Surgical Treatment of Malignant Melanoma
Practical Guidelines

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KEYWORDS

• Malignant melanoma • Cutaneous malignany • Skin cancer • Surgical treatment

KEY POINTS

- Melanoma is currently the fifth and sixth most common solid malignancy diagnosed in men and women, respectively.
- Melanoma accounts for more than 75% of all deaths from skin cancer.
- Treatment of this malignancy relies on appropriate staging.
- Biopsy technique and tissue diagnosis are crucial to developing the appropriate treatment plan for melanoma.

INTRODUCTION

The incidence of cutaneous malignant melanoma has been rising steadily over the past century. In the United States, the lifetime risk of developing an in situ or invasive melanoma is now estimated to be 1 in 30 in comparison with 1 in 1500 in 1935.[1–4] Melanoma is currently the fifth and sixth most common solid malignancy diagnosed in men and women, respectively.[5] Although accounting for only 4% of cases of all cutaneous malignancies, melanoma accounts for more than 75% of all deaths from skin cancer.[6] In 2012, it is estimated that 70,230 Americans will be diagnosed with invasive melanoma as well as an additional 53,360 with in situ lesions, and 8790 people, 1 person every hour, will die.[7] Efforts during the past decade to make the clinical characteristics of early cutaneous melanoma more widely known[8,9] have resulted in most patients (82%) being diagnosed in the early stages, when the primary tumor is confined to the skin.[10] Five-year survival rates exceeding 90% are achieved in patients with invasive melanomas confined to the skin in comparison with rates of approximately 60% and 5% in those with regional lymph node and distant metastases, respectively.[11]

EPIDEMIOLOGY AND RISK FACTORS

Melanoma is diagnosed within a broad range of ages beginning in the third decade of life, although occurring slightly more commonly in women younger than 40 and in men older than 40. Although the peak incidence is in the late 40s, melanoma is the commonest cancer diagnosed in young adults 25 to 29 years of age and the second most frequently diagnosed malignant tumor in patients 15 to 29 years of age. Melanoma most frequently arises on the skin of the back in men and on the lower extremities in women. In darker-skinned ethnic groups (African American, Asian, and Hispanic), melanoma frequently arises in the volar and plantar skin (acral) or in the nail bed (subungual). Although 95% of melanomas originate in the skin, they develop in other anatomic locations, such as the eye and mucous

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membranes, including the vagina and anus.[12] Approximately 3% to 10% of patients present with metastatic disease in the absence of a clinically identified primary melanoma.[13,14] Patients with metastases from an unknown or occult primary melanoma have the same prognosis and should be managed in the same manner as patients with known primary lesions.[15,16]

The typical patient with melanoma has light-colored eyes, reddish or blonde hair, and a fair or ruddy complexion that tans poorly and burns easily during brief periods of intense sun exposure.[9] Blistering sunburns sustained as a child or teenager are a significant risk factor for the development of melanoma and more deleterious than prolonged sun exposure in the later years.[17] More recently, an association between the exposure of teenagers and young adults to UV radiation through the use of tanning beds and the development of cutaneous malignancies including melanoma has been reported and is currently under intense scrutiny.[18]

The development of atypical (dysplastic) nevi is a significant risk factor for melanoma. Although patients with more than 100 dysplastic nevi (atypical mole syndrome) have a 10% to 15% incidence of melanoma in their lifetime, the presence of even a single atypical mole also increases the risk.[19–21] The prophylactic excision of dysplastic nevi is not justified, however, because in most patients melanoma arises from normal skin, as opposed to from within a preexisting benign nevus.[22,23] Children with large congenital nevi are at increased risk for melanoma, although this occurs uncommonly (10%–15%), and almost exclusively in patients with truncal lesions and within the first 2 decades of life.[24–26]

A thorough physical examination includes an inspection of the entire cutaneous surface (including the volar and plantar skin, webspaces, and mucous membranes) of a completely undressed patient under appropriate lightning conditions. The ABCDE rule helps to identify those pigmented lesions most likely to be melanoma.[27–30] Lesions that are Asymmetric have irregular Borders, Color variation, and Diameters exceeding 6 mm (the size of a pencil eraser) are considered to be suspicious. In addition, any pigmented lesion that Evolves (or becomes darker or lighter in color, increases in size or becomes raised, or itches or bleeds) should immediately arouse suspicion. The use of dermoscopy,[31] as well as more recently developed advanced computer-aided digital imaging tools,[32] may be used to more selectively identify lesions for biopsy that are more likely to be malignant, obviating the need for excision of less suspicious moles. Complete excisional biopsy, however, of any preexisting mole that has changed in appearance, itches, or bleeds is recommended.

Patients diagnosed previously with a melanoma have a 3% to 6% risk of developing a second primary cutaneous melanoma in the course of their lifetime.[33,34] In addition, there is a 3% to 10% incidence of melanoma in first-degree family members.[35] Formal genetics consultation should be considered in patients with significant family history of melanoma, as well as families affected by cancers of the breasts and ovaries. These patients may harbor a deleterious BRCA mutation that confers a risk of developing melanoma in addition to other known solid tumors.[36] Lifelong total cutaneous surveillance of all patients with melanoma and their immediate families is also strongly recommended.

