Current surgical management of melanoma

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The surgical management of melanoma has changed dramatically over the last few decades. Through the development and conduction of well-designed, prospective, randomized trials, we have been able to refine the way that we surgically manage patients with melanoma. Indeed, many important issues have been addressed through such trials: the proper surgical margins for the primary melanoma, utility of the elective lymph node dissection and the role for selective lymphadenectomy, to name a few. This review will also discuss what we have learned from past clinical trials and address several issues with regards to where we are going in the future.

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History of surgical treatment for melanoma

The first reported case of a patient described as having melanoma appears within the medical writings of Hippocrates in approximately 460 BC, with several mummies recently discovered from this era. Several 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]. Over the centuries, there have been only a few well-described cases of pigmented malignant lesions, with the first published account of a recurrent melanoma of the lower jaw described by Hunter in 1787 [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 English literature [4], later publishing the first comprehensive study of melanoma, entitled 'Eight cases of melanosis with pathological and therapeutic remarks' [5]. This manuscript was 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; many of these observations remain true to the present day (BOX 1).

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 [6]. 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 lesion, 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 slowly gained favor with a small group of surgeons. 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 [7]. 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

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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 1907, William Sampson Handley 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 [8]. 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 approximately 1 inch from the edge of the tumor, and another 2 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 (MA, USA), described a classification system of melanoma based on the extent of tumor invasion relative to the anatomical layers of the skin and related the depth of penetration to overall patient survival [9]. In 1970, Alexander Breslow added a second method of measurement, based upon the true vertical thickness of the tumor, measured in millimeters [10]. 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 histological parameters revealed that the tumor thickness, measured in millimeters, was a better predictor of metastasis and overall survival compared with the Clark's level of tumor invasion [11].

It is important to recognize the significant 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. The future holds great promise for the development of novel treatment strategies for those patients with advanced disease, many of which do not require the scalpel. However, the basic tenets for the surgical management of primary melanoma and regional nodes have been forged from previous trials, while questions still remain as to the optimal management of patients with later stage disease.

Obtaining a diagnosis

It is imperative that the diagnosis of cutaneous melanoma be made as early as possible, as this correlates directly 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, and the correct diagnosis is made in only approximately 65% of all cases [12–17]. 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 [18,19]. 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.

Most 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 [12–14]. The depth of the biopsy should encompass the subcutaneous fat, with complete

Box 1. Observations on melanoma.

- There is a correlation between moles and melanoma
- Most of patients have light-colored hair and fair complexions
- There is a family history of melanoma in some cases and probably a hereditary predisposition to the disease / cancer may run in families
- Although often black in color, the degree of pigmentation was varied, with some amelanotic
- Tumors were often nodular and pedunculated / satellite tumors can develop around the primary growth / subcutaneous deposits could develop anywhere
- Widespread dissemination could involve the lungs, liver, bone heart
- Melanoma accurred more often in men and heavy smokers
- Patients usually remained in good health until a very late stage of the disease
- Fever was not a feature, in contrast to tuberculosis
- Local lesions can recur with minimal excisions
- Wide excision is essential for long-term survival (reported an 8-year survivor with this treatment)
- Neither medical nor surgical treatment was effective when the disease was widely disseminated

William Norris, 1857 [5].

removal of the lesion for a complete and unencumbered histological examination that will include an accurate Breslow's depth of invasion and other prognostic features [20–22]. The definitive surgical procedure of the primary melanoma should be deferred until the final histological diagnosis has been made, even for suspected thinner melanomas, such as melanoma *in situ* [23–25]. 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 possible speciality surgical consultation. Definitive excision of such areas must be deferred until the final diagnosis has been completed, as the pathological diagnosis often yields a benign result that does not require any further surgical intervention [26,27].

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 a melanoma. This is usually performed with either a scalpel or a single-edged razor blade held in a semicurved position [12]. 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 [28].

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 decision making for the appropriate surgical margins and whether the draining lymph node basin needs to be evaluated. A second consideration is that the biopsy site from a shave biopsy heals by secondary intention, resulting in an inferior cosmetic outcome compared with 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 one or two interrupted sutures, which results in a superior cosmetic outcome compared with a shave biopsy. 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 histological architecture. The architectural pattern of the entire specimen, in combination with other cytological features, is of particular importance when diagnosing melanoma [29].

In addition, 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, 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 only is performed and the type of biopsy must be taken into account by the dermatopathologist [28]. 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.

Surgical margins of excision

The surgical management of cutaneous melanoma must always begin with the proper identification and treatment of the primary lesion. When diagnosed early, over 90% of all early stage primary melanomas can be cured by surgical excision alone [30,31]. Most thin, primary lesions can be excised locally and closed primarily, generally this is 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 (STSG) 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, the extent of surgical resection and margins began to be questioned, allowing for the completion of several prospective, randomized trials that have addressed this issue. The first trial addressed the efficacy of 2- versus 4-cm margins for primary melanomas between 1 and 4 mm in Breslow's thickness [32]. The results of this trial the Intergroup Melanoma Trial) clearly demonstrated an insignificant difference in 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 required a skin graft (compared with 46% in the 4-cm excision group).

This same trial was recently updated to provide 10-years of follow-up, again revealing no significant differences in the local recurrence rate, disease-free or overall survival [33]. This trial clearly demonstrated that a 2-cm margin of excision is both safe and effective compared with a 4-cm margin for primary melanomas between 1 and 4 mm, with a significant decrease in the need for skin grafting. There have been two other trials that have examined 2- versus 5-cm margins for intermediate-thickness primary melanomas of less than 2 mm in Breslow's thickness, with both studies showing no difference in local recurrence rates or overall survival [34,35].

