17 Current Surgical Management of Primary Cutaneous Melanoma

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Abbreviations

CLND	Complete lymph node dissection
ELND	Elective lymph node dissection
NCCN	National Comprehensive Care Network
PET	Positron emission tomography
SLN	Sentinel lymph node(s)
SLNB	Sentinel lymph node biopsy

A Brief History of the Surgical Treatment for Melanoma

The first reported case of a patient described as having melanoma appears within the medical writings of Hippocrates around 460 B.C. Several mummies have been recently discovered from this era, and paleopathologists have noted the presence of diffuse metastases in the bones of the skull and extremities, many with rounded melanotic masses in the skin [1]. John Hunter, of St George's Hospital in London, England, was the first physician who successfully surgically removed a recurrent melanoma of the lower jaw in 1787. The specimen is still preserved as Hunter's specimen #219 at the Hunterian Museum of the Royal College of Surgeons in London [2]. It was Renee Laennec, more famous for his invention of the stethoscope, who first described melanoma as the "cancer noire," or the black cancer, later coining the term "melanosis" in 1812 [3].

In 1820, William Norris described the first case of melanoma in the English literature. When he incised through the original tumor, he said, "I found the texture to be heterogeneous; it was of a reddish and whitish brown tint throughout, not very unlike the internal structure of a nutmeg" [4]. Norris later published the first comprehensive study of melanoma, titled "eight cases of melanosis with pathological and therapeutic remarks" [5]. This manuscript is the first observational analysis of a group of patients with melanoma, accurately describing many of the epidemiological, clinical, and pathological features of patients with melanoma, of which many of his observations remain true to the present day. In 1837, Isaac Parish, a 26-year-old surgeon, published the first case of melanoma in North America, and after a treatment of purgatives, leeches, and poultice of ground elm, his patient quickly fell victim to her disease [6].

Samuel Cooper, a British surgeon, recognized in 1840, that metastatic melanomas were untreatable and he stated, "the only chance for benefit

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depends upon the early removal of the disease…" [7], an observation that has held true until recent times. In 1858, Oliver Pemberton published his observations on a collection of 60 cases of cutaneous and ocular melanoma, by far the largest series of patients with melanoma to date, noting the postmortem findings in 33 cases [8]. He was also one of the first surgeons to note the futility of many treatments for advanced disease and was a strong advocate of surgical management of melanoma with wide excision of the primary and extensive resection and removal of the draining lymph node basins.

The concept of the surgical management of melanoma was not uniformly accepted, shunned by many in favor of traditional local therapies with salves and other medicinal treatments passed down from previous generations. However, excision of the primary lesion with wide margins was slowly gaining favor with a small group of surgeons. In 1892, the London surgeon Herbert Snow advocated that melanoma be treated by excision and he noted that: "it is essential to remove, whenever possible, those lymph glands which first receive the infective protoplasm" [9]. In 1903, Frederick Eve described a case series of 45 patients with melanoma treated at the London Hospital, remarking that 80% of the melanoma cases had originated from pigmented moles on the skin [10]. He strongly expressed his views on the surgical management of melanoma, stating in his lecture, "The treatment of melanoma can be given in a few words, free excision or amputation, in accordance with the position and extent of disease…The removal of the nearest chain of lymphatic glands, whether palpably involved or not, should never be omitted; for it may be taken as a matter of certainty that in the great majority of cases they are infected."

In 1905, the Scottish physician William Handley analyzed the lymphatic spread of a melanoma originating from a woman's leg [11]. In 1907, he gave the Hunterian Lecture entitled "Melanotic growths in relation to their operative treatment," in which he strongly supports the views of Frederick Eve, advocating wide excision of the primary melanoma in combination with elective regional lymph node dissection or possibly amputation in selected cases [11]. In this manuscript, he accurately notes that the "permeation of the lymphatics is the principle agent in this local centrifugal spread" of melanoma, recommending a circular incision of about one inch from the edge of the tumor, and another two inches into the subcutaneous fat. This article is of great historical significance, as the recommendations of Handley became the basis for the surgical management of melanoma for the next 50 years.

