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Review Article

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MALIGNANT MELANOMA OF THE HEAD AND NECK

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ABSTRACT

The management of malignant melanoma of the head and neck is marked by many controversies. The treatment modalities have evolved over the past few decades along with various changes in the TNM classification for head and neck melanoma. The purpose of the present review is to discuss the outcomes of various controversies which led to the present treatment protocols.

KEYWORDS: Melanoma head and neck, surgical management, treatment, malignant melanoma.

Though Hippocrates made the first recorded clinical observation of melanoma, it was Carswell who coined the term melanoma in a treatise during the early part of nineteenth century. Several reports appeared in the literature during the seventeenth century, referring to the "fatal black tumour". Laennec and Dupuytren published on melanosis in 1806, while Sir James Paget in 1864, stated that cancer could develop in a mole. It was in 1892 that Hutchinson published his Archives of Surgery in which he described the senile freckle which we now call Hutchinson's melanotic freckle. Clark[1] gave his classification of melanocytic lesions in 1969, while Breslow[2] published the staging system in 1975.

The worldwide incidence of cutaneous melanoma continues to rise about 6% per year.[3] Approximately 20% of primary lesions are located on the head and neck.[4] As far as etiology is concerned, sun exposure remains one of the most important risk factors.[5,6] Other major risk factors include pale skin, blue or green eyes, fair or freckled complexion, blond or reddish hair and inability to tan.[7,8]

The clinical appearance of malignant melanoma may be described as a pigmented lesion that displays the often-cited ABCDE of melanoma: A refers to asymmetry of the lesion, B to border irregularity, C to variegated colour, D to diameter greater than 6 mm and E to elevation. One should also evaluate the surrounding skin for recent changes and elicit subjective symptoms such as pain or itching at the lesion site. It is also important to document ulceration of the lesion prior to biopsy as ulceration plays a critical role in the current TNM staging system. Apart from this, the clinician should be alert that all melanoma lesions are not pigmented. Up to 10% of all the lesions lack melanin and some may spontaneously regress leaving a hypopigmented "halo".

The anatomic locations of cutaneous head and neck melanoma correlate with the areas of greatest sun exposure. Face, scalp, neck and external ear are the leading sites for melanoma.[9-16] Of all these sites, patients with lesions of the scalp exhibit the poorest overall survival.[17,18] The rich regional lymphatics of the head and neck play an integral part in staging and prognosis for an individual case. Mucosal melanomas are mainly found in the sinonasal cavity or the oral cavity. These exhibit poorer survival rates than cutaneous sites.[19-26] Postoperative radiation therapy has shown promise in locoregional tumor control but has yet to show any benefit for overall survival.[27,28]

Types of Melanoma

The appearance and growth of melanoma differ depending on the morphologic type. Table 1 shows the incidence and features of 6 types of melanoma.

(a) Superficial spreading

This variety accounts for 65% to 75% of all cases, making it the most common subtype. These lesions may present in a wide variety of colours. The radial growth phase may be extended, lasting between 5 and 7 years. The transition from radial to vertical growth pattern is sometimes heralded by bleeding or ulceration. Rare cases of spontaneous regression have been described. The standard treatment of primary lesion includes excision with depth-appropriate margins.

(b) Nodular

This is the most aggressive subtype, accounting for 10% to 15% of all cases. It may occur on sun-exposed and non-exposed areas alike. It is generally seen in those over 50 years of age. The peculiar characteristic of nodular melanoma is that it may lack a radial growth phase and may progress rapidly through the vertical

phase. Treatment includes wide excision with depth-appropriate margins.

(c) Lentigo maligna melanoma

These are characterized by a prolonged radial growth phase. They tend to start as a slow-growing, flat patch in sun-exposed areas (often the face and neck). They exhibit a proclivity for dermal-epidermal junction and tend to follow the hair follicles.

(d) Acral lentiginous melanomas

These lesions are characteristically located on the palms or soles. Not all such lesions are acral lentiginous. However, they have a well defined histologic appearance.

(e) Desmoplastic melanomas

These can be seen in association with pre-existing melanocytic lesions and can more frequently be amelanotic, making their diagnosis more difficult. They tend to be characterized by infrequent metastasis with a higher local recurrence rate, as well as more frequent perineural involvement.

(f) Neurotropic melanoma

Neurotropic melanoma is so-called for its histologic resemblance to nerves and neural structures and because of its tendency to infiltrate peripheral nerves. This lesion may arise out of pre-existing melanoma lesions in the vertical growth phase. This tumor is highly aggressive with an exceedingly poor prognosis.