PROPER BIOPSY TECHNIQUE

Accurate sampling of any lesion suspicious for melanoma may be considered adequate only if sufficient tissue is obtained to definitively confirm or exclude a histologic diagnosis of malignancy. The biopsy must accurately assess the depth of tumor penetration of the skin, which strongly determines the scope of the initial diagnostic evaluation, the extent of surgical resection in terms of margin width, and appropriateness of sentinel lymphadenectomy in newly diagnosed clinically node-negative patients.[37,38]

Complete surgical excision has long been considered the biopsy method of choice for all cutaneous lesions suspected of being melanoma.[39] This technique can be performed rapidly in the office setting using local anesthesia and enables complete assessment of tumor thickness, should the lesion indeed prove to be melanoma. Although punch and shave biopsies may be suboptimal because insufficient sampling of atypical elements may occur and/or tumor thickness in malignant lesions is underestimated, recent studies have confirmed the adequacy of these techniques when performed properly.[40] If a biopsy is nondiagnostic or significant clinical concern persists, complete excisional biopsy should be performed. Incisional biopsy of unusually large or broad lesions is acceptable only if the diagnosis of melanoma is confirmed and tumor thickness is assessed accurately. For extremity lesions, surgical biopsy incisions should always be oriented vertically so as not to interfere with or complicate subsequent definitive excision and reconstruction.

ADVANCED HISTOLOGIC EVALUATION OF BIOPSY MATERIAL

Immunohistochemistry is used routinely to complement standard histopathologic techniques in confirming the diagnosis of melanoma. The monoclonal antibody HMB-45[41,42] and the polyvalent

antibody recognizing the S-100 antigen[43,44] are used most extensively. Although a combination of the 2 may improve the histopathologic characterization of difficult lesions, neither has proved to be completely reliable. For example, the S-100 protein, although expressed in almost all melanomas, is also detected in other tissues of neural crest derivation. Although HMB-45 staining may be used to distinguish unusual melanomas from unusual benign nevi, it is sometimes not identified in amelanotic and desmoplastic melanomas[42] nor in the metastatic lesions.

Further microscopic evaluation of melanoma to identify histologic evidence of ulceration and to quantify mitosis (if present), is now required to determine melanoma staging and plan surgery appropriately.[45,46] The presence of histologic regression may also indicate a more aggressive phenotype than a melanoma of equivalent thickness, and may influence the diagnostic evaluation and possibly the extent of surgery. The identification of unusual melanoma subtypes, such as nevoid, spitzoid, and desmoplastic variants, refines the diagnosis, and in some instances may also influence the scope of surgery. In patients with purely desmoplastic melanomas, wide margins should be maintained, but sentinel lymphadenectomy may be unnecessary in patients with lesions thinner than 4 mm, which are associated with increased rates of local recurrence, yet rarely metastasize to the regional nodes.[47] Malignancy is sometimes difficult to confirm in lesions exhibiting nevoid or spitzoid features especially when arising in children and teenagers. Obtaining additional expert dermatopathologic review is essential in many such cases.

Molecular profiling and the identification of biomarkers, such as mutations in BRAF and KIT, in thicker or locally advanced primary, recurrent, or metastatic lesions, is also now routinely requested to guide newly available adjuvant targeted therapies.[48,49]

ASSESSMENT OF TUMOR THICKNESS AND STAGING

Tumor thickness is a measure of the vertical growth phase of the melanoma and is a significant prognostic indicator of the potential for local recurrence, metastases, and death.[11] An accurate assessment of tumor thickness is therefore critical in the planning of an appropriate metastatic survey, surgery, adjuvant treatment, and follow-up schedule. Melanoma thickness is assessed in millimeters by ocular microscopy as described by Breslow[50] or by increasing levels of dermal penetration in the manner described by Clark and colleagues.[51] The micro staging techniques of both Clark and colleagues[51] and Breslow[50] have enabled a more accurate grouping of patients with primary melanomas based on reproducible measurements of tumor thickness and are predictors of survival. Melanoma is staged according to published American Joint Committee on Cancer (AJCC) guidelines using the TNM system.[52] The AJCC staging system for melanoma has been officially revised and expanded in recent years.[53,54] The current 2010 version further stratifies groups of patients by including important prognostic factors, such as ulceration and the presence of mitoses in the primary lesion. The new classification revises the importance of Clark level in the T classification of tumor thickness, and further delineates the extent of nodal involvement by recognizing the extent of microscopic nodal involvement of the sentinel node and number of nodes affected.[55–57] Other parameters, such as lactate dehydrogenase (LDH) level and anatomic site of distant metastatic disease, are also maintained in this more recent staging system.[52] Patients seeking an opinion after lesion excision at another institution should be encouraged to submit all outside reports and biopsy slides for an in-house review to confirm not only the diagnosis of melanoma but also to precisely measure tumor thickness before planning definitive surgery.

PREOPERATIVE METASTATIC EVALUATION

Preoperative metastatic survey is determined primarily by the thickness and histologic features of the primary melanoma and disease stage at presentation. No laboratory or radiologic metastatic evaluation is required for patients with malignant melanoma in situ or invasive lesions thinner than 0.5 mm. Patients with invasive melanomas thicker than 0.5 mm but thinner than 1.0 mm undergo chest radiograph and routine blood chemistries (including LDH) primarily as a baseline, although the risk of distant metastases is minimal (<3%). Patients with intermediate-thickness lesions (1–4 mm) are also evaluated initially with chest radiography and routine blood chemistries, although the yield of confirming metastatic disease is low. Patients presenting with thick lesions (>4 mm), less thick lesions (>2 mm) with ulceration or mitoses, or in the presence of satellite or in-transit metastases have a significant risk of metastases to the regional nodes (60%–75%) and distant sites (30%–50%). These patients should be evaluated with advanced imaging modalities with intravenous contrast, which may include computed tomography (CT) or fluorodeoxyglucose (FDG)-based positron emission tomography (PET) CT scans, and magnetic resonance imaging (MRI) of the brain. Although the actual benefit of

performing such advanced and often expensive examinations is controversial,[58] they do allow for more precise staging and allow for stratification on entry into clinical trials. The degree of suspicion with which ambiguous radiologic findings are viewed is dependent on the risk of metastases as assessed by physical examination, melanoma thickness, and disease stage. Indeterminate findings suspicious for metastases on any scan are investigated further and confirmed cytologically or histologically using image-guided needle aspiration biopsy.

