the scar that is formed. Because the margins of any necessary re-excision will extend circumferentially along the entire length of the scar, the initial scar should be oriented accordingly. For example, the initial incisional biopsy or wide local excision of a lesion on an extremity should be oriented longitudinally along the long axis of the extremity. If re-excision is required (such as in a case where what was thought to be a thin melanoma on initial biopsy is found to be of intermediate thickness after complete excision), then a longitudinal orientation along the extremity will maximize the chances that the scar can be removed with adequate margins and still allow for primary closure of the wound. The possible need for re-excision should be considered when determining the best approach to excision of every lesion based on both size and location.

Role of Lymphadenectomy in Primary Cutaneous Melanoma

Early observations suggested that metastatic cutaneous melanoma initially spreads through intradermal lymphatics to regional nodal basins and then to more distant sites. As early as the 1890s, it was recognized that individuals with clinically evident nodal disease were more likely to have distant metastases. As a result routine, early elective complete lymphadenectomy evolved as part of standard surgical management of intermediate-thickness primary cutaneous melanomas to try to prevent distant spread of metastatic disease. Unfortunately analyses of the nodes excised revealed that only 20% of patients undergoing elective lymphadenectomy had nodal metastases at the time of resection (Beitsch and Balch 1992), exposing 80% of patients undergoing this procedure to the associated risks without an obvious benefit. Moreover, there was no survival benefit when elective early lymphadenectomy was compared to performing complete lymphadenectomy only once a patient had developed clinically palpable nodal disease (Balch 1999; Balch et al. 1996). However, the alternative of nodal observation with lymphadenectomy only once a patient developed clinically evident nodal disease was thought to potentially compromise long-term control of metastatic disease (Balch et al. 2010; Cascinelli 1998; Morton et al. 2006). Lymphatic mapping and sentinel lymph node biopsy was developed by Morton and colleagues as a method to try to identify in a less-invasive manner which patients had nodal metastases (Wong et al. 1991). In this setting, completion lymphadenectomy could be limited to individuals with clinically occult metastatic disease where the goal would be to prevent the progression to clinically evident nodal disease. Multiple studies have since demonstrated the prognostic value of sentinel node biopsy. However, completion lymphadenectomy based on the presence of sentinel lymph node metastases without clinically evident nodal disease has not been definitively shown to improve melanoma-specific survival.

Technique of Sentinel Lymph Node Biopsy

Sentinel lymph node biopsy is based on the premise that lymphatic channels draining from specific cutaneous sites drain to specific first, or sentinel, lymph nodes that can be identified and resected. The presence or absence of melanoma metastases in these sentinel nodes accurately correlates with the presence or absence of metastatic melanoma in the entire nodal basin.

Sentinel node biopsy is performed using preoperative injection of a radioactive tracer, technetium-99 sulfur colloid, into the dermis surrounding a lesion or biopsy scar on the day of wide local excision and sentinel lymph node

biopsy. This dye is taken up by the dermal lymphatics which label the drainage basin. Deep injection below the dermis may map the wrong lymphatic channels and lead to the harvesting of the incorrect lymph nodes or prevent migration of the isotope to a regional lymphatic basin. Subcutaneous injection should be suspected if subsequent imaging does not reveal a draining nodal basin. Following injection, a scintillation camera may be used to identify patterns of lymphatic drainage and sentinel nodal basin (s) (Fig. 2). Labeled lymph nodes are apparent within 30 min of injection, and the radioactive signal persists for several hours. This technique