Several randomized trials have established that the overall thickness of the primary melanoma dramatically influences the likelihood of a local recurrence [36]. The WHO Melanoma Group study was a prospective, randomized trial comparing patients with primary melanomas of 2 mm or less in Breslow's thickness with either 1- or 3-cm surgical margins [37]. There were no local recurrences observed among those patients with primary melanomas of less than 1 mm, regardless of what margin was taken. There were four local recurrences observed 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 recently updated with 15-year follow-up and again there were no differences noted in disease-free or overall survival [38]. This study provides a clear demonstration

that a surgical excision margin of 1 cm is safe and provides excellent local control for melanomas that are less than 1 mm in Breslow's thickness.

For primary melanomas with a tumor thickness of 1–2 mm, current National Comprehensive Cancer Network guidelines suggest that the margin of excision can be between 1 and 2 cm, depending on the anatomical 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 margin larger than 2-cm. Recently, Thomas and colleagues prospectively examined the excision margins in a defined high-risk group of patients with primary melanoma, considered a Breslow's thickness of above 2 mm in this study [39]. All patients were randomized to either 1- 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 with a 3-cm margin. It is important to note that this high-risk group included all primary lesions that were greater than 2 mm in thickness (median tumor thickness was 3 mm) and, therefore, the results and conclusions of this trial cannot be applied directly to those patients with only thick (>4 mm) primary lesions. Regardless, this is an important trial since 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 than 1-cm margin. However, there was no statistically significant difference noted in the death rate from melanoma associated with a narrow (≤1 cm) 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 [40]. 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 [41,42].

Truncal & 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 anatomical locations may alter the surgeon's approach to management, such as melanomas located along the forearm, leg and digits. In particular, a melanoma that is larger than 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. Owing to the anatomical limitations of skin mobility in such areas, it is often necessary to utilize a 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.

Most 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 with 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 midportion of the defect, attention should be given to the optimal 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 & neck melanoma

Special attention should be paid to the patient with a primary melanoma of the head and neck owing to the added anatomical complexity posed within this region. Although the established guidelines are generally followed whenever possible, melanomas arising within esthetic areas of the face 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 discussed carefully with the patient, including any 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 simultaneous reconstructive procedures [43]. The surgeon should be well versed in the anatomy of the face, considering the relaxed skin tension lines and functional esthetic units of the entire face. Special consideration should be given to primary melanoma excisions that involve overlying lymph node-bearing areas, such as the parotid gland and neck. A pre-auricular vertical incision followed by the development of an anterior cervicofacial flap is able to adequately expose the parotid gland or peri-auricular and upper neck lymph nodes. In the neck, an upper neck transverse incision or a midneck 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 esthetic 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 excisions, local random rotational skin flaps 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, possibly obtained from several sites, such as the rectus, 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 esthetic result. For upper lip defects that are lateral to and above the vermillion border, we utilize a cheek advancement flap for good cosmetic results. Defects along the medial and central upper lip are best suited for a lower lip–cross lip 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 orbicularis oris myocutaneous flap can be an excellent reconstructive choice for lip excisions that have removed between 25 and 75% of the lower lip. If the entire lower lip must be excised, utilization of a radial forearm free flap may be necessary as part of the reconstructive process.

Current surgical guidelines & 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 very low 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 saving in terms of morbidity, yet risk higher rates of local recurrence. Even patients with thin melanomas (≤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. The current recommendations for the appropriate surgical margins of the primary melanoma are based upon several well-designed and executed prospective, randomized clinical trials and are summarized in TABLE 1.

Table 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

Role of sentinel lymph node biopsy

The evaluation and management of the draining lymph node basins for patients with clinically localized melanomas that are larger than 1 mm in Breslow's thickness has evolved over the last 20 years. In the past, we relied upon the staging information gained from performing an elective lymph node dissection (ELND). Although information on staging was obtained, several prospective, randomized trials examining the therapeutic role of ELND have failed to show an overall survival advantage for this technique. However, there is one trial of special note, the Intergroup Melanoma Surgical Trial, reporting 10-year survival results for those patients undergoing ELND [44]. A prospective, stratified subgroup of patients were found to have a significant decrease in their overall mortality, namely those with nonulcerated melanomas (30% reduction), tumor thickness of 1–2 mm in Breslow's thickness (30% reduction), aged over 60 years (27% reduction) and location of the melanoma on an extremity (27% reduction) [44].

There is some evidence of a potential survival benefit for early evaluation and management of the draining lymph nodes from the WHO trial that compared ELND with observation [45]. This trial randomized those patients with a primary melanoma larger than 1.5 mm into either observation or an immediate ELND. Although there was no evidence of an overall survival benefit, the group who underwent an immediate ELND and were found to have positive lymph nodes had a 5-year survival of 48% compared with the observation arm and delayed complete lymphadenectomy (CLND) with an overall 5-year survival of only 27% ($p = 0.04$). A second trial by Morton and colleagues compared the survival of matched groups of patients undergoing immediate (after a positive sentinel lymph node [SLN]) versus delayed (after nodal recurrence) CLND [46]. They found a significantly higher survival rate (at 5, 10 and 15 years) in the group that underwent immediate CLND following a positive SLN compared with the latter group that underwent a delayed procedure.

Intraoperative lymphatic mapping and selective lymphadenectomy was therefore developed to provide a minimally invasive staging procedure that reduced the associated morbidity and expense of an ELND. The minimally invasive technique of SLN biopsy (SLNB) for appropriately selected patients with melanoma has become part of the standard discussion of operative intervention, with the available data demonstrate that SLNB is the best available diagnostic test to date in detecting nodal metastases. Obvious advantages of SLNB over ELND include a less invasive procedure, smaller skin incisions, reduced peri- and postoperative complications, less extensive dissection of the nodal basin and improved staging information for both the physician and patient.

The concept of SLN mapping is based upon the hypothesis that cancer cells from the primary lesion gain entrance into the lymphatic channels and travel to the nearby draining nodal

basin. The SLNB technique is further supported by a large amount of data that clearly indicates that the identification of a tumor-free SLN will translate into a negative remaining draining nodal basin, that is, without evidence of metastatic cancer cells [47]. The evaluation of the draining lymph node basins for patients with clinically localized melanoma has resulted in a true paradigm shift in our surgical management.