EXCISION MARGINS

The propensity of melanoma to disseminate and recur locally is well documented and has historically influenced the surgical approach to this tumor.[59,60] The surgical treatment of melanoma in terms of margin excision width has been studied extensively in prospectively randomized trials. Appropriately, the margins recommended for definitive melanoma excison have become increasingly more conservative and esthetically sensitive over the past several decades (**Table 1**).[61–69] Excision margin width is determined primarily by lesion thickness as measured in millimeters. The peripheral border or edge of a faintly pigmented or regressed melanoma may be difficult to ascertain in some patients, especially in those with extremely sun-damaged skin. Examination of the lesion using dermoscopy or a Wood lamp may help delineate the periphery of these melanomas to avoid excising the lesion too narrowly, resulting in inadequate surgical margins.

Malignant melanoma in situ is excised with 5-mm margins. Mohs micrographic surgery has been attempted in the treatment of these early noninvasive lesions but the results have been disappointing, possibly owing to the presence of clinically occult discontinuous microscopic foci of disease.[70] Thin (<1 mm) melanomas have an extremely low rate of local recurrence (<2%) and are excised with 1-cm margins.[67,71,72] For intermediate-thickness (1–4 mm) lesions, the safety of 2-cm excision margins has been confirmed in prospectively randomized studies.[69] Excision of narrower 1-cm margins have also more recently been shown to be adequate for lesions thinner than 2 mm in prospective randomized trials. Despite a slightly higher rate of local recurrence, there appears to be no significant impact on overall survival.[65,73] These data support the use of narrower excision margins for selected lesions and may greatly enhance the cosmetic result in anatomic areas such as the face. For thicker melanomas (>4 mm) the guidelines are less certain. Whereas 2-cm margins may be appropriate for these lesions based on currently available data, in selected circumstances (very thick lesions or in the presence of multiple satellite metastases) many surgeons advocate wider excision margins of 3 cm. It is unlikely, however, that margins exceeding 2 cm significantly impact on the higher rates of local recurrence (12%) and poor survival (55% at 5 years) with which these lesions are associated.[74] The failure of more radical procedures using wider (3–5 cm) excision margins, or in the past, limb amputation,[75] to diminish local recurrence rates and increase survival in patients with thick (>4 mm) melanomas, is further evidence that local recurrence reflects the biologic aggressiveness of the primary lesion, not the inadequacy of the primary excision.

Most excision site defects may be closed primarily, although split- or full-thickness skin grafting, or flap closure, may be required for the reconstruction of larger defects. In patients requiring a skin graft for closure of a wound located on the extremity, skin should not be harvested from an area in close proximity to the melanoma, as this could potentially reintroduce tumor cells into the reconstructed wound. Similarly, the changing of gloves and surgical instruments is prudent and should be performed routinely after melanoma excision to avoid wound contamination.

Table 1
Guidelines for excision margins for primary cutaneous melanoma

Melanoma Thickness	Excision Margin
In situ	5 mm
<1 mm	1 cm
≥1 to <4 mm	2 cm[a]
≥4 mm	2 cm[b]

[a] May be 1-cm margin for lesions thinner than 2 mm in aesthetically sensitive areas.
[b] Margin should be no less than 2 cm, although when available, a 3-cm margin is often used.

TREATMENT OF THE REGIONAL LYMPH NODES

Clinically Negative Regional Lymph Nodes

Most patients with newly diagnosed melanoma exhibit no evidence of regional lymph node metastases. The potential for regional lymph node metastases is assessed most accurately by tumor thickness. Malignant melanoma in situ by definition has no significant potential for lymph node metastases. For thin melanomas (<1 mm) the risk of nodal metastases is minimal (<5%) and therefore the complete elective dissection of the regional lymph

nodes is not required. Patients with intermediate-thickness lesions (1–4 mm) have a 20% to 25% incidence of microscopic regional disease and a 3% to 5% risk of distant metastases. For these reasons, this group is traditionally thought to most likely derive a therapeutic benefit from elective lymph node dissection. Prospectively randomized studies, however, have consistently failed to demonstrate a significant survival advantage with elective lymph node dissection in most patients.[61,72,76–79]

Sentinel Lymph Node Biopsy

Sentinel lymph node biopsy (SLNB) has effectively replaced elective lymph node dissection for the evaluation of clinically negative regional lymph nodes in patients with invasive primary cutaneous malignant melanoma. The technical details of intraoperative lymphatic mapping, with vital blue dye and filtered technetium radiolabeled sulfur colloid, and sentinel lymph node biopsy have been well described.[80–83] The safety, reproducibility, and validity of the procedure has been demonstrated through the results of the prospectively randomized Multicenter Selective Lymphadenectomy Trial I (MSLT I).[84,85] Precisely which specific patients will derive the greatest benefit from the sentinel lymph node biopsy procedure is less clear.