Until the 1960s, invasive melanoma was considered a high-risk disease that required an extensive local excision for all tumors. In 1969, Wallace H. Clark, Jr., a pathologist at the Massachusetts General Hospital, described a classification system of melanoma based on the extent of tumor invasion relative to the anatomic layers of the skin and related the depth of penetration to overall patient survival [12]. In 1970, Alexander Breslow added a second method of measurement, based upon the true vertical thickness of the tumor, measured in millimeters [13]. This system was found to be a more accurate and reproducible method of measurement, providing an excellent correlation with overall 5-year survival. Comparison of the two systems and other histologic parameters revealed that the tumor thickness, measured in millimeters, was a better predictor of metastasis and overall survival compared to the Clark's level of tumor invasion [14].

In 1978, the pioneering surgeon Donald Morton published the first report of the use of cutaneous lymphoscintigraphy to determine the direction of regional lymphatic drainage in 32 patients with primary malignant melanoma of the trunk [15]. In 1990, at the Society of Surgical Oncology meeting, Morton introduced the use of lymphatic mapping to determine the sentinel lymph node and described the technique of obtaining a sentinel-node biopsy which created a minimally invasive way to stage the tumor status of all nodes in the regional basin [16]. His paper on intraoperative lymphatic mapping for early stage melanoma was initially rejected by several journals until its publication in the *Archives of Surgery* in 1992 [17]. He later developed and published the first landmark trial on sentinel-node

biopsy versus nodal observation in melanoma, the MSLT I trial [18].

It is important to recognize the important contributions of past physicians and surgeons, learning from their experiences in the clinical management of patients with melanoma. It is clear that we must continue down the pathways of our predecessors and strive to improve the quality of surgical care for all melanoma patients. Though the basic tenets for the surgical management of primary melanoma and regional nodes have been forged from previous trials, many questions still remain as to the optimal management of patients with later stage disease. As new research continues to surface, physicians, surgeons, and researchers alike continue to develop novel treatment strategies for those patients with advanced disease, many of which do not require the scalpel.

Obtaining the Diagnosis

It is imperative that the diagnosis of cutaneous melanoma be made as early as possible, as this directly correlates with long-term outcome. For decades, physicians have utilized the clinical examination of the skin as the primary screening modality for detecting melanoma. Yet, the ability of the clinician to accurately identify those lesions that are melanoma is highly variable in most cases, making the correct diagnosis in only about 65% of all cases [19–24]. The accuracy rate of detection can be improved by 10–20% with the addition of other imaging tools, such as epiluminescence microscopy and sequential full body photography [25, 26]. However, no matter what observational threshold is being followed, many lesions that are deemed suspicious for melanoma will ultimately undergo a biopsy to obtain a definitive diagnosis. Obtaining a tissue sample by means of whatever method of biopsy, followed by histological examination of the tissue is still considered the "gold standard" for accurately making the diagnosis of primary cutaneous melanoma.

The majority of clinical management guidelines recommend that a pigmented lesion or mole that is deemed suspicious undergo an excisional biopsy as the preferred method of biopsy, obtaining a margin of normal skin of 1–2 mm [19–21]. The depth of the biopsy should encompass the subcutaneous fat, with complete removal of the lesion for a complete and unencumbered histologic examination that will include an accurate Breslow's depth of invasion and other prognostic features [27–29]. The definitive surgical procedure of the primary melanoma should be deferred until the final histologic diagnosis has been made, even for suspected thinner melanomas such as melanoma-in-situ [30–32]. It is imperative for the clinician to be cognizant of cosmetically sensitive areas when performing a biopsy, as this will dictate the type of biopsy performed and the necessity for possibly specialty surgical consultation. Definitive excision of such areas must be deferred until the final diagnosis has been completed, as often the pathological diagnosis yields a benign result that does not require any further surgical intervention [33, 34].

If a punch biopsy is performed, one should obtain the sample from the thickest portion of the lesion, avoiding areas of crusting, ulceration, or necrosis that may grossly underestimate the overall thickness of the tumor. Although the preferred method of biopsy is the excisional biopsy, others will perform a deep shave, or saucerization, of a lesion suspected of being melanoma. This is usually done with either a scalpel or a single-edged razor blade held in a semi-curved position [19]. A saucerization is essentially a modified shave biopsy that samples the deeper dermis, and is achieved by pinching the skin around the lesion while curving the razor blade [35].