We currently utilize a dual technique, combining the preoperative radiolymphoscintigraphy with intraoperative injection of vital blue dye (Lymphazurin™, 1% isosulfan blue dye), resulting in a high accuracy rate for the proper identification of the SLN. The current available evidence would strongly support the notion that the status of the SLN (positive or negative) is the most powerful predictor of overall patient survival, having the highest sensitivity and specificity of any test available today [30,31,48]. The information gained from the SLNB can then be discussed thoroughly with the patient, translating into a patient and family that have a better understanding of the disease process and are better able to apply this information in order to make an educated and informed decision regarding further surgical and adjuvant treatment options.

It should be clearly stated that the conceptual development and subsequent utility of the SLNB procedure was never designed as, or meant to be used as, a therapeutic procedure. The utility of SLNB is that of a diagnostic test that provides a significant improvement in the overall sensitivity, specificity and accuracy of identifying metastatic disease within the SLN of the draining nodal basin. Few would argue that SLNB provides the most accurate staging information available for melanoma patients. However, there are those who will continue the discussion as to the utility of SLNB, insisting that it must also provide a therapeutic advantage before being accepted into standard surgical practice. It is akin to the argument for the development and utility of the positron emission tomography scanner, a similarly new technology developed as a staging tool. McMasters and colleagues eloquently describes this parallel development and reinforce the notion that we should never have to raise the bar any higher for a diagnostic procedure that was never meant to show or give an overall-survival benefit to patients [47]. Thus, although SLNB is not 100% accurate, it is a far better test than clinical staging of regional lymph nodes, and it would seem illogical to revert back to a delayed nodal dissection for those patients who present with palpable regional disease [49].

Others have strongly argued that since this procedure does not provide a survival advantage, 'it should be abandoned immediately, without question' [50,51]. In addition, those opposed to SLNB argue that the involvement of the lymph nodes (sentinel or not) with melanoma is a harbinger of distant spread of disease and associated poor outcome in all cases, with the only uncertainty being when the metastatic disease will manifest itself [50,51]. The currently available evidence would strongly refute this notion, faced with several lines of evidence showing that surgical therapy alone can result in long-term cures of patients with stage III melanoma. Young and colleagues recently evaluated the role of definitive surgical management for patients with stage III disease [52]. At a maximum follow-up of 386 months (32 years) for the total population of 1422 patients in the trial, the 15-, 20- and 25-year melanoma-specific survival rates were 36, 35 and 35%, respectively. In addition, they found that survival rates were significantly lower if the regional nodes were palpable. Although some risk factors decreased the likelihood of long-term survival, the high overall-survival rates in all groups clearly support the utility of surgery as the primary treatment option for regional metastatic melanoma.

The Multicenter Sentinel Lymphadenectomy Trial (MSLT)-I is a prospective, randomized, multinational trial specifically designed to address the possible therapeutic utility of SLNB. In this study, a total of 1269 patients with intermediate-thickness melanomas (1.2–3.5 mm) were randomized to either wide excision only followed by observation (no SLNB) or to wide excision and SLNB. In the observation-only group, complete lymphadenectomy was performed only when there was clinical evidence of nodal recurrence (delayed), while the SLNB group underwent a complete (immediate) lymphadenectomy if nodal micrometastases were detected within any of the SLNs. The results from this trial were first reported in December 2004, updated in May 2005 and most recently published in September 2006, based upon the third interim analysis [53,54]. They found that the mean estimated 5-year disease-free survival rate was significantly higher in the SLNB group compared with the observation-only group (78.3 vs 73.1%, respectively; $p = 0.009$). Although 5-year melanoma-specific survival rates were similar in the two groups, the presence of metastatic disease within the SLN was found to be the single most important prognostic factor predictive of overall survival. The 5-year survival rate was 72.3% in those patients with tumor-positive SLNs and 90.2% in those with tumor-negative SLNs.

Interestingly, the incidence of SLN micrometastases was 16% compared with a very similar rate of nodal relapse of 15.6% in the observation-only group, strongly suggesting that occult micrometastases in the sentinel node usually progress to aggressive regional or distant disease, rather than remaining dormant within the SLN [54]. Furthermore, the mean number of clinically detectable tumor-positive lymph nodes in the delayed CLND group was 3.3 compared with 1.4 lymph nodes within the immediate CLND group. This would indicate that disease progression is indeed occurring during the observational period, with a significant difference noted between the two groups in both disease-free survival and the rate of nodal relapse (4.0% in patients with tumor-negative SLNs and 15.6% in the observation-only group). It would appear that such results support the notion that observation of metastatic lymph nodes allows enlargement and adjacent spread to other nodes, thereby increasing the chances of the patient developing distant metastatic disease and a poorer long-term survival [54]. This is most evident when a direct comparison is made between the immediate versus delayed CLND groups, revealing a melanoma-specific survival of 72.3% for the immediate CLND compared with 52.4% in the delayed CLND group. Thus, these recent data are quite compelling in support of performing a

SLNB in those patients with an intermediate-thickness melanoma compared with observation only (no SLNB). Immediate CLND after the finding of SLN-positive disease prolongs survival compared with a delayed CLND performed only upon the discovery of clinically evident disease [53,54].

We believe that it is in the patient's best interest to be fully informed as to the possible diagnostic and therapeutic tests available to them. A thorough discussion regarding the risks and benefits of SLNB should be included for those patients deemed appropriate candidates. It has been our experience that the vast majority of melanoma patients who are candidates for SLNB will chose to undergo this procedure in order to gain useful information on their disease. The discussion is not focused on the argument of whether we are providing a survival benefit, but rather centered on if we are providing a diagnostic procedure capable of answering the question of a primary melanoma cell metastasizing to the draining lymph node basin(s). Thus, the available data support a role for SLNB, able to accurately identify the first draining lymph nodes in a basin and to predict the outcome and staging for melanoma patients.