The *ideal* candidate for SLNB is the patient with a melanoma at least 1-mm thick in the absence of clinical or radiologic evidence of regional lymph node or distant metastases (**Table 2**). Lymphoscintigraphy performed before surgery must clearly demonstrate the lymphatic drainage pathway and regional nodal drainage basin to precisely localize and excise the appropriate sentinel node. As the risk of metastasis to the regional lymph nodes is closely correlated with the thickness of the primary lesion, planning definitive surgery may be problematic for melanomas sampled incompletely by punch or shave biopsy, especially when they are thinner than 0.76 mm but extend to a biopsy margin. Repeat biopsy or complete excision of these lesions may ultimately be required to more precisely assess thickness.

Table 2
Sentinel lymph node biopsy for melanoma

Melanoma Thickness[a] (mm)	SLN Biopsy
<0.76 mm	No
<0.76 mm, (+)ulceration, mitotic rate >1, tumor extends to deep biopsy margin	No
≥0.76 to <0.85 mm, no ulceration, regression, or mitoses	No
≥0.76 to <0.85 mm, (+) ulceration, regression, or mitoses	Yes
≥0.85 to <1.00 mm	Yes
≥1.00 mm	Yes

[a] Guidelines refer to thickness determined after final excision. When the melanoma extends to the deep margin of the biopsy, actual tumor thickness may be underestimated.

Regional lymph node metastasis occurs rarely (<5%) in patients with melanomas thinner than 1.00 mm, and most often with melanomas thicker than 0.85 mm, and in lesions with extensive ulceration and mitoses.[86] In our own unpublished series of 100 SLNBs in patients with melanomas thinner than 1.00 mm, only 3 patients had positive nodes, and all 3 had primary lesions thicker than 0.85 mm. Although unproven by clinical trials, it would therefore seem reasonable to defer SLNB in patients with melanomas thinner than 0.86 mm in the absence of significant ulceration or mitoses. Melanomas with predominantly desmoplastic features similarly appear to be associated with a diminished propensity to metastasize to the regional nodes, making SLNB less compelling especially in those patients with thinner (<4 mm) desmoplastic lesions.[87] Patients with thick primary melanomas (>4 mm) and no evidence of regional lymph node metastases are still at high (50%–75%) risk to have microscopic nodal metastases and are also appropriate candidates for intraoperative lymphatic mapping and sentinel lymphadenectomy in the absence of documented distant metastatic disease or limited life expectancy from associated comorbidities.

Intraoperative lymphatic mapping and SLNB may be suboptimal for technical reasons in the following groups: patients who have already undergone definitive wide and deep excision of the melanoma (≥2 cm margins or flap closures), when lymphoscintigraphy demonstrates multiple (>2) potential regional nodal drainage basins, in patients with melanomas situated in close proximity or directly over the regional nodal drainage basin such that the weaker signal from the sentinel node is obscured by the stronger primary injection ("shine-through effect"), or when a head and neck melanoma maps to an intraparotid sentinel node (risk of facial nerve branch injury). SLNB should not be performed if lymphoscintigraphy does not clearly demonstrate a regional lymph node drainage basin and sentinel node, in patients with confirmed regional nodal or distant metastases, or in patients with limited life expectancy from melanoma or associated medical conditions.

Intraoperatively, the sentinel node is sent immediately for microscopic examination, which may include touch preparation, frozen section analysis, or rapid immunostains. If no definitive evidence of metastatic melanoma is noted, wide and deep excision is performed as planned and the procedure is terminated. If micro metastases are confirmed in the sentinel lymph node, then formal (therapeutic) lymphadenectomy is performed at this time. Postoperatively, the sentinel lymph node is serially sectioned and examined in greater detail using standard hematoxylin and eosin staining and S-100 and HMB-45 immunostaining. The utility and clinical relevance of staging the sentinel node further on a molecular level using advanced techniques, such as reverse polymerase chain reaction, is currently being evaluated.[88–90]

Complications of SLNB are fortunately rare but should be discussed with the patient preoperatively and include, but are not limited to, dye reactions (<1%),[91] wound complications, seroma formation, the development of lymphedema (<5%), and a false-negative sentinel node (5%–15%).

Sentinel lymph node metastasis has proven to be a powerful independent predictor of subsequent disease progression and survival when confirmed histologically, immunologically, or on a molecular level.[80] Metastasis to the SLN also provides useful information, allowing for improved tumor staging that led to several major revisions of the AJCC staging system for melanoma beginning in 2002. Unfortunately, no histologic factors have been identified to date to consistently predict which patients have microscopically positive sentinel node involvement as an isolated event and which patients have additional nonsentinel node metastases.[92–94] Although the risk of additional nonsentinel lymph node metastasis appears to be low (<15%) in patients with positive sentinel nodes, it is currently recommended that patients with confirmed micrometastases in the sentinel node undergo complete regional lymph node dissection as a second procedure. The efficacy and precise role of a complete lymph node dissection in these patients is unclear and is currently being evaluated in the prospective randomized Multicenter Selective Lymphadenectomy Trial II (MSLT II).