(g) Mucosal melanomas

Such lesions must frequently present in the nose and / or sinuses, followed by the oral cavity and nasopharynx. These are rare lesions but have a poor prognosis. As their development is hidden in clinically silent areas, the diagnosis often occurs late, requiring more radical treatment and contributing to a poorer prognosis.

Staging

In 2002, the American Joint Council on Cancer (AJCC) revised the melanoma staging system last modified in 1997 using a database of more than 17,000 patients.[29,30] Multiple features of the primary tumor and subsequent nodal status were added to better stratify and stage new melanoma patients (Table 2).[31] In the past, Breslow depth of invasion has been shown to have prognostic significance, as has Clark level of invasion. In the new system, Breslow depth plays a more vital role, while Clark level is de-emphasized (relevant only for T1 lesions). Other changes include the presence or absence of tumor ulceration, as well as tumor (T) thickness limits at 1.0-mm, 2.0- mm and 4.0-mm depth for defining T stage. Stages I and II were confined to clinical staging, while stages III and IV used pathologic information from the nodes to define staging. Where the 1997 system used the size of nodal metastases to judge prognosis, new data have shown that the number of metastatic nodes is more relevant. The new system reflects that relevance by basing the N (nodal) stage on number of nodes as follows: 1 vs 2–3 vs ≥4 metastatic nodes. In-transit metastases, which were grouped with the T staging in the 1997 system, are now included with the N staging. In general, in-transit metastases have been recognized to portend a poorer prognosis, which is reflected in the new system. Distant metastases are now grouped into one of three groups: M1a (including subcutaneous nodules/distant nodes), M1b (confined to lung metastases), and M1c (for all other visceral sites). Elevated lactate dehydrogenase (LDH) serum level also is associated with poor prognosis, and patients with distant metastases and increased LDH are stage M1c regardless of site of metastasis.

Table 1: Incidence and characteristics of various subtypes of melanoma.

Subtype	Incidence	Special Features
Superficial spreading	75%	Flat during early phase, typically from pre-existing nevus
Nodular	15%	Early vertical growth
Desmoplastic	low	Associated with perineural invasion
Lentigo maligna	10%	Prolonged radial growth
Acral lentiginous	2%–8%	Palms, soles, nail beds
Mucosal	2%	Poorer prognosis

Table 2: TNM Classification of Melanoma as per 7th edition of AJCC Staging.

Classification	Thickness (mm)	Ulceration Status/Mitoses
T		
Tis	NA	NA
T1	≤ 1.00	a: Without ulceration and mitosis < 1/mm² b: With ulceration or mitoses ≥ 1/mm²
T2	1.01-2.00	a: Without ulceration b: With ulceration
T3	2.01-4.00	a: Without ulceration b: With ulceration
T4	> 4.00	a: Without ulceration b: With ulceration
N	No. of Metastatic Nodes	Nodal Metastatic Burden
N0	0	NA
N1	1	a: Micrometastasis* b: Macrometastasis†
N2	2-3	a: Micrometastasis* b: Macrometastasis† c: In transit metastases/satellites without metastatic nodes
N3	4+ metastatic nodes, or matted nodes, or in transit metastases/satellites with metastatic nodes	
M	Site	Serum LDH
M0	No distant metastases	NA
M1a	Distant skin, subcutaneous, or nodal metastases	Normal
M1b	Lung metastases	Normal
M1c	All other visceral metastases	Normal
	Any distant metastasis	Elevated

Abbreviations: NA, not applicable; LDH, lactate dehydrogenase.
*Micrometastases are diagnosed after sentinel lymph node biopsy.
†Macrometastases are defined as clinically detectable nodal metastases confirmed pathologically.

Table 3: Recent NCCN guidelines for surgical margins in melanoma of the head and neck.

Primary T Stage	Tumor Thickness, mm	Recommended Excision Margin, cm
In situ	NA	0.5
T1	≤1.00	1.0
T2	1.01-2.00	1.0-2.0
T3	2.01-4.00	2.0
T4	>4.01	2.0

Surgical Management of the Primary Tumour

Wide Local Excision and Surgical Margins

The standard of care for primary melanoma treatment is complete surgical excision. However, the extent of surgical margins remains an unanswered question despite numerous retrospective studies, meta-analyses, and clinical trials. Historically, an extensive 5-cm margin of surrounding normal tissue was practiced. However, this recommendation was based on a 1907 autopsy report of a patient with advanced melanoma.[32] The use of 5-cm surgical margin was routine practice until the 1970s when Breslow and Macht challenged the concept by successfully treating a cohort of 35 patients with thin melanomas using narrower margins.[33]