Role of SLNB for thin melanoma (<1 mm)

The risk of regional nodal involvement for thin melanomas (<1 mm in Breslow's thickness) is in the range of 0 to 9.7%, with an average risk of approximately 5% [55]. For those primary melanomas with other higher risk factors or between 0.75 and 1 mm, the risk of nodal involvement is slighter higher (approximately 5–8%). It is well recognized that patients within this group also are heterogeneous in nature, with some patients at a much higher risk compared with others who may have minimal-to-no risk. There are several factors that may be considered as higher risk when discussing the risks and benefits of SLNB in the patient with a thin melanoma. The presence of a vertical growth phase, Clark's level of invasion IV or V, ulceration, regression, high mitotic rate and a younger age are all considered high-risk features for those with thin melanoma [31,56–60]. There is strong evidence that indicates that tumor mitotic rate and a younger age are more powerful predictors than most, if not all, other prognostic factors available today [58–60]. The focus of our discussion for patients with thin melanomas is centered around two points [61]: does an incidence of nodal progression of approximately 5% warrant the added morbidity and cost of SLNB? Are there specific prognostic/predictive risk factors that could be utilized to determine the need for SLNB among thin-melanoma patients?

There are many patients and physicians who consider a 5% likelihood of nodal metastasis an adequate risk in order to justify the relatively low morbidity of SLNB. However, one cannot forget the intrinsic false-negative rate of approximately 3% with the procedure itself, with the caveat that such statistics are only meaningful for those patients who indeed have positive lymph nodes, providing a minimal true benefit to most of the overall patient population with a thin melanoma. Thus, a thorough discussion describing the risks and benefits of SLNB for patients with thin melanoma is necessary.

Clearly, certain recommendations can be made for melanomas that are very close to 1 mm in Breslow's thickness, with a strong argument made for performing a SLNB for those melanomas within a few tenths of a millimeter on either side of 1 mm. Likewise, it is extremely rare to have a truly thin melanoma that is smaller than 0.75 mm metastasize via the lymphatic channels or hematogenously. Such patients are unlikely to benefit from a SLNB and it is fairly safe to recommend to the vast majority of patients (if not all) with melanomas smaller than 0.75 mm that they may be safely and adequately treated with a 1-cm margin of excision without a SLNB [62]. A recent analysis of 223 patients with thin melanomas who underwent a SLNB reveals that there was a 3.6% rate of nodal metastasis, all in patients with a primary melanoma of greater than 0.75 mm in Breslow's thickness [55]. Furthermore, Thompson and colleagues reported on 187 similar patients with thin melanomas from the Sydney Melanoma Unit, finding a positive SLN rate of 5%, with all patients having a primary melanoma of greater than 0.9 mm in Breslow's thickness [62].

It is important to take an evidence-based approach when considering the role of SLNB for thin-melanoma patients owing to the increasingly large number of patients within this subset. Many have tried to define a specific population of patients that will benefit the most from this staging procedure. The biopsy specimens of those patients within the so-called gray zone (primary melanoma between 0.75 and 1 mm) must be histologically examined very carefully for all of the previously described pathological features, which may sway the surgeon to proceed with a SLNB. We approach such patients by first re-examining all of the pathological slides from the original biopsy or excision, utilizing the expertise and experience of a dermatopathologist. The presence or absence of all pathological features should then be carefully examined and a full and detailed report issued.

It has been our practice to fully explain the risks and benefits involved with SLNB and weigh them against the small risk of nodal metastasis of approximately 5%. In particular, if a patient is found to have any one (or more) of the previously considered poor prognostic features, we will thoroughly discuss the role of SLNB with each patient. For those patients with no evidence of such prognostic features, we will still have an in-depth discussion of performing the SLNB with the full understanding of the risks and benefits of the procedure. It has been our experience that the overwhelming majority of patients within this subset will choose to undergo the SLNB after carefully examining their options of either excision of the primary lesion (alone) versus combining this with SLNB.

Role of SLNB for thick melanoma (>4 mm)

The patient with a thick primary melanoma (>4 mm) has an overall poor prognosis, with average 5- and 10-year survivals of 45 and 39%, respectively [30,31]. For this reason, many question the utility of performing a SLNB in this group of patients, since it is presumed that the patient will already have evidence of either microscopic or macroscopic systemic disease. However, the role of SLNB in this group of patients remains a

valuable tool for the most accurate staging and associated survival data based upon clinical and pathological stage. Although there is a clear consensus that such patients have a much poorer long-term survival, it is of benefit to perform the SLNB for two reasons: accurate surgical staging and early locoregional control of disease. The best opportunity to provide locoregional disease control is at the earliest possible time of diagnosis, which often represents an earlier time in the progression of the disease process. It is fairly well recognized among surgical oncologists that locoregional control of microscopic disease is associated with a markedly decreased morbidity, with a much simpler surgical procedure compared with surgical excision of bulky regional lymphadenopathy, which is fraught with intraoperative and postoperative complications, including nerve dysfunction, chronic pain, decreased functional ability and life-long lymphedema [47].

The final decision to undergo a SLNB for a primary cutaneous melanoma must be made by the patient. We believe it is our obligation as physicians and surgeons to have an objective, data-driven and understandable discussion with our melanoma patients addressing the risks of nodal involvement and what this actually means to the patient. This is weighed equally against the morbidity and possible adverse outcomes of the SLNB procedure, to include a discussion regarding the costs, false-negative rates and the current paucity of data with regards to any proven survival benefit from this staging procedure.

Role of SLNB for head & neck melanoma

In general, primary cutaneous melanoma of the head and neck has an overall worse prognosis compared with those located in other locations, such as the trunk and extremities and, therefore, it is of particular importance to obtain the most accurate staging information available, which will then dictate the adjuvant course of management. The lymphatic drainage of the head and neck is variable and involves a higher number of lymph nodes within the five levels of the cervical region. There are also added concerns in regards to esthetic outcome that can often be overlooked for head and neck melanoma in comparison with other locations, such as the trunk and extremities.