Clinically Positive Lymph Node Metastases

Any palpable lymph node in a patient with melanoma should be considered indicative of metastasis until proved otherwise. Fine-needle aspiration biopsy is an accurate, reliable method of confirming metastatic melanoma.[95,96] If the fine-needle aspiration is biopsy is not available or results are indeterminate, excisional biopsy of the lymph node is performed. Patients presenting with or subsequently developing regional lymph node metastases are at high risk for distant metastases and should undergo advanced imaging including CT scanning (with intravenous contrast) of the chest, abdomen, and pelvis or FDG-PET scanning and MRI scanning of the brain. In patients with cytologically or histologically proven regional nodal metastases, formal complete lymph node dissection is performed. The development of palpable lymph node metastases is correlated significantly with substantially diminished survival (10%–50%), which is influenced strongly by the number of and the extent to which the lymph nodes are involved, as well as the primary melanoma thickness.[15,97]

Regional lymph node dissection should not be performed routinely in patients with documented distant metastases that are extensive or in those patients with large lymph node metastases fixed to adjacent structures. Significant palliation of inoperable bulky or bleeding regional nodal metastases may be achieved with radiation therapy in such situations, which are associated with an extremely poor prognosis.

TREATMENT OF LOCAL RECURRENCE

Local recurrence in a patient with malignant melanoma is an ominous clinical event and is almost always associated with the development of systemic metastases. The survival of these patients is extremely poor, averaging less than 5% at 10 years.

Primary melanoma thickness remains the most significant prognostic indicator of local recurrence and death, with other important predictive variables being the presence of ulceration and anatomic location of the primary lesion.[11] Large multi-institutional randomized trials confirm that local recurrence, and the incidence of in-transit, regional lymph node, and distant metastases, rises significantly with increasing primary melanoma thickness.

Local recurrence most often appears clinically as a blue-tinged subcutaneous nodule, arising in close proximity (within 2–5 cm) to an excision site of a primary melanoma (satellite metastasis), or en route to the regional lymph node basin (in-transit metastasis). Any subcutaneous nodule arising in the vicinity of a melanoma excision site should be considered to be disease recurrence or progression until proved otherwise. Diagnosis is accomplished rapidly and accurately by fine-needle aspiration biopsy. Excisional biopsy of the nodule under local anesthesia may sometimes be required for diagnostic confirmation. A

complete metastatic survey, including CT or MRI and FDG-PET scans, should then be performed because most of these patients will now also have evidence of systemic metastases.

SURGICAL TREATMENT OF LOCALLY RECURRENT MALIGNANT MELANOMA

Although no standardized surgical approach to all patients with locally recurrent melanoma has been established, treatment guidelines have been developed based on clinical trials in patients selected by the extent and specific anatomic site of the disease recurrence. The realization that local recurrence is not simply the result of inadequate surgical excision but is an outward manifestation of the biologic aggressiveness of the primary melanoma has led to a more rational approach to the treatment of these patients.

Complete surgical resection with primary wound closure is the most straightforward means of treating single recurrent lesions. Patients with multiple subcutaneous metastases grouped within a single focus can similarly be treated with wide local excision with skin grafting or flap closures necessary for wound coverage. Although wide resection margins are not as well defined in the resection of locally recurrent disease as they are in the treatment of primary cutaneous melanoma, recurrent lesions should be resected with a margin of normal tissue if possible. Fracturing of the tumor mass is often followed by further rapid local recurrence. The changing of surgical instruments and gloves immediately after surgical resection or debulking of extensive metastases is recommended because rapid recurrence in the surgical wound and surrounding soft tissues is not uncommon.

Despite complete surgical resection of multiple cutaneous metastases, further local and regional recurrence may occur in up to 67% of patients and is strongly associated with subsequent disease progression,[98] with as many as 70% to 82% of such patients ultimately succumbing to distant metastases.[99]

SPECIAL CLINICAL SITUATIONS

Subungual Melanoma

Subungual melanoma is rare clinical entity representing up to 3% of cases of melanoma in whites, but a higher proportion of melanomas (15%–35%) in dark-skinned ethnic groups.[99,100] More than 75% of subungual melanomas involve either the great toe or the thumb. Early signs of this lesion include a darkening of the nail bed. Dark pigmentation of the proximal nail fold, Hutchinson sign, is a classic stigmata of subungual melanoma. Many patients with subungual melanoma report a recent history of trauma to the digit and attribute the lesion to a poorly healing wound. The differential diagnosis of subungual melanoma includes benign pigmented lesions of the nail bed mechanism (melanonychia striata),[101] chronic bacterial fungal infection, and subungual hematoma.

The major pitfall in the diagnosis of subungual melanoma is an inadequate biopsy. Although nodular and amelanotic lesions do occur, most subungual hematomas appear as a sharply demarcated blue-black to brown discoloration of the nail, which does not involve the adjacent cuticle. A diagnosis of subungual hematoma may be confirmed by releasing the clotted blood through a large-bore puncture (trephination) or partial removal of the nail plate. Formal biopsy of the nail bed is performed under digital or regional anesthesia block in the office or as an outpatient procedure in the operating room. The nail plate is then elevated carefully from the nail bed and the lesion in question is clearly visualized. An elliptical incision in the nail bed down to the underlying periosteum is then performed allowing for complete excisional biopsy of the lesion and primary closure of the defect with fine absorbable sutures. Larger defects may be repaired with nail bed flaps or skin grafting. Generous incisional biopsy through the central portion of pigmentation is performed for larger lesions not amenable to simple excision.

Melanoma in situ of the nail bed is treated with complete wide local excision, including the entire nail bed and proximal matrix. Negative surgical margins of at least 5 mm are optimal. The surgical defect may be repaired with a local flap of skin or may require skin grafting.

