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## Surgical Management of Melanoma

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**Abstract** This chapter discusses the surgical principles in the management of melanoma. Surgery remains the mainstay of treatment of primary melanoma, and in the majority of cases it is curative. Appropriate surgical management is critical for the diagnosis, staging, and optimal treatment of both *in situ* and invasive primary cutaneous melanoma. Surgical management is dependent on the stage of the disease, and therefore this chapter evaluates localized, regional, and metastatic disease. The concept of sentinel lymph node biopsy is discussed along with its benefits, pitfalls, and prognostic significance. Furthermore, several important surgical issues are discussed, including the extent of surgical margins, Mohs micrographic surgery for melanoma *in situ*, and the role of metastasectomy.

**Key words:** Lymphadenectomy; Lymph node; Melanoma; Sentinel node biopsy; Surgery

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## Introduction

The incidence of melanoma is increasing worldwide, with most cases diagnosed at an early stage. However, unlike many other cancers, the mortality rate for melanoma remains stable largely as a result of decreasing mortality among younger individuals and increasing mortality among older individuals. Surgery remains the mainstay of treatment of primary melanoma, and in the majority of cases it is curative. Appropriate surgical management is critical for the diagnosis, staging, and optimal treatment of invasive primary cutaneous melanoma. The goals of surgery include histologic confirmation of the diagnosis, accurate microstaging, followed by appropriate excision of the margin around the primary site to minimize the risk of local recurrence. This chapter describes the surgical management of the primary site, the regional lymph node basin, as well as surgical options for distant disease.

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## Surgical Treatment of Localized Disease

Surgery remains the best option for cure in localized, invasive melanoma, with an overall 5-year survival rate of 92% (1). Wide local excision is the current standard of care for localized cutaneous melanoma. This wide excision contrasts to a narrow excision (1–2 mm) used to biopsy a lesion clinically suspicious for melanoma. A biopsy will provide the pathologist with a specimen that can then be examined to confirm the diagnosis of melanoma and determine the Breslow thickness. The margin required when carrying out a wide local excision is determined by the Breslow thickness. When carrying out a wide local excision, the excised specimen should extend down to the level of the underlying muscular fascia. Currently, there is no evidence to suggest that excising the underlying fascia leads to improved outcome (2).

### REVIEW OF CURRENT GUIDELINES FOR EXCISION

Standards are well established for peripheral margins of excision (Table 1). These guidelines are based on data from randomized controlled trials. The excision margins are measured intraoperatively on the skin. Current guidelines for melanoma *in situ* recommend a 5 mm–1 cm peripheral margin. For large melanoma, *in situ* surgical margins >0.5 cm may be necessary to achieve histologically negative margins. A 0.5-cm margin for lentigo maligna melanoma *in situ* on the head and neck often results in an incomplete excision (4). This is often managed as a staged procedure, where histological clearance is confirmed prior to definitive reconstruction. A depth of excision that includes subcutaneous fat is generally sufficient for melanoma *in situ* (5).

### MOHS MICROGRAPHIC SURGERY

Mohs micrographic surgery (MMS) is a surgical procedure which involves stepwise tangential excision of specimen margins up to normal-appearing skin,

TABLE 1	Recommended Margins for Surgical Excision
Tumor thickness	Recommended clinical margins <sup>a</sup>
In situ	0.5–1.0 cm
≤1.00 mm	1.0 cm
1.01–2.00 mm	1–2 cm
2.01–4.00 mm	2.0 cm
≥4.01 mm	2.0 cm

<sup>a</sup>Guidelines from National Comprehensive Cancer Network on Melanoma 2016 (3).

followed by immediate microscopic examination of the entire surgical margin. In contrast to surgical excision, MMS allows for the examination of 100% of the peripheral margins. Despite the advantages of MMS as a tissue-sparing procedure, controversy surrounds the use of frozen sections to identify malignant melanocytic cells (6). Pathological difficulties encountered include: vacuolated keratinocytes mimicking melanocytes, processing artifact, and dermal inflammatory cells that may obscure the melanocytes in frozen sections (7). MMS is a useful approach for clinically ill-defined lentigo maligna lesions; however, its use is not generally supported for invasive melanoma. Although the literature is controversial, enough studies exist with 5-year follow-up to suggest this approach is superior to traditional surgical excision in ill-defined lentigo maligna lesions (8). The central component of the tumor specimen should always be sent for permanent section assessment to rule out an invasive component. Mohs is not an acceptable modality for invasive melanoma.