Owing to the relatively small anatomical region of the cervical triangles within the head and neck, SLNs may be located very close to, and occasionally directly beneath, the primary site. This may pose some difficulties in visualization as to the exact location of the sentinel node(s) as they may be obliterated by the shine-through effect of the Te99 injection around the primary site as seen on preoperative radiolymphoscintigraphy. It is important to perform a thorough exploration of the area directly beneath the primary tumor site for evidence of SLNs, especially in the area of the pre- and postauricular face and neck. An additional tool that may be helpful is the utilization of a small amount of vital blue dye injected around the primary melanoma site. It is only necessary to utilize a small amount of dye, usually of 0.5 ml or less, as larger amounts can diffuse into the surrounding skin of the face and neck, possibly resulting in the permanent discoloration of the area outside of the margins of excision. The excision of the primary tumor site should be performed simultaneously with the lymphatic mapping and sentinel node removal, thereby eliminating the background radiation from the primary tumor site.

Once the primary melanoma has been completely removed, subplatysmal skin flaps are raised for identification and localization of the SLN utilizing the hand-held gamma probe to pinpoint the exact location. Careful blunt and sharp dissection is critical within all anatomical nodal levels of the cervical region, as many vital structures are at risk for injury and transection. Utilizing the combined techniques of preoperative radiolymphoscintigraphy and intraoperative vital blue dye injection is the most accurate method of SLN identification, with an accuracy rate of more than 90% [47]. One caveat of performing SLNB in the head and neck is the essential inclusion of side-view 3D preoperative images that note whether the sentinel nodes are within the posterior versus anterior triangle or deeper portions of the cervical region.

There are several structures within the neck that demand particular attention. The greater auricular nerve, external jugular vein, spinal accessory nerve and branches of the facial nerve should be spared from division during the SLN excision. The great auricular nerve to the ear should be identified and can be retracted anteriorly and posteriorly to remove SLNs in the jugulodigastric area. The spinal accessory nerve is often identified deep in the jugulodigastric area along the posterior border of the sternocleidomastoid muscle during sentinel lymphadenectomy. The marginal mandibular branch of the facial nerve must be carefully protected and is particularly prone to a retraction injury against the hardened surface of the mandible. Blunt dissection around the submandibular gland spares any sharp division of the facial nerve at this site.

Lymphatic mapping of the scalp will usually identify SLNs within the occipital and postauricular area, or along the surface or within the superficial portion of the parotid gland. The parotid gland is exposed through a pre-auricular, vertical skin incision followed by retraction and raising of a facial flap. The parotid gland can be fully visualized and careful blunt dissection is utilized to identify and remove the SLN that may be within the parenchyma of the superficial lobe of the parotid gland. The hand-held gamma probe is very helpful in guiding the surgeon towards the identification of a radioactive SLN that has a hint of blue staining within it. The SLN in this area can often be found between the parotid gland fascia and the auricular cartilage, while others may be identified along the posterior surface of the facial vein that lies within the tail of the parotid gland.

If micrometastatic melanoma is found within the SLN of the head and neck, a completion neck dissection should be performed. This will usually involve a modified radical neck dissection in order to remove all of the lymph node-bearing tissue within the various cervical regions. If micrometastatic disease is found within a SLN removed from the parotid gland, a superficial parotidectomy with preservation of the facial nerve is also performed in combination with a modified radical neck dissection.

Complete & selective lymph node dissection

Historically, the ELND was the main operation performed for the staging of patients presenting with localized melanoma. This involved the removal of clinically nonpalpable lymph nodes, by contrast with palpable adenopathy that would be removed by a therapeutic lymph node dissection. An ELND provides durable local control and accurate staging for most patients with occult lymph node metastases. In contrast, a therapeutic lymph node dissection is performed for patients with clinically evident regional lymphadenopathy, providing optimal locoregional control of disease and a chance of cure, with 5-year survival rates of 20–40% [63–65]. Meyer and colleagues performed 144 therapeutic lymph node dissections in 140 melanoma patients (14 cervical, 49 axillary and 73 groin) and found a 5-year survival for all patients of 30% [66].

For palpable inguinal lymphadenopathy, the mainstay of surgical therapy will usually include a superficial inguinal lymphadenectomy with inclusion of the deep pelvic region for either clinical evidence of disease (palpable pelvic lymph nodes), radiographic or intraoperative evidence of obvious lymph node involvement. Intraoperative pathological analysis of clinically suspicious lymph nodes may be necessary in order to determine the presence of metastatic disease and possibly more extensive nodal dissection. Hughes and colleagues describe 132 patients presenting with clinically palpable inguinal lymphadenopathy, with the extent of dissection determined by preoperative radiographic studies, clinical suspicion of pelvic nodes, patient morbidity and performance status and evaluation of Cloquet's node [67]. They found that those patients who underwent a superficial and deep nodal dissection (n = 72) had a lower regional recurrence rate compared with those who underwent a superficial dissection only (n = 60), with no statistical difference in overall survival for either group.

Cloquet's node is defined as the highest lymph node within the superficial inguinal node basin, often located at the entrance of the femoral triangle at the inguinal ligament, sometimes adjacent and medial to the femoral vein or within the femoral canal. This lymph node is considered by many to be the last (highest) lymph node within the superficial inguinal region prior to entrance into the deep iliac and obturator nodal system. Thus, it has been hypothesized that the status of Cloquet's node can be predictive of metastatic involvement of the deep nodal basin, thereby selectively performing a deep pelvic lymphadenectomy only in those patients with a positive Cloquet's node. The sensitivity and predictive value of Cloquet's node is variable, ranging from 44 to 90 % [68–70].