One potential drawback of either method is that there remains the possibility of transecting the base of the lesion, thus resulting in a deep margin that is involved with melanoma. This is problematic in that the true Breslow's thickness is not known, creating a diagnostic dilemma for the surgeon in terms of the decision-making for the appropriate surgical margins and whether the draining lymph node basin needs to be evaluated. A second consideration is that biopsy site from a shave biopsy heals by secondary intention, resulting in an inferior cosmetic outcome compared to other techniques.

The main benefit of a punch biopsy is that the specimen can be accurately measured for true depth of invasion. The defect is closed primarily with 1 or 2 interrupted sutures that results in a superior cosmetic outcome compared to a shave biopsy that heals by secondary intention. The primary limitation of the punch biopsy is that for larger lesions (>6 mm), the largest available punch biopsy will be unable to adequately remove the entire lesion, thereby inadequately sampling the adjacent normal skin and histologic architecture. The architectural pattern of the entire specimen, in combination with other cytological features, is of particular importance when diagnosing melanoma [36].

Additionally, there are several other important features that require special attention in order to obtain an accurate diagnosis of melanoma, such as the presence of asymmetry, the lack of circumscription, and the presence (or absence) of scattered atypical melanocytes throughout the epidermis and adnexal epithelium. Such features may not be present if a small punch biopsy is performed and the type of biopsy must be taken into account by the dermatopathologist [35]. In cases of inadequate sampling, it may be necessary to completely remove the lesion with an excisional biopsy in order to confirm the diagnosis of a suspected melanoma.

Once a diagnosis of melanoma had been obtained, staging is essential for prognosis and effective treatment. In 2016, the 8th edition of the American Joint Committee on Cancer (AJCC) staging system for cutaneous melanoma was revised and updated, based on the primary tumor (T), regional lymph node involvement (N), and distant metastatic spread (M) [37].

Surgical Margins of Excision

The surgical management of cutaneous melanoma must always begin with the proper identification and treatment of the primary lesion. With early diagnosis, over 90% of all early stage primary melanomas can be cured by surgical excision alone [38, 39]. The majority of thin primary lesions can be locally excised and closed primarily, generally accomplished with a fusiform excision. Thus, it is important to recognize that achieving negative surgical margins with the appropriate margins of excision will result in the lowest possible local recurrence rates.

The standard operative approach in the past usually included a 3–5 cm margin of normal skin measured from the outer edge of the melanoma in all directions, with most patients requiring a split-thickness skin graft to cover the resulting defect. This extensive surgical procedure resulted in a prolonged hospital stay and associated perioperative complications such as wound infection and skin graft necrosis. Fortunately, as the extent of surgical resection and margins was questioned, several prospective, randomized trials have been performed to address this issue. The first trial that this question, the Intergroup Melanoma Trial, focused on the efficacy of 2-cm vs. 4-cm margins for primary melanomas between 1 and 4 mm in Breslow's thickness [40]. The results of this trial clearly showed an insignificant difference between the local recurrence rate between the two groups, 0.8% in the group who received 2-cm margins and 1.7% for those who had received 4-cm excision margins. Of importance, only 11% of the patients in the 2-cm excision group (compared to 46% in the 4-cm excision group) required a skin graft.

In this trial's 10-year follow-up, no significant differences in the local recurrence rate, disease-free or overall survival was seen [41]. This trial clearly demonstrated that a 2-cm margin of excision is both safe and effective compared to a 4-cm margin for primary melanomas between 1 and 4 mm, with a significant decrease in the need for skin grafting. In a recent prospective, multicenter randomized trial of 936 patients by the Swedish Melanoma Study group, patients were randomly allocated to receive either a 2-cm resection margin or a 4-cm resection margin. The 5-year overall survival of both groups was 65% ($p = 0.64$) and no significant difference was found, further clarifying that 2-cm resection margins is sufficient [42]. There have been two other trials that have examined 2-cm vs. 5-cm margins for intermediate thickness primary melanomas <2 mm in Breslow's thickness, with both studies

showing no difference in local recurrence rates or overall survival [43, 44].