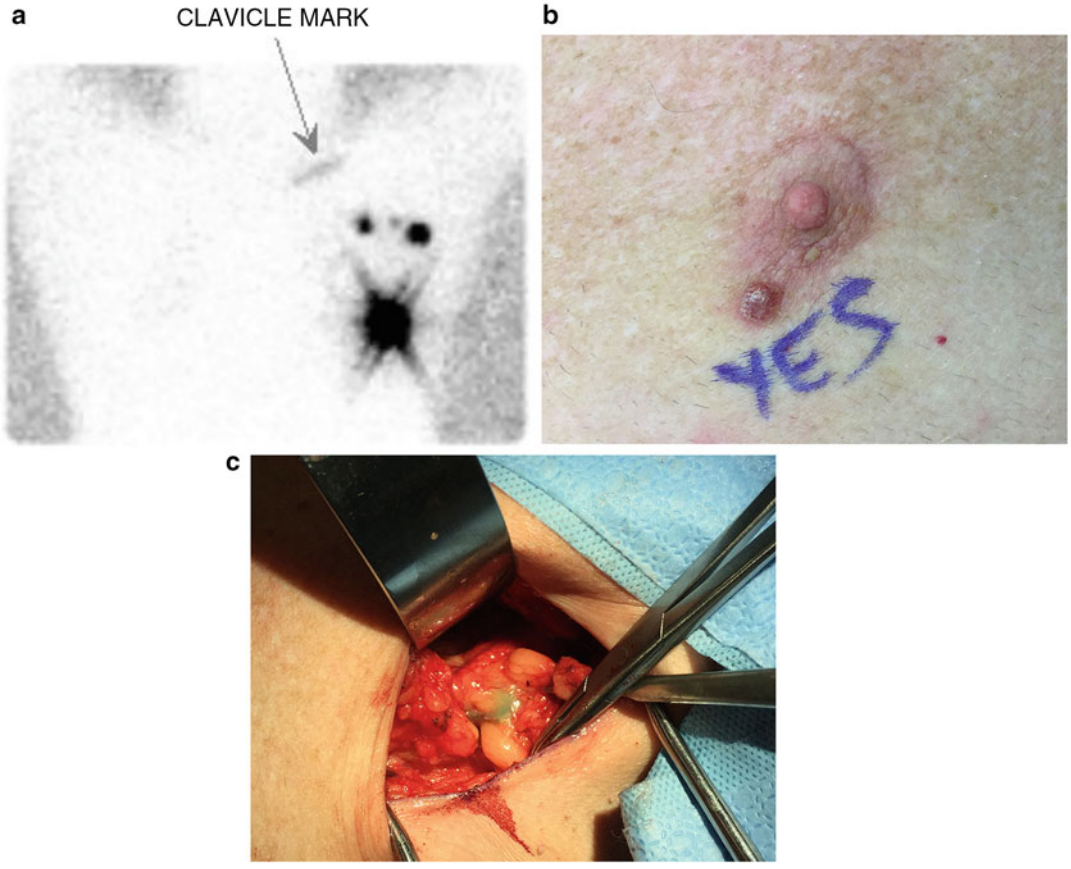

Fig. 2 Lymphoscintigram localizes regional drainage basin containing sentinel nodes. Sentinel node biopsy is performed using preoperative injection of a radioactive tracer, technetium-99 sulfur colloid, into the dermis surrounding a lesion. This dye is taken up by the dermal lymphatics which label the drainage basin. Following injection, a scintillation camera is used to identify patterns of lymphatic drainage and sentinel nodal basin(s) by imaging the radioactive signal, as shown here. (**a**) **Lymphoscintigram of chest and bilateral axillae**. Lymphoscintigram taken 5 min after injection of technetium-99 adjacent to the melanoma excision scar located on the left anterior chest (marked with white * on image). The additional foci of radioactive uptake represent three sentinel nodes within the left axilla. Patterns of lymphatic drainage are not predictable for non-extremity lesions and may even involve contralateral nodes, making preoperative lymphoscintigraphy helpful in focusing intraoperative dissection efforts. In this case, the left anterior chest lesion drained to the left axillary nodal basin. (**b**) **Left chest melanoma prior to resection**. Intraoperative photo of left chest melanoma which has been labeled with technetium-99 sulfur colloid (see lymphoscintigram in **a**). Sentinel nodes were double labeled with radioisotope and isosulfan blue prior to resection to aid in their identification (**c**). Tumor is marked "YES" as part of the preoperative universal protocol prior to induction of anesthesia to ensure resection of the correct lesion. (**c**) **Left axillary sentinel node**. Intraoperative photo of left axillary sentinel node draining left chest melanoma (**b**) identified both by the presence of radioactivity as demonstrated in lymphoscintigram (**a**) and by the presence of isosulfan blue

may also identify interval or in-transit nodes. Patterns of lymphatic drainage are not reliably predictable for non-extremity lesions and may even involve contralateral nodes, making preoperative lymphoscintigraphy helpful in focusing intraoperative dissection efforts. Intradermal injection of isosulfan blue at the lesion or biopsy scar further helps guide dissection (Fig. 1). The injected site is typically resected as part of the wide local excision; however, if this is not planned (e.g., when sentinel node biopsy is performed after wide local excision), it should be kept in mind that the isosulfan blue injection may leave behind a small but permanent tattoo. A handheld gamma probe and results of lymphoscintigraphy guide the initial target area for incision, while blue lymphatic channels help lead the dissection to the sentinel node(s). Using this double labeling technique, the sentinel node is defined by its blue color as well as by its radioactivity (Figs. 1 and 2). All nodes with radioactivity count at least 10% of the most radioactive node are defined as sentinel nodes and harvested, a technique which minimizes the rate of false-negative sentinel lymph node biopsy results (Luo et al. 2015). The sentinel lymph node can be successfully identified and removed in more than 99% of patients (Gershenwald et al. 1998). Usually between one and three sentinel nodes are identified per basin and sent for permanent pathology to evaluate for the presence of micrometastases using H&E staining and immunohistochemistry of multiple sections. When occurring as part of the same procedure, sentinel lymph node dissection is often performed prior to wide local excision of the primary lesion to prevent disruption of the labeled lymphatics that help to identify the sentinel node(s). However, in some cases, it is beneficial to reverse this sequence to prevent radiation from injection of the primary tumor site from interfering with localization of the sentinel node.