Recently, Essner and colleagues have updated their previous experience with Cloquet's node and have reported a positive predictive value of 66% (negative predictive value of 97%) when basing the decision to perform a deep groin dissection upon the status of Cloquet's node being positive or negative [71]. They found that the pathological status of Cloquet's node was superior to the clinical status of the superficial groin nodes for predicting occult iliac node metastases. However, although most surgeons will agree with the utility of performing a superficial inguinal lymphadenectomy for metastatic disease within this nodal basin, it remains controversial regarding the utility and benefits of performing a deep pelvic lymphadenectomy, regardless of the status of Cloquet's node [72,73]. In summary, surgeons should use all possible available data in order to determine whether a patient should undergo further dissection and removal of deep pelvic lumph nodes.

There will also be those patients who will present with more advanced regional disease. Bulky lymphadenopathy of the axilla is best managed surgically, with a therapeutic complete level I and II axillary lymph node dissection being performed in most cases. The level III lymph nodes should also be carefully palpated and examined in order to determine if further dissection needs to be performed. If there is evidence of palpable adenopathy within level III, consideration should be given for their removal, as it is possible that such disease may have extended into this region. If necessary, transaction of the pectoralis muscle is performed in order to improve the overall exposure of this area. Operative removal can be problematic as matted adenopathy of the axilla can be associated with involvement and possibly encasement of adjacent structures such as the thoracodorsal neurovascular bundle, long thoracic and intercostal–brachial nerve, axillary vein and even the brachial plexus. Dissection may result in injury of these structures and attention to detail and anatomical localization of the thoracodorsal and long thoracic nerves is essential; sacrifice of either of these nerves should be reserved for cases when the tumor is intimately involved these nerves. Within the groin, complete surgical resection of disease can be equally challenging in the presence of bulky lymphadenopathy, with the overall complication rate with regional lymphadenectomy relatively high [74,75].

Isolated limb perfusion/infusion for melanoma

The technique of isolated limb perfusion (ILP) was originally developed by Creech and Krementz at Tulane University (LA, USA) in 1958, as a method to deliver higher concentrations of regional chemotherapy compared with systemic administration, but without the systemic side effects [76]. In approximately 10% of extremity melanoma cases, the recurrence of melanoma is confined to the same extremity where the previous excision was performed, referred to as in-transit disease or satellitosis. Although surgical resection should be considered as the first line of treatment in all cases if possible, there are those patients where resection is not a viable option, either due to an overwhelming tumor burden within the extremity or possibly the disease is spread out over a large area, thus precluding a surgical option. In such situations, ILP may be a favorable therapeutic option as a limb-sparing regional treatment modality. The surgical technique of ILP is a complex and highly invasive procedure that is associated with a number of possible intra- and postoperative complications. However, although complex and requiring a considerable amount of experience from the surgeon, ILP has an established role for patients with in-transit and satellite metastases of the extremity. The addition of hyperthermia (mild

hyperthermia: 39–40°C) to the technique of ILP has further enhanced the overall response rates, while limiting the toxicity associated with higher temperatures (40–43°C).

The reported complete response (CR) rates for melphalan-alone, mild hyperthermic ILP range from 40 to 82%, with a median response rate of 54% in a large retrospective meta-analysis [77]. The addition of tumor necrosis factor (TNF)-α to melphalan was previously thought to enhance the complete response rate to 60–85%, with suspected increased therapeutic value in patients with large, bulky lesions or recurrent disease after a previous ILP [77]. However, a recent, randomized, multicenter trial conducted through the American College of Surgeons Oncology Group (ACOSOG) has compared hyperthermic ILP with melphalan alone to melphalan plus TNF [78]. The results revealed that in locally advanced extremity melanoma treated with ILP, the addition of TNF to melphalan did not demonstrate a significant enhancement of short-term response rates (3-month follow-up) compared with melphalan alone. Furthermore, the addition of TNF to melphalan was found to significantly increase the overall complication rate. Other excellent reviews have described the clinical experience with melphalan alone, or in combination with several other agents, such as TNF, interferon (IFN)-α and chemotherapeutic agents, concluding that ILP has earned a permanent place in the treatment of patients with unresectable or recurrent melanoma of the extremity [78–81].

Despite the clear evidence for the effectiveness of ILP, it is a technique that is only utilized in a select few hospitals around the world. Although the technical concept is simple and elegant, it continues to challenge surgeons as a technically complex, labor-intensive and time-demanding procedure that remains costly [80]. For these reasons, Thompson and colleagues developed the isolated limb infusion (ILI) technique in 1994, as a simpler and less invasive technique compared with ILP [81]. Similar in concept to ILP, ILI was designed as a method with broader applicability, such as in the elderly or those patients with comorbid conditions, which would make an ILP prohibitive [82]. The overall response rates of ILI with melphalan and actinomycin D for the treatment of recurrent or advanced melanoma of the extremity are comparable with those achieved with conventional ILP with melphalan alone [83]. It appears that ILI provides an equivalent treatment option compared with ILP, possibly providing an alternative technique that is technically easier to perform with fewer postoperative complications versus ILP.

Role of surgery in patients with advanced melanoma

It is well established that the overall prognosis for patients with advanced stage III and IV melanoma is poor [30,31]. Most patients who experience recurrence with regional nodal disease and subsequently undergo a complete lymphadenectomy will have a 5-year survival of approximately 25%, while those that recur at any other distant site carry a much poorer prognosis of approximately 5% [84]. The surgical options for patients with metastatic melanoma will generally fall into three categories: curative, palliative or immunotherapeutic. It is very important that detailed discussions are undertaken with the patient in order to address the ultimate intent of surgical intervention with a special focus upon the realistic view of expected complications, outcomes and goals.

Curative attempts with surgery for metastatic melanoma should carefully weigh the risks of the surgery against the potential benefits. Recent data on the surgical management of metastatic melanoma note that certain factors are associated with an improved overall survival [85]:

- Ability to achieve a complete surgical resection with negative margins
- Location of the initial site of metastasis
- Extent of metastatic disease (single or multiple sites)
- Disease-free interval after surgical removal of the primary melanoma
- Stage of initial disease.