Invasive subungual melanomas of the lower extremity are treated most easily with amputation of the toe. The appropriate surgical resection margin width of 1 or 2 cm for lesions with thickness less than 1 mm or greater than or equal to 1 mm, respectively, is achieved through complete amputation of the affected toe. Ray amputation may be required for lesions extending into the webspace. In most patients, the resulting surgical defect closes easily, heals well, and allows for ambulation without a specialized prosthesis or orthotic device, even when complete or partial amputation of the great toe is required. For upper extremity subungual invasive melanomas, surgical treatment is more individualized. Amputation is performed through the joint most proximal to the lesion, which represents a more conservative and functionally superior approach to the more radical amputations performed in the recent past.[102] Wound closure is achieved with a flap of volar tissue while ideally

maintaining a margin of at least 1 cm of normal tissue. For subungual melanomas of the thumb, a reconstruction is performed by webspace deepening using a Z-plasty, reducing the length of digit loss by approximately 50%.[101]

Sentinel lymph node mapping and excision is performed according to guidelines established for the treatment of melanomas of equivalent thickness and histology arising in the skin in the absence of clinically palpable regional nodes. Patients presenting with palpable nodal metastases undergo concurrent complete regional lymphadenectomy.

Plantar Melanoma

Melanoma arising on the sole of the foot, characteristically in an acral lentiginous growth pattern, is a rare clinical entity in whites, accounting for only 2% to 8% of melanoma cases in that population.[103] In dark-skinned ethnic groups, such as patients of African American, Asian, or Hispanic descent, however, melanoma arises on the plantar surface of the foot in 35% to 90% of patients diagnosed with melanoma in those populations.[104]

Although the metastatic potential of these lesions is correlated significantly with the thickness of the primary melanoma, as it is for cutaneous melanomas arising elsewhere, these lesions are often diagnosed at later stages and therefore generally have a less favorable prognosis. The frequent delay in diagnosis of plantar lesions may be explained in part by their rarity and their unusual and infrequently examined anatomic location. In addition, the increased thickness of the epidermis of the plantar surface may obscure the characteristic clinical appearance of the melanoma. Even melanomas that appear flat may be revealed after adequate biopsy to be thick lesions. A major pitfall in the early diagnosis of this lesion, however, is the failure to obtain a satisfactory biopsy specimen for histologic confirmation of malignancy. The extreme thickness of the plantar epidermis limits the use of shave biopsy as a diagnostic modality. In addition, the haphazard pigment pattern of these lesions also makes accurate diagnosis and assessment of lesion thickness by other techniques, such as punch or even incisional biopsy, less likely to be successful.

The preferred method of biopsy for these difficult lesions is complete excisional biopsy. Definitive wound closure may be deferred until rapid histologic diagnosis and margin inspection are complete. Once the diagnosis of melanoma is confirmed, the lesion is excised and staged according to guidelines established for other cutaneous primary melanomas of comparable thickness. Sentinel lymph node mapping and excision are performed according to guidelines established for the treatment of melanomas of equivalent thickness and histology arising in other cutaneous sites in the absence of clinically palpable regional nodes. Patients presenting with palpable nodal metastases undergo concurrent complete regional lymphadenectomy.

Dissection of the deep inguinal nodes is performed in patients with involvement of Cloquet node or extensive disease in the upper aspect of the femoral triangle. Lesions confirmed to be melanomas on shave, punch, or incisional biopsy that approach or exceed 1 mm in thickness may be treated definitively as outlined previously and may not require a preliminary excisional biopsy procedure.

Wound closure of the plantar surface requires special consideration. The exact location of the melanoma on the plantar surface, stage of disease, age, associated medical conditions, and lifestyle of the patient must be considered in the determination of wound closure. Defects on non–weight-bearing aspects of the plantar surface or those in patients with sedentary lifestyles, significant medical comorbidities, or advanced metastatic disease may be closed most easily primarily or more commonly with split-thickness or full-thickness skin grafts. Closure of defects on the weight-bearing surface of the plantar region in ambulatory patients is accomplished with a variety of flap reconstructive procedures. These include relatively straightforward cutaneous rotational or advancement flaps and more complex reconstructive procedures, such as musculocutaneous free flaps with microvascular anastomosis. These latter procedures are usually performed with a plastic reconstructive surgeon who ideally has been involved in the care of the patient once the diagnosis of melanoma has been confirmed.

Locally advanced, recurrent, or metastatic acral lentigenous melanomas should also be evaluated for mutations in KIT, which are more frequently noted in acral lentigenous and mucosal melanomas than in lesions arising elsewhere in the skin. Demonstration of KIT mutations may make the patient a candidate for targeted therapy with imatinib (Gleevec), developed originally for the treatment of central nervous system and hematologic malignancies, that now shows promise in melanoma.[48]

Melanoma on the Face

Melanoma occurs rather commonly on the face often as a broad, somewhat ill-defined situ lesion, known traditionally as a Hutchinson melanotic

freckle or lentigo maligna.[105] Despite their diminished biologic aggressiveness, however, the cosmetic and functional considerations of performing tumor surgery on the face makes treating these thin lesions especially challenging.