Sentinel Lymph Node Biopsy Provides Prognostic and Staging Information

Currently the results of sentinel lymph node biopsy are used for accurate staging and prognosis and to help determine whether completion lymphadenectomy or adjuvant therapy would be of benefit. Sentinel lymph node biopsy at the time of wide local excision is recommended for any patients with melanomas greater than 1 mm thick, as well as for melanomas equal to or less than 1 mm thick which have other high-risk features such as ulceration, a high rate of mitoses, or lymphovascular invasion. In terms of prognosis, it has been estimated that individuals with negative sentinel lymph node biopsies have a 90% 3-year disease-free survival, which decreases to 60% if they are found to have positive sentinel lymph nodes (Gershenwald et al. 1999). Moreover, a number of studies have shown that the histological status of the sentinel lymph node is the best predictor of survival in clinically node negative melanoma patients (Table 2).

The Multicenter Selective Lymphadenectomy Trial (MSLT-I) was a phase 3 trial designed to determine whether identifying patients with clinically occult nodal melanoma metastases via sentinel node biopsy and then performing an immediate completion lymphadenectomy in those patients improved outcomes (Morton et al. 2014). A total of 2001 patients were enrolled, and ultimately 1270 patients with intermediate-thickness tumors between 1.2 and 3.5 mm thick completed the trial. Another 314 had thicker

Table 2 Multiple multivariate analyses suggest that the presence of regional node metastases are the most important prognostic factors in early-stage melanoma and most reliably predict survival across studies

Prognostic factor
Node status
Number of involved nodes[a, b, c]
Tumor burden within nodes[b]
Primary tumor thickness[a, b, c]
Ulceration[b]
Site of primary lesion[a, b]
Patient age[b]

An individual patient's risk of sentinel lymph node metastases can be calculated using a number of available tools (Mahar et al. 2016), including the Memorial Sloan Kettering Cancer Center Melanoma Nomogram which is available at https://www.mskcc.org/nomograms/melanoma (Wong et al. 2005)

Based on [a]Morton et al. (1991), [b]Balch et al. (2001), and [c]Gershenwald et al. (1999)

primary melanomas. Of the individuals enrolled in the trial, 60% were randomized to wide local excision with 2–3 cm excision margins as well as sentinel lymph node biopsy, while the remaining 40% of patients enrolled underwent wide excision with nodal observation. A positive sentinel node biopsy triggered immediate completion lymphadenectomy. Otherwise, patients were observed and underwent lymphadenectomy only in the case of clinically evident nodal recurrence.

As predicted by previous studies, MSLT-I demonstrated that in the biopsy group, patients with sentinel node metastases had worse outcomes as compared to those without evidence of metastatic disease. In those with intermediate-thickness tumors, the 10-year melanoma-specific survival rate was 62.1% in node-positive patients, compared to 85.1% in patients without a positive sentinel lymph node biopsy ($p < 0.001$). For patients with thick tumors, the respective rates were 48% and 64.6% ($p = 0.03$). While there seemed to be little debate regarding the prognostic value of the sentinel lymph node biopsy, there remained significant controversy regarding whether SLNB itself actually reduces rates of recurrence and improves disease-free survival.

Much of the controversy surrounding MSLT-I stemmed from the fact that the trial was ultimately insufficiently powered to address the primary endpoint of melanoma-specific survival in all randomized subjects. This was due to the fact that the majority of patients with intermediate-thickness melanomas, 80%, demonstrated no nodal metastases – the survival of this group therefore could not be expected to be improved by early nodal excision, making it difficult to detect a significant benefit of sentinel node biopsy across the entire population. However, when subgroups were analyzed to examine the 20% of patients who ultimately developed nodal metastases (either demonstrated by initial sentinel node biopsy or during the observation period), immediate lymphadenectomy was suggested to improve outcomes. Individuals with intermediate-thickness melanomas and node-positive disease demonstrated a 10-year melanoma-specific survival benefit with early removal of nodal metastases (62.1% in biopsy group vs. 41.5% in observation group, hazard ratio 0.56, $p = 0.006$). Disease-free survival was also significantly improved (hazard ratio 0.62, $p = 0.02$). There was no treatment-related difference demonstrated among those individuals without nodal metastases at sentinel node biopsy or during the observation period. These results suggested that sentinel node biopsy and early completion lymphadenectomy might provide survival benefit to patients with intermediate-thickness melanoma.