Several prospective, randomized trials investigating surgical margins for cutaneous melanoma have since followed. The World Health Organization (WHO) conducted an international trial in which 612 patients with thin melanomas (up to 2 mm) were randomized to surgical excision with 1-cm vs. greater than 3-cm margins.[34] At a mean follow-up of 8 years, the disease-free survival and overall survival rates were reported to be equivalent between the 2 groups.[35] The WHO concluded that wide excision did not influence survival for patients with thin melanomas; for patients with melanomas less than 1 mm in thickness, the authors advocated "narrow" 1-cm margins to the muscular fascia plane. Within the WHO trial, a subset of 245 patients had tumors measuring 1.1 to 2.0 mm in thickness. Although a difference in disease-free survival and overall survival was not observed with respect to margins, a local recurrence rate of 3.3% was reported among patients undergoing "narrow" excision. This finding prompted the Intergroup Melanoma Surgical Trial, which prospectively randomized 740 patients with intermediate thickness (1-4 mm) melanomas to WLE with 2-cm vs. 4-cm margins.[36] Local recurrence rates and 10-year survival rates were reported to be equivalent between the 2 groups. This finding led to the recommendation of a 2-cm surgical margin for patients with intermediate melanomas measuring 1.1 to 4.0 mm in thickness. The prospective clinical trial conducted by the United Kingdom Melanoma Study Group randomized 900 patients with localized cutaneous melanomas of at least 2 mm in thickness to 1-cm vs. 3-cm margins.[37] A statistically significant difference was not identified between the 2 groups when local, regional, and distant recurrences were individually compared. Overall mortality rates were found to be identical between the 2 arms. However, when all recurrences (local, in-transit, and nodal) were pooled together, the 1-cm margin group experienced a statistically higher recurrence rate. This is the first clinical trial comparing tumour margins to report a statistically significant difference in tumour recurrence. From a practical standpoint, however, it is the 1-cm vs. 2-cm margin that is debated more often in the clinical setting.[38]

There is a paucity of literature regarding prospective randomized trials for investigating the optimal surgical margin for thick (> 4 mm) melanomas. A retrospective study of 278 thick melanomas found that surgical margins greater than 2 cm did not lead to a difference in local recurrence rate, disease-free survival, or overall survival when compared with margins less than 2 cm.[39] Within this study, 16% of the tumours involved head and neck subsites.

The primary goal of melanoma excision is to eliminate local recurrence secondary to persistent disease. The rate of local recurrence from narrow-margin excisions is admittedly low; however, the consequences are potentially fatal. It has been estimated that 100% achievement of ideal margins would lead to a reduction in melanoma-related mortality and an increase of life expectancy of melanoma patients by 0.4 years.[40] Although this difference appears small at first glance, it equates to an estimated 11 additional years of life expectancy for those individuals who would have recurred locally following a 1-cm margin, but instead achieved a disease-free state following a wider surgical margin.

Recent guidelines for surgical margins are based on primary tumour thickness (Table 3). It is important to realize that these recommendations serve merely as a guideline. Each melanoma case must be individualized. The depth of excision includes full thickness skin and underlying subcutaneous tissue. Resection of fascia, perichondrium, and periosteum is required only in the setting of direct tumour invasion or if the surgical plane was violated during a previous biopsy.[41] Lentigo maligna melanoma warrants special consideration because it has a propensity for wide subclinical spread, which often results in positive margins.[42] In an attempt to address this challenge, Johnson et al developed the "square" procedure."[43] This staged procedure entails complete excision of the peripheral margins using a double-bladed instrument, followed by permanent histologic evaluation of 100% of the peripheral margins surrounding the entire tumour.

Closure and Reconstruction

The majority of surgical sites can be closed primarily with the use of wide undermining. Larger defects may require reconstruction with a split thickness skin graft, full thickness skin graft, local advancement flap, or

regional flap. The method of reconstruction depends on the anatomic location including skin colour and texture, depth of the defect, and patient, as well as surgeon, preference. Initially surgeons were reluctant to graft excision sites for fear that surveillance for future melanoma recurrence within the surgical bed would be hindered. However, the method of closure has not been shown to impact survival.[44] Once clear margins have been confirmed, surgeons are encouraged to close surgical defects using the technique that they think will yield the best cosmetic result.

Auricular Melanoma

Originally, auricular melanoma was thought to carry a worse prognosis compared with other sites within the HN region.[45,46] This increased risk was attributed to rich lymphatics, complex anatomic subdivisions of the ear, and a paucity of subcutaneous tissue between the thin auricular skin and underlying perichondrium.[47] For these reasons, full thickness excision or total auriculectomy was often advocated. Research conducted over the past few decades has led to a shift in the treatment paradigm for auricular melanoma. After accounting for tumor thickness, recent studies have demonstrated that melanoma in this region carries the same prognosis as other HN sites.[48] Outcome differences were not observed between auricular