## Clinically Negative Regional Lymph Nodes

### SENTINEL LYMPH NODE BIOPSY

#### Concept

Since its introduction in 1992, Sentinel Lymph Node Biopsy (SLNB) has become an established investigation in melanoma (9). Lymphatic mapping and SLNB is the standard approach for the management of patients with melanoma in whom there is a substantial risk of regional node metastasis. The concept behind lymphatic mapping is that sites of cutaneous melanoma have stepwise patterns of lymphatic spread and that one or more nodes are the first to be involved with metastatic disease within a given lymph node basin. If the sentinel lymph nodes are not involved, the entire basin should be free of tumor (10).

Indications

Sentinel node biopsy is indicated for melanomas  $\geq 1.0$  mm in Breslow thickness. There is no consensus regarding the application or clinical implications of SLNB in patients whose melanomas are  $<1$  mm in thickness, and indications continue to evolve (Table 2). Based on available evidence, high-risk patients with melanomas between 0.75 and 1.00 mm in thickness may be appropriate candidates to be considered for SLN biopsy; however, there is little rationale in performing SLNB on the overwhelming majority of patients with melanomas  $<0.75$  mm in thickness (14).

Sentinel node sensitivity and specificity

Morton et al. reported the sensitivity rate of SLNB as 95.3% overall: 99.3% for the groin, 95.3% for the axilla, and 84.5% for the neck basins (15). Reported rates of SN metastasis are 12 to 20% for 1- to 2-mm melanomas, 28 to 33% for 2- to 4-mm melanomas, and 28 to 44% for melanomas thicker than 4 mm (16). The rate of false-negative SLNB in thin melanomas was reported in a recent meta-analysis to be 12.5% (17). Current standard therapy for patients with a positive SLNB is completion dissection of all involved nodal basins. The recent DeCOG-SLT trial showed for patients with micrometastatic sentinel node disease (metastases  $<1$  mm diameter), no survival benefit was present comparing nodal observation and completion lymphadenectomy (18).

TABLE 2		Current Guidelines for Performing SLNB	
Guideline		Year	
National Comprehensive Cancer Network Practice Guidelines (NCCN) (3): “In general, SLNB is not recommended for primary melanoma $<0.75$ mm thick. For melanomas 0.76–1.00 mm, SLNB may be considered in the appropriate clinical context”		2017	
National Institute of Clinical Excellence (NICE) (11): “Do not offer imaging or sentinel lymph node biopsy to people who have stage IA melanoma or those who have stage IB melanoma with a Breslow thickness of 1 mm or less”		2015	
American Society of Clinical Oncology and Society of Surgical Oncology Joint Clinical Practice Guideline (ASCO/SSO) (12): “Available evidence does not support routine SLN biopsy for patients with melanomas that are T1 or $<1$ mm Breslow thickness although it may be considered in selected high-risk cases” Such high-risk factors may include Breslow thickness $>0.75$ mm, ulceration, or mitoses $\geq 1/\text{mm}^2$		2012	
European Society for Medical Oncology (ESMO) (13): “SLN biopsy should be performed for tumour thickness of $>1$ mm and/or ulceration”		2012	

## Benefit

A positive SLNB is the best predictor of recurrence and survival in patients with clinically node negative cutaneous melanoma (19). Indications for performing SLNB is a balance between the likelihood of finding a positive SLN, the risk of the procedure, as well as the likely benefits that will accrue to the patient from the knowledge of their SLN status (14). It selects appropriate patients for completion lymph node dissection with potential for regional disease control. It also identifies a homogenous group of patients who may benefit from adjuvant therapy and enrollment in clinical trials.