Favorable sites of resection include the skin, subcutaneous tissue, lymph nodes, lung and gastrointestinal tract; unfavorable sites are associated with metastasis to the brain, adrenal and liver [86]. Skin and subcutaneous sites demonstrated the best long-term outcome, with a 20–30% 5-year survival and a median survival of 48 months. Among patients with metastases to unfavorable sites, there were no 5-year survivors, with a median survival of only 18.2 months. In reality, the overall survival and possible long-term outcomes for most patients with stage IV disease will ultimately depend upon the intrinsic biological activity and nature of the melanoma itself.

Often, surgical intervention for metastatic melanoma is performed for palliation, with the primary goal to relieve identifiable symptoms caused directly by growing and metastatic tumor deposits. For instance, patients will often present with bulky, recurrent lymphadenopathy of the axilla or groin that cause severe pain in addition to motor and sensory limitations of the involved extremity. Other sites for successful surgical palliation may include a single metastatic deposit within the gastrointestinal tract that is causing either bleeding or a high-grade obstruction. Single metastatic deposits within the brain can also be resected for palliative intent, as waiting may result in surrounding brain edema that may be fatal if left untreated. However, the outcome for such patients has been uniformly dismal, with a median survival of less than 1 year [86]. Careful consideration should be given to any palliative surgical intervention, weighing the benefits of surgery in alleviating the symptoms against the true morbidity and complexity of the surgical procedure.

The last type of surgical intervention to be performed for patients with stage IV melanoma can best be described as cytoreductive immunotherapeutic surgery. An immunotherapeutic surgical approach has been described, whereby complete cytoreductive surgery is hypothesized to play a central role in eliminating the tumor burden. This, in turn, allows for an improved overall function of the host antitumor immune response [87]. It is hypothesized that removing the tumor burden by definitive

cytoreductive and complete surgical resection may allow the host immune system to overcome tumor-induced immunosuppression [87]. Indeed, Morton has recently described his results from the premature closure of the onamelatucel-L (Canvaxin™) trial, designed to assess the efficacy of this vaccine in both stage III and IV melanoma patients. Although both trials were closed to further accrual early, owing to an interim analysis that revealed no probable efficacy over placebo, some very interesting results were nonetheless found in stage IV patients. The design of the Canvaxin trial for stage IV patients required that all patients receive definitive surgical removal of all metastatic disease prior to entry into the trial. Although there was no advantage to receiving the Canvaxin vaccine over placebo, they found that a remarkably high number (40%) of all patients (in both arms) were alive at 5 years, suggesting that prolonged survival may be due not to the vaccine, but instead to complete surgical resection of metastatic disease [88]. It is clear that our understanding of the tumor biology of melanoma remains limited; however, there is a suggestion that complete surgical resection of metastatic disease may play an important role in long-term survival in selected patients with stage IV disease.

Multidisciplinary care of the melanoma patient

The multidisciplinary care of the melanoma patient begins with the initial diagnosis. Once the definitive biopsy has been performed, usually in the office, every attempt should be made for a subsequent follow-up visit to thoroughly discuss the pathology results and to examine the biopsy site for signs of infection and the overall healing process. We believe it is in poor form to provide such results over the telephone, often delegated to a member of the office staff who may be ill prepared for questions and/or emotional outbursts as a result of a patient receiving the diagnosis of cancer over the telephone. Every attempt should be made by the treating physician to sit down with the patient (and family members) and thoroughly review the entire pathology report in detail, allowing the patient to comprehend the results and possibly ask pertinent questions regarding their situation.

The care of the patient with melanoma can be complex, often requiring the opinions of peers from multiple specialities. The management of a thin primary melanoma that simply requires a 5-mm or 1-cm excision can be fairly straightforward. However, a considerably higher level of expertise and complexity are added to the patient with an intermediate or thick primary melanoma. The discussion must be understood by the patient, no matter what their educational background, and encompass a global perspective on what lies ahead for them. This, of course, should include a thorough discussion as to the surgical treatment options, as well as the possible pathological outcomes and its implications with regards to further surgical or medical therapy. With regards to the planned surgical intervention, all options should be discussed, focusing on the current data and literature that support the procedure. A detailed explanation of SLNB and other such staging procedures should be given, including all of the possible risks and benefits of the procedure.

We encourage the participation of all family members in these discussions, often providing an extra set of ears and to ask intuitive questions that the patient may not ask. Ample time should be given for the patient and family to ask questions regarding the surgery and also the bigger picture of their disease. Such detailed conversations are very important to alleviate the fears and to dispel many of the common myths associated with cancer surgery. It is important to remember that the patient with melanoma, or any cancer for that matter, can be emotionally distraught over such news and may not be focused on the discussion at hand. Receiving the diagnosis of cancer is a life-changing event and it is imperative that the surgeon be cognizant of the emotional issues at hand, providing a compassionate and supportive environment for the patient and family members.

The patient's case will often be presented in detail at a weekly, multidisciplinary cutaneous oncology conference, attended by the radiologist (radiographic interpretation of studies), dermatopathologist (review of all biopsy slides), medical oncologists (adjuvant options for appropriate patients), surgical oncologists (expert surgical opinions), radiation oncology (expert opinion on adjuvant radiation therapy) and dermatologist (who may have performed the original biopsy). Other important members of the multidisciplinary team should include the clinical and research nurses, social workers, physician extenders and a recorder for each meeting, who will provide written documentation of each weekly proceeding.

Many hospitals and institutions will not have the luxury of such coordinated care of the melanoma patient. Indeed, there are only a handful of places in the USA able to provide such comprehensive care within a single institution, while the vast majority of melanoma patients will be seen outside of such a setting. It is our recommendation that patients who are diagnosed with intermediate and thick primary melanomas be referred to an institution with an established record of multidisciplinary care of the melanoma patient, such as an National Cancer Institute-designated cancer center. If the geographical location does not allow for this, referral to an academic medical center may benefit the patient, as most institutes will have at least a few physicians with a special interest and training in melanoma patients. Optimally, this would include a surgical oncologist who is well versed in the latest surgical treatment options and who is up to date on the most recent literature with regards to the surgical management of melanoma.