Biopsy should be performed to fully assess melanoma thickness to plan definitive surgical treatment appropriately and to determine the risk of regional lymph node metastases and the need for additional procedures, such as lymphatic mapping and sentinel lymphadenectomy. As in other anatomic locations, complete excisional biopsy or extensive and deep shave biopsy is required to confirm the diagnosis of melanoma and tumor thickness. Other techniques, such as punch and incisional biopsy, clearly have a role in certain circumstances but are less optimal because melanocytic neoplasms arising on the face, especially on significantly sun-damaged skin, are often far more extensive microscopically in terms of their radial extension than they appear clinically. If complete excisional biopsy of such a large lesion is required, and the defect created is not amenable to cosmetically acceptable primary closure, then a moist, sterile dressing should be placed until the pathologic examination of the surgical specimen is complete. Care should be taken, however, with any biopsy technique chosen, to avoid injury to the branches of the facial nerve. The marginal mandibular division, because of its superficial location and diminutive size, is particularly at risk. The possibility of facial nerve injury should be discussed with the patient and documented appropriately before any biopsy procedure.

On the face, achieving an appropriately wide resection margin may be particularly challenging for melanomas located in close proximity to structures, such as the eye, nose, and mouth. A good rule of practice is to obtain as close to the desired surgical margin as possible based on the thickness of the melanoma when excising invasive melanomas thinner than 2 mm arising in cosmetically important areas of the face. This practice is a reasonable approach in such circumstances because prospective randomized trials designed to define the width of melanoma excision have demonstrated that although narrower margins obtained for melanomas thicker than 1 mm but thinner than 2 mm are associated with slightly higher local recurrence rates, they have no significant impact in long-term survival.[72]

Traditional resection margin widths for the excision of in situ and thin invasive melanomas have been challenged by investigators advocating the technique of Mohs micrographic surgery as an alternative to wider local excision.[106] Although study is ongoing, the efficacy and overall safety of this technique in the treatment of melanoma of the face remains unproven and is not recommended.

A plastic reconstructive surgeon should be included in the planning and performance of any resection of a melanoma on the face that will result in a significant surgical defect. A range of reconstructive techniques is now widely available to make the final cosmetic and functional surgical result more acceptable. All patients should have the advantage of such a multidisciplinary approach, including the dermatologist, surgical oncologist, and plastic reconstructive surgeon.

As in other anatomic areas, patients with melanomas on the face approaching 1 mm in thickness are at risk for occult micrometastases in the regional lymph nodes. The advent and refinement of cutaneous lymphoscintigraphy has better delineated the often-complex lymphatic drainage patterns unique to this region. Accordingly, elective lymph node dissection of presumed sites of micrometastatic disease in the head and neck region has been replaced by cutaneous lymphoscintigraphy and sentinel lymphadenectomy using a radiolabeled tracer substance, such as technetium sulfur colloid alone. The additional use of vital blue dyes to perform sentinel lymphadenectomy is often superfluous in this region and carries with it a remote risk of permanent discoloration of the skin, necrosis, or anaphylaxis.[91,107–109] Regional lymphadenectomy is performed selectively in those patients with histologically confirmed micrometastases in the sentinel nodes. Superficial parotidectomy with dissection of all facial nerve branches is recommended for patients with micrometastases in periparotid nodes. Selective cervical lymph node dissection based on the precise location of a positive cervical sentinel node has replaced more traditional modified radical and formal radical neck dissections. Patients presenting with or developing palpable lymph node metastases in the absence of significant distant metastases should undergo formal regional lymphadenectomy.

In a small but not insignificant number of patients with melanoma of the face, preoperative cutaneous lymphoscintigraphy reveals a complex pattern of lymphatic drainage from the primary lesion to multiple sentinel nodes widely dispersed throughout the head and neck region. The diagnostic accuracy may decline and risk of facial or spinal accessory nerve injury rises, as the complexity and number of individual sentinel nodes to be identified and excised increases. It seems reasonable to forgo sentinel lymphadenectomy in individualized circumstances when multiple sentinel node sites are revealed by

preoperative cutaneous lymphoscintigraphy. The reasons for this decision and the risks and benefits of not identifying potential microscopic regional nodal metastases should be discussed fully with the patient and carefully documented.

SURGICAL TREATMENT OF UNUSUAL ATYPICAL MELANOCYTIC CUTANEOUS LESIONS OF UNCERTAIN DIAGNOSIS

Occasionally, unusual melanocytic lesions pose serious diagnostic challenges even though the histopathologic criteria of melanoma have been well described. In these difficult clinical situations, a second (or third) dermatopathologic opinion is prudent. Whenever possible, additional material should be acquired and a new set of slides prepared from the original cell blocks and histologic and immunohistochemical staining repeated. If any of the original lesion of concern remains at the primary site, a complete excisional biopsy should be performed in an attempt to secure an accurate diagnosis.

The treatment of patients with lesions that have not been definitively confirmed to be melanoma or a benign lesion, as well as those lesions generating divergent dermatopathologic diagnoses, is difficult; however, some guidelines may be established. A detailed discussion should be initiated with the patient, family, and referring physicians, which addresses specifically the advantages and disadvantages of treating the lesion as a melanoma as opposed to a benign lesion. The management of lesions suspicious for melanoma in situ is usually handled easily with complete surgical reexcision, maintaining 5-mm margins if possible. Complete wide and deep excision, maintaining 1-cm margins, is also recommended for lesions that may possibly represent invasive melanomas less than 1 mm in Breslow thickness. In anatomic areas where 1-cm surgical margins cannot be obtained easily because of cosmetic or functional considerations, such as on the face or near the mouth, nose, or in proximity to the eye, complete excision is still advisable with as wide (although <1 cm) a margin as is reasonably possible.