## Potential risks

Sentinel node biopsy carries significantly less risk of complications compared to lymph node dissection. Sentinel node biopsy has an overall complication rate of 5% (20). Potential complications include infection (1%), lymphedema (0.7%), hematoma/seroma (2%), and sensory nerve injury (0.2%) (20). Furthermore, there is a risk of incorrectly biopsying a node which is not the sentinel node for the primary site, that is, a false-negative sentinel node. This is relatively high in head and neck melanomas, with a false-positive rate of 18–29% reported in some studies (21).

## The multicenter selective lymphadenectomy trial

The landmark Multicenter Selective Lymphadenectomy Trial-I (MSLT-I) is the largest trial comparing the use of SLNB and elective lymph node dissection (ELND) to observe patients with intermediate thickness melanomas in determining prognosis and its impact on survival (15, 22). Long-term data from the MSLT-I show improved 10-year disease-free survival but fail to show improved melanoma-specific survival (22). The MSLT-I reported their morbidity associated with SLNB to be 10.1%, with nearly half of these complications from seroma or hematoma, followed by infection (4.6%) and wound dehiscence (1.2%) (15). The recent MSLT-IIR trial showed that complete lymph node dissection, following a positive sentinel node biopsy, increased the rate of regional disease control and provided prognostic information but did not increase melanoma-specific survival (23).

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## Elective Lymph Node Dissection

There are two different approaches toward lymphadenectomy: prophylactic or ELND of the regional nodes draining the primary tumor versus delayed lymphadenectomy only when recurrences occur in the nodal basin (24). Opponents of ELND consider prophylactic excision of lymph nodes unnecessary because the incidence of histologically positive regional nodes at the time of resection of the primary melanoma in patients with clinical Stage I disease is only 20% (25).

Prior to the introduction of SLNB, ELND was advocated as an approach to the regional lymph nodes. However, the success of SLNB in predicting regional lymph node involvement has obviated a possible role for ELND. Multiple prospective randomized trials were conducted to evaluate the role of ELND, but these did not confirm a substantial survival benefit from ELND (26). ELND should not be considered in treating patients with melanoma.

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## Clinically Apparent Regional Lymph Nodes

### THERAPEUTIC LYMPHADENECTOMY

Regional lymph node involvement can be diagnosed cytologically using either fine needle aspirate or image-guided biopsy. Therapeutic lymphadenectomy is the preferred treatment in patients with regional clinical lymph node involvement from melanoma (27). The 10-year survival rate in patients with metastatic involvement of regional lymph nodes is approximately 20–40% (28). The tumour burden within the regional lymph node is an important prognostic factor, with a high nodal involvement associated with a poorer outcome (28). Since melanoma has a high risk of involvement of multiple regional lymph nodes within a nodal basin, a complete regional lymphadenectomy, rather than partial dissection or sampling, is necessary (29). In the axillary basin, a complete dissection (levels I, II, and III) should be carried out. The role of a deep ilioinguinal dissection is controversial, since no survival benefit has been demonstrated with the addition of a more extensive dissection (30). Some surgeons choose to include a deep ilioinguinal dissection to the superficial inguinal node dissection when the highest superficial node (Cloquet's node) contains metastatic melanoma. However, this practice is disputed, and not standard of care (30).

### SURGICAL CONSIDERATIONS

In the head and neck region, lymph nodes at risk for metastatic melanoma include the parotid, cervical (levels I through V), and post-auricular and occipital nodal basins. Typically, lesions in the face and anterior scalp drain to the parotid and cervical levels I–IV (31). Lesions in the posterior scalp drain to cervical levels II–V, and occipital and post-auricular basins (31). Most frequently, a functional neck dissection is performed, thereby preserving the internal jugular vein, sternocleidomastoid muscle, and the spinal accessory nerve.