Several randomized trials have established that the overall thickness of the primary melanoma dramatically influences the likelihood of a local recurrence [45]. The World Health Organization (WHO) Melanoma Group study was a prospective, randomized trial comparing patients with primary melanomas ≤2 mm in Breslow's thickness to either 1-cm versus 3-cm surgical margins [46]. There were no local recurrences seen among patients with primary melanomas <1 mm, regardless of what margin was taken. There were four local recurrences seen in patients with primary melanomas between 1 and 2 mm, all occurring within the group that had received 1-cm margins. However, there were no statistically significant differences noted in either group in terms of disease-free and overall survival. This trial has been updated with 15-year follow-up, and again there were no differences noted in disease-free or overall survival [47]. This study provides a clear demonstration that a surgical excision margin of 1 cm is safe and provides excellent local control for melanomas <1 mm in Breslow's thickness.

For primary melanomas with a tumor thickness between 1 and 2 mm, current NCCN guidelines suggest that the margin of excision can be between 1 and 2 cm depending on the anatomic circumstances. If possible, a 2 cm margin of excision should be performed whenever feasible; however, a 1 cm margin is acceptable if placement of a skin graft or an excessively high amount of skin tension will result from taking a larger 2 cm margin. In a review of 576 patients with a melanoma between a 1 and 2 mm in thickness, a comparison between 1 cm vs. 2 cm margins showed no significant difference in overall survival at 8.3 years of follow-up, but the 1 cm margin group did have a local recurrence of 3.6% compared to 0.9% in the 2 cm group [48]. In 2016, Doepker et al. published a retrospective study that compared the use of a 1- or 2-cm resection margin for 965 patients with a 1–2 mm melanoma and reported that using a margin of 1 cm did not increase the risk of local recurrence or disease-specific survival, but the 5-year overall survival for a 1-cm margin was 61.9% vs. 71.2% for a 2-cm margin ($p = 0.004$) [49]. Further data is needed in order to elucidate whether there is a survival benefit for a 2-cm surgical margin vs. a 1-cm margin.

Thomas et al. prospectively examined the excision margins in a defined "high-risk group" of patients with primary melanoma, considered >2 mm in Breslow's thickness in this study [50]. All patients were randomized to either 1-cm or 3-cm margins of excision and they found that a 1-cm margin of excision for melanomas of at least 2 mm in Breslow's thickness was associated with a significantly greater risk of combined (local and regional) recurrence when compared to a 3-cm margin. It is important to note that this high-risk group included *all* primary lesions >2 mm in thickness (median tumor thickness was 3 mm), and therefore the results and conclusions of this trial cannot be directly applied to those patients with only thick (>4 mm) primary lesions. Regardless, this is an important trial because it is the first time that a randomized trial examining surgical margins of excision has demonstrated a significant increase in combined locoregional recurrence with a narrower 1-cm margin. However, there was no statistically significant difference noted in the death rate from melanoma associated with a narrow (1 cm or less) margin of excision for thicker melanomas.

The appropriate surgical margins for a thick primary melanoma (>4 mm) have also been addressed in both retrospective and prospective analyses. The first study was a multi-institutional retrospective review of surgical margins and associated prognostic factors in 278 patients with a thick primary melanoma [51]. This study revealed no significant difference in the local recurrence rate, disease-free or overall survival if margins larger than 2 cm were taken. There does not appear to be any clear advantage (or disadvantage) to removing the deep muscular fascia as part of the definitive excision of the primary melanoma. Several studies have addressed this issue and it does not appear that there is any significant difference in recurrence rates, locally or distant, when the fascia was either left in place or removed as part of the definitive surgery [52, 53].

Truncal and Extremity Melanoma

The surgical management of truncal and extremity melanoma is fairly straightforward, with the basic tenets of surgical therapy to remove the primary melanoma with the appropriate surgical margins. However, certain situations and anatomic locations may alter the surgeon's approach to management, such as melanomas located along the forearm, leg and digits. In particular, a melanoma >2 mm in Breslow's thickness on the forearm will require a 2 cm circumferential excisional margin with a resultant defect of at least 4 × 4 cm. Due to the anatomic limitations of skin mobility in such areas, it is often necessary to utilize a split-thickness skin graft (STSG) for adequate coverage, often taken from the anterolateral aspect of the thigh. Other possible donor sites may include a full-thickness skin graft from the lower quadrant of the abdomen with primary closure of this defect, thereby sparing the patient the increased pain and discomfort associated with a STSG from the thigh.