Lesions thought to represent, but not definitively confirmed to be, invasive melanoma greater than or equal to 1 mm are more difficult to manage because of the more complex surgery required and potential metastatic capability of lesions of this thickness. Once again, a detailed discussion with the patient and all parties concerned carefully delineating the pros and cons of treating such a lesion is essential and should be well documented in the official patient care record. For those lesions arising in such anatomic areas as the chest wall, back, abdominal wall, or thigh, surgical excision with 2-cm margins seems reasonable because primary closure with an acceptable cosmetic and functional outcome can almost always be achieved. Although complete excision of the lesion with clear margins should be performed, in those anatomic areas where 2-cm excisional margins leave a defect not amenable to simple primary wound closure and necessitate more complex reconstructions or result in significant functional or cosmetic deformity, the actual excision margin width should be individualized and planned and discussed carefully with the patient preoperatively. Sentinel lymph node mapping and biopsy may also be offered to patients with lesions that may represent melanomas greater than or equal to 1 mm in thickness. The risks and benefits of undergoing or declining this procedure should also be discussed carefully with the patient and family.

Any patient who undergoes excision of a lesion of uncertain malignant potential should be followed carefully postoperatively, as if the lesion were definitively proved to be melanoma. This includes routine physical examination and periodic laboratory and radiologic assessment appropriate for a patient with a melanoma of that particular thickness.

MELANOMA IN PREGNANCY

Approximately one-third of the increasing numbers of women diagnosed with melanoma each year are of childbearing age, and melanoma accounts for about 8% of malignancies diagnosed during pregnancy.[110] The overall incidence of melanoma in pregnancy is estimated to be 0.14 to 0.28 cases per 1000 births.[111] Although occurring extremely rarely, melanoma is one of the most common tumors known to metastasize to the placenta and fetus.[112,113]

Although melanocytic nevi commonly become larger and darker under the hormonal influence of pregnancy, presumably because of increased levels of estrogen and melanocyte-stimulating hormone,[114,115] there exists no conclusive evidence that pregnancy significantly affects the biologic aggressiveness of a melanoma in terms of increasing the incidence of metastasis or lowering overall survival.[116–118] Moreover, pregnancy occurring either before or after the diagnosis and treatment of melanoma, similarly seems to have no significant effect on the clinical course of the disease.[118,119] Based on the data presently available, the termination of pregnancy of a patient recently diagnosed with melanoma, as a therapeutic measure, cannot be recommended. Because the overwhelming (>75%) majority of melanoma recurrences happen within 2 to 3 years

after treatment of the primary lesion, many women are encouraged to avoid becoming pregnant during that period of time postoperatively.

The frequent observation that melanocytic lesions may become more pronounced during pregnancy makes the diagnosis of melanoma even more difficult. As in any other patient, however, any cutaneous lesion suspicious for melanoma in a pregnant patient should undergo biopsy without delay. This is accomplished with shave, punch, incisional, or, preferably, complete excisional biopsy, which may be performed safely in the pregnant patient under local lidocaine anesthesia, without the addition of epinephrine. Although most of these biopsy procedures may be performed safely and rapidly in the office setting, the excision of larger lesions may be performed more prudently in the ambulatory surgery unit with an anesthesiologist who is knowledgeable in the care of the pregnant patient, as well as with intraoperative fetal monitoring in patients with viable pregnancies.

Once the diagnosis of the melanoma is confirmed histologically, an abbreviated metastatic survey may be ordered, but surgical treatment is planned commensurate with the thickness of the primary lesion and clinical lesion and clinical stage if disease. Routine laboratory tests, including determination of LDH level should be ordered. Radiologic workup should be reviewed with the patient's obstetrician and may include radiographs of the chest, which may be performed safely during pregnancy with the appropriate shielding. In patients with thicker melanomas or those presenting with palpable regional nodal metastases, a search for metastases is more individualized and may include abdominal ultrasound or MRI.

Wide local excision with 5-mm margins is performed under local anesthesia in patients with melanoma in situ. Invasive melanomas thinner than 1 mm are similarly treated under local anesthesia in the ambulatory surgery suite, with appropriate maternal fetal monitoring, with wide and deep excision maintaining 1-cm margins.

Patients with melanomas greater than or equal to 1 mm thick undergo wide and deep excision, maintaining 2-cm margins. These larger excisions may require additional anesthesia given by an anesthesiologist with experience in the care of the obstetric patient. Formal therapeutic regional lymph node dissection is performed concurrently in the presence of palpable nodal metastases. Lymphatic mapping and sentinel lymph node biopsy in clinically node-negative pregnant patients with a variety of malignancies, such as breast cancer, appears to be safe and technically accurate and are performed with technetium radiolabeled sulfa colloid alone. Vital blue dyes including isosulfan blue (Lymphazurin) are not recommended for use in pregnant patients.[120–122] It would seem prudent that the surgical approach to evaluating the regional lymph nodes in pregnant patients be individualized and commensurate with the risk of concurrent subclinical regional nodal disease, however, with all possible outcomes discussed in detail with the patient and her family and the obstetrician of record. In concerned patients or in those in the more tenuous early stages of pregnancy, a reasonable approach is to perform an appropriate wide and deep excision of the primary melanoma and defer lymphatic mapping and sentinel node biopsy to be performed as a second procedure after completion of the pregnancy. Complete regional node dissection should be performed during pregnancy in those patients presenting with or developing confirmed regional nodal metastases.

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