Axillary lymphadenectomy should involve lymphatic clearing of levels I–III. This can be achieved through an S-shaped incision with attention during dissection to protect the axillary vein, and the long thoracic, thoracodorsal, and medial pectoral nerves.

Inguinal lymphadenectomy involves dissection of the superficial (inguinal) with or without the deep (ilioinguinal) nodes. Access is through a straight incision just below and parallel to the inguinal ligament, with extensions onto the abdomen laterally or down the thigh medially if needed. The superficial nodes lie within the femoral triangle (bounded by the adductor longus muscle medially, the sartorius muscle laterally, and the inguinal ligament superiorly).

A sartorius muscle transposition to protect the femoral vessels is often carried out to protect against postoperative wound problems, especially if adjuvant radiotherapy may be necessary (32). More recently, minimally invasive inguinal lymphadenectomy can be carried out, which obviates the need for routine sartorius muscle transposition (33).

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## In Transit Metastatic Disease

In transit metastatic disease includes any skin or subcutaneous metastases that are more than 2 cm from the primary lesion but are not beyond the regional nodal basin (34). Satellite metastases are defined as lesions occurring within 2 cm of the primary tumor. In the absence of distant metastatic disease, surgical excision is the treatment of choice when feasible. Regional chemotherapy in the form of isolated limb perfusion (ILP) or isolated limb infusion (ILI) is reserved for unresectable recurrent disease. ILP allows higher concentrations of drugs to be administered to the affected limb without systemic toxic effects. This is done by surgically separating the inflow and outflow, of the affected limb, from the rest of the body (35). ILI involves percutaneously placed venous and arterial catheters to allow infusion of chemotherapy via an arterial catheter, and a pneumatic tourniquet is used proximally to isolate the extremity (36). ILI differs from ILP in that ILI circulates blood in an affected extremity at a much slower rate than ILP and for only 30 min, and hyperthermia is not achieved (35). There are no randomized controlled trials comparing ILP to ILI, but recent studies showed the overall response rate was higher with ILP than with ILI (79% in 294 patients vs. 64% in 313 patients), but ILP resulted in more grade 5 toxicity (37). If neither surgery nor regional chemotherapy is appropriate, radiation therapy may provide palliative benefit. Furthermore, talimogene laherparepvec (T-VEC) is an option to treat unresectable, injectable, cutaneous, dermal, subcutaneous, or nodal metastases for patients with limited visceral disease (38).

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## Surgical Treatment of Metastatic Melanoma

The introduction of effective systemic therapies (e.g., BRAF/MEK, Anti-CTLA4, and PD-1 inhibitors) for patients with metastatic melanoma has altered the approach to management of patients with metastatic disease (39). Surgical metastasectomy plays a role in carefully selected patients who have limited sites of metastatic disease, either at first presentation of metastatic disease or if they have had a high-quality response to immunotherapy or potentially molecularly targeted therapy (40).

For in transit or satellite metastases confined to skin and subcutaneous tissue, the most appropriate management is complete excision with a small margin (41). Although widespread metastatic disease usually develops in most cases, complete resection of metastatic disease is associated with prolonged survival in up to 40% of cases (42). Symptomatic, easily resected metastases are also appropriately resected in a palliative setting, even in patients with multiple other sites of disease.

## Conclusion

Surgery remains the best option for cure in localized, invasive melanoma, with an overall 5-year survival rate of 92%. MMS is a useful approach for clinically ill-defined lentigo maligna lesions; however, its use is not generally supported for invasive melanoma. Sentinel node biopsy is indicated for melanomas  $\geq 1$  mm in Breslow thickness.

Therapeutic lymphadenectomy is the preferred treatment in patients with regional lymph node involvement, with a 10-year survival rate in approximately 20–40% of patients with metastatic involvement of regional lymph nodes

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