The majority of primary melanomas located on the back can be treated with the appropriate excision margin followed by skin edge approximation and primary closure. The skin on the back is generally thicker with more laxity compared to other areas of the body, with the resulting defect successfully closed primarily without the need of skin grafting. In order to minimize the amount of tension along the mid-portion of the defect, attention should be given to the orientation of the surgical excision related to the optimal lines of skin tension in order to minimize the need for extensive undermining of the surrounding skin edges. Occasionally, the surgeon may encounter an undue amount of skin tension and this situation is best treated with the placement of a STSG or possibly one of several plastic reconstructive options such as a rotational, advancement or rhomboid skin flap.

Head and Neck Melanoma

The use of SLNB for head and neck melanomas has been recently reviewed in depth and it has been shown to be a safe and valuable tool for experienced surgeons in order to achieve valuable staging information to help guide treatment [54]. Special attention should be paid to the patient with a primary melanoma of the head and neck due to the added anatomic complexity posed within this region. Although the established guidelines are generally followed whenever possible, a melanoma arising within aesthetic areas of the face will often require a compromise in such margins. Every attempt is made at obtaining the appropriate surgical margin and concomitantly achieving the best cosmetic outcome with the lowest possible chance of local recurrence. It is imperative that a thorough discussion of the planned excision be made with the patient, outlining the operative plan and any associated reconstruction being performed. The risks, benefits, and expected cosmetic outcomes should be carefully discussed with the patient, specifically addressing unrealistic expectations of any surgical procedure.

The surgical treatment of the primary tumor of the head and neck includes planning the complete excision of the primary melanoma as well as the reconstructive procedures simultaneously [55]. Some surgeons prefer to stage the excision, waiting for the final pathology prior to performing a definitive reconstruction of the residual defect. In any case, the surgeon should be cognizant of the unique anatomy of the face, considering the relaxed skin tension lines and functional aesthetic. Special consideration should be given to primary melanoma excisions that involve overlying lymph node-bearing areas, such as the parotid gland and neck. A preauricular vertical incision followed by the development of an anterior cervicofacial flap is able to adequately expose the parotid gland or periauricular and upper neck lymph nodes. In the neck, an upper-neck transverse incision or a mid-neck posterior vertical incision provides optimal exposure to the appropriate cervical lymph node basin.

The method of reconstruction of the primary melanoma excision site depends upon several factors such as the location and size of the defect, the functional and aesthetic requirements, and the overall medical condition of the patient. There are numerous possible reconstructive options such as the utility of a STSG, local vascularized and regional tissue flaps as well as myocutaneous

flaps. The most common surgical excision of a primary scalp melanoma involves the removal of the appropriate skin margins and underlying subcutaneous fat down to the galea. The underlying periosteum is well vascularized and provides a good base for the proper healing of a STSG. For smaller and even intermediate size scalp excisions, local rotational may be suitable in lieu of skin grafting. In rare cases, extensive surgical excision of the primary melanoma with a large residual defect may require a free flap for adequate wound closure, usually from sites such as the anteriolateral thigh, latissimus or radial forearm muscle.

Small excisions of the cheek can usually be closed within the exaggerated "smile lines" on the face. For larger defects involving the medial portion of the cheek, an inferiorly based cervicofacial rotation advancement flap may provide the optimal aesthetic result. For upper lip defects that are lateral to, and above, the vermillion border, we commonly utilize a cheek advancement flap for optimal cosmetic results. Defects along the medial, central upper lip, and philtrum are best treated by an Abbé lip switch flap for lower lip defects, local rotation flaps are often utilized, bearing in mind that if the defect is a result of a complete excision of the lip, muscle, and mucosa, then one of several lip advancement techniques can be employed. The Karapandzic flap, a rotational, musculomucosal circumoral flap, is an excellent reconstructive choice for lip excisions that have removed between one-third and two-thirds of the lower lip. It allows for muscular continuity and maintains oral competence. Defects that affect the oral commissures are best served with a local rotational flap, such as the Estlander lateral lip-switch flap. If the entire lower lip must be excised, utilization of a radial forearm free flap with palmaris longus sling may be necessary as part of the reconstructive process.