A positive result on pathological examination of the sentinel node(s) indicates that the patient has had clinically occult spread of their melanoma into the lymphatic drainage basin examined. Given the aggressive nature of metastatic melanoma until very recently, the standard of care for a patient with a positive sentinel node biopsy was to offer completion lymphadenectomy, which involves dissection of the remainder of the regional lymphatic tissue to remove any other occult disease that may be present. Complete regional lymphadenectomy can be complicated by wound infection and seroma in the short term, as well as chronic lymphedema and neuronal dysfunction, prompting the need to ensure that this relatively morbid procedure results in improved outcomes.

The DeCOG-SLT study randomized patients with sentinel node-positive melanoma to close clinical observation of the nodal basin or completion lymphadenectomy (Leiter et al. 2016). Four hundred eighty-three patients were randomized, and as a whole, they had low risk of harboring disease in non-sentinel lymph nodes, as nearly 70% of the patients had less than 1 mm of sentinel lymph node tumor burden. The study was underpowered, and insufficient events were recorded to reach statistical significance. No melanoma-specific survival difference was observed after a median follow-up of 3 years, despite a significant increase in the nodal basin recurrence rate in the patients randomized to nodal basin observation. Patients randomized to completion lymphadenectomy had more frequent adverse events – primarily wound complications and lymphedema – compared to those in the observation arm.

MSLT-II was a randomized, prospective trial designed to specifically address whether patients with intermediate-thickness melanomas and sentinel node metastases would incur a survival benefit from immediate completion lymphadenectomy (Faries et al. 2017). One thousand nine hundred thirty-four individuals with a positive sentinel node biopsy were assigned to undergo either dissection of the affected lymph node basin or close observation with clinical examination and nodal ultrasonography. Completion lymphadenectomy did provide additional prognostic information in terms of the pathologic status of the non-sentinel nodes and led to a reduction in locoregional recurrence by about 70%. Despite these findings, with relatively short median follow-up of 43 months, there was no significant survival benefit with completion lymphadenectomy as compared to the observation group.

Together these data suggest that patients with melanoma metastatic to a sentinel lymph node are just as likely to have systemic metastases as they are to have metastases to the remainder of the lymph node basin. Completion lymphadenectomy therefore provides no therapeutic advantage over sentinel lymph node biopsy itself. While there are some complications associated with the sentinel lymph node biopsy, including wound infection and seroma formation, multiple studies comparing the rates of postoperative complication demonstrate that the risk is significantly lower for sentinel node biopsy alone as compared to completion lymphadenectomy (10% vs. 37% in MSLT-I, 24% vs. 6% MSLT-II, and 4.6% vs. 23.2% in the Sunbelt Melanoma Trial (Wrightson et al. 2003)). Therefore, as sentinel node biopsy provides equivalent benefit in terms of survival, completion lymph node dissection should not be recommended in patients who can undergo close clinical and ultrasonographic observation. In this new era of effective systemic treatments for melanoma, the true utility of sentinel lymph node biopsy will likely derive not from selecting patients for early completion lymphadenectomy but from identifying patients who will benefit from aggressive systemic therapies.

Conclusions and Future Directions

Despite the increase in the incidence of malignant melanoma, there have been dramatic improvements in the diagnosis and treatment of patients with melanoma in recent years. Surgical resection of early disease remains the mainstay of curative treatment. Current margin guidelines are derived from randomized, controlled studies and are based on tumor thickness. Reduction in surgical margins over the past several decades has limited the need for skin grafting, resulted in fewer wound complications, and led to faster recovery times without compromising disease-free or overall survival. The development of sentinel node biopsy has provided essential prognostic information and may prove to provide sufficient debulking of regional metastatic disease to make completion lymphadenectomy unnecessary. Moving forward, as our understanding of the molecular basis of malignant melanoma evolves, we will be even better able to predict disease behavior based on a tumor's molecular profile. Understanding which markers confer increased risk for metastatic disease will provide the information needed to further tailor surgical management, reserving aggressive surgical resection for those individuals at highest risk. Even with the development of targeted therapies that are transforming the landscape of care for advanced melanoma, surgical management will continue to provide the mainstay of curative treatment for patients with early disease.

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