Expert commentary

It is vitally important that we continue to learn from past trials in order to improve upon the way that we treat patients with melanoma currently and in the future. There are four major reasons to perform SLNB, all linked to providing the most accurate information available [89]. The first reason is to improve the accuracy of staging. The second is to facilitate early therapeutic lymph node dissection for those patients with nodal metastases. Third, SLNB identifies patients who are candidates for adjuvant treatment with IFN-α-2b. Fourth, SLNB identifies homogeneous patient populations for entry into

experimental clinical trials. The latter reason is critically important, recognizing the importance of enrolling similarly staged patients to strengthen results and develop more effective treatment strategies for such patients.

There is a renewed enthusiasm for the surgical management of select patients with metastatic melanoma. Although the Canvaxin trials failed to show any clinical efficacy, they did reveal a surprisingly higher 5-year overall survival in both arms of the study compared with historical controls, with all patients undergoing complete surgical resection of their metastatic disease prior to being enrolled in the trial. The concept of removing the tumor cell factory with surgery, as described by Morton, has started to gain renewed interest, directly addressing the intimate relationship between the host immune system and tumor microenvironment. As we begin to improve our understanding of tumor cell biology and immunology through a committed research effort around the world, we may apply such surgical efforts in a more directed fashion, possibly selecting those patients who will most benefit.

Five-year view

Although it is recognized that a 2-cm margin of excision is adequate for melanomas that are larger than 1 mm, there may not be overwhelming support for a trial that wishes to address the value of a smaller margin, such as a 1-cm compared with 2-cm margin of excision for primary melanoma. This would certainly be interesting to conduct for cosmetically sensitive areas, such as the face and head and neck; however, this would require a tremendous amount of resources in order to answer this question. Rather, we foresee that much of our effort will be directed towards research into developing better prognostic markers of outcome, whereby we can apply such markers to specific subgroups of melanoma patients. This will allow us to select those patients who will benefit the most (and exclude those who will not) from a given procedure, such as SLNB for thin or thick melanoma. In addition, the revolution of genomic profiling is upon us, with much research dedicated to the development of specific signatures of melanoma tumor progression, metastatic potential and aggressive phenotypes. Other research has focused on distinguishing primary from metastatic melanoma, analyzing specific cellular pathways and the associated genes involved with this process. The implications of this research are far-reaching and have opened up completely new areas of opportunity in our quest to translate such research efforts into improved prognostic factors and targeted therapy for patients with melanoma.

For those who will continue to hold SLNB to a higher standard, requiring proof that it provide a therapeutic benefit, the results of the third interim analysis of the MSLT-I are now published, strongly supporting the role of SLNB in accurately identifying patients with nodal metastases (by SLNB) whose survival can be prolonged by immediate (versus delayed) lymphadenectomy. These results will again spark a heated dialogue regarding SLNB, often a healthy exercise for all involved. The ongoing MSLT-II trial will determine, in patients with histopathological or reverse transcriptase-PCR positive SLNs, whether there is an outcome difference comparing SLNB plus CLND versus SLNB alone. Despite clear evidence for the efficacy of IFN-α-2b for stage III patients, a few individuals continue to argue that since existing adjuvant therapy for melanoma is completely ineffectual, there is no compelling reason to identify nodal metastasis early in its clinical course [50,51,90]. Although it is good to question the results of any trial, it is essential that we do not ignore the currently available data simply owing to the fact that it is not the answer that we may have been looking for. Instead, we

Key issues

- The surgical management of melanoma has dramatically changed over the last 100 years.
- Several clinical trials have adequately addressed the appropriate surgical margins to obtain for primary cutaneous melanoma.
- Sentinel lymph node biopsy (SLNB) as a diagnostic procedure has greatly enhanced our ability to accurately stage patients with melanoma.
- SLNB is the single most important prognostic factor in determining the likelihood of survival.
- SLNB is a far better diagnostic procedure than clinical staging or elective lymph node dissection in terms of both sensitivity and morbidity.
- SLNB provides superior locoregional disease control compared to delayed lymphadenectomy for recurrent or palpable lymphadenopathy.
- The multicenter selective lymphadenectomy trial-I study strongly supports the role of SLNB and immediate (vs delayed) delayed complete lymphadenectomy if SLN-positive disease is found.
- Management of head and neck melanoma is complex and may require combined surgical specialties for best management.
- There is increasing evidence for a surgical role in the management of metastatic melanoma.
- Multidisciplinary care of the melanoma patient is essential for optimal patient care and outcome.
- Ultimately, it is the biology of the tumor itself that will determine the overall progression and long term outcome of the patient.
- Continued research is focused on the development of novel treatment strategies for advanced melanoma
- There is a need to develop sensitive and accurate prognostic markers as a guide for future management of patients with melanoma.

must critically analyze the data and utilize it to provide what is deemed best possible therapy for each of our patients with advanced melanoma. We must continue to move forward in our design of future trials deemed to have therapeutic efficacy, with the development of multimodal strategies at the forefront of translational research and trial design.

We must never forget the melanoma patient in all of this discussion, for it is impossible for those of us who are cancer free to experience the emotional rollercoaster that many, if not all, will experience. In treating patients with melanoma on a daily basis, it is clear that the melanoma patient does not accept the wait-and-see attitude supported by other physicians and, fully understanding that the SLNB does not have a survival benefit, will overwhelming choose to undergo this procedure. Regardless of such deep-seeded beliefs regarding SLNB, the diagnostic utility of SLNB is unmatchable, firmly established as a necessary part of the discussion that we have on a daily basis with our patients.

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