Subungual Melanoma

Subungual melanoma is a type of malignant skin melanoma most commonly diagnosed as an acral lentiginous subtype on histology. This subgroup is more prevalent in darker-skinned individuals, occurring mainly on the palms, soles, and subungual regions. For this reason, such melanomas are often found at a more advanced stage. A subungal melanoma will typically present as a linear brown or black discoloration of the nail known as melanonychia. While melanonychia can be caused by other benign causes, the presence of color variegation, size, ulceration, and extension beyond the nail plate warrant a full-thickness biopsy.

The current standard of care for the surgical treatment of a subungal melanoma remains amputation of the digit one joint space proximal to the subungal melanoma. The appropriate surgical margins should still be measured intraoperatively, with special attention to any evidence of proximal spread beyond the nail bed. Despite the gold standard of digit amputation (with or without a concomitant SLNB), recent literature has suggested that a less aggressive approach may be as beneficial [56–59].

Current Surgical Guidelines and Recommendations

The evolution and collection of data from well-designed clinical trials has allowed us to develop a set of surgical guidelines that are safe, well tolerated, and associated with acceptable locoregional recurrence rates. Strategies that rely on lesser margins of excision, including approaches that rely solely on the pathologist's report of a tumor-free biopsy site margin, offer little savings of morbidity yet risk higher rates of local recurrence. Even patients with thin melanomas ($\leq$1 mm in thickness) deserve an appropriate surgical margin, as recurrence does occur even in this group and is often a harbinger of very poor prognosis and outcome.

National Comprehensive Cancer Network (NCCN) Treatment Guidelines

The National Comprehensive Cancer Network (NCCN) was started in 1995 with the goal of developing a comprehensive set of diagnostic, treatment, and supportive care guidelines for all cancer patients [60]. The NCCN guidelines have

become an essential tool to provide comprehensive, evidence-based care of cancer patients. With the rapid increase in knowledge of melanoma driver pathways and immunobiology, a record number of new treatments have been approved in the last few years. These treatment guidelines are constantly updated as new data and information from clinical trials is published, resulting in an effective tool for treatment of cancer patients based upon expert opinion of evidence-based medicine [60].

For a melanoma in-situ [stage 0], we recommend a 5-mm margin of excision. For a primary melanoma that is ≤0.75 mm in Breslow's thickness, the recommendations are to perform a wide local excision with a 1-cm margin. For a stage IA melanoma between 0.76 and 1.0 mm in Breslow's thickness, a further discussion is had as to the risks and benefits of concomitant SLNB. For a stage IB or II melanoma that is greater than 1 mm in Breslow's thickness, a wide local excision with 1–2 cm margins should be performed, with concomitant SLNB. For truncal or proximal extremity melanoma with a Breslow's thickness >2 mm, wide local excision with 2-cm margins should be performed (Table 17.1). In the head and neck region, distal extremities, or other cosmetically sensitive areas, a surgical excision margin of at least 1 cm should be attempted for a primary melanoma with Breslow's thickness >1 mm. If a stage III melanoma is encountered, complete nodal dissection should follow positive SLNB. If nodes are clinically positive, FNA or an alternate form of node biopsy should be obtained prior to excision of the primary tumor. If there is suspicion for clinical, satellite, or in-transit metastasis, biopsy should also be obtained prior to excision of the primary melanoma. Complete surgical excision should still be considered in stage IV disease if the patient is a favorable candidate. For unresectable disease, consideration should be given to a clinical trial or to palliative care in certain situations.

Table 17.1 Recommendations for excision margins of primary cutaneous melanoma

Location	Tumor thickness	Margins
Trunk/proximal extremity	Melanoma in-situ	0.5 cm
	≤1 mm	1 cm
	1–2 mm	1–2 cm
	>2–4 mm	2 cm
	>4 mm	2 cm
Head/neck, distal extremity (or cosmetically sensitive area)	≤1 mm	1 cm
	≤1 mm	At least 1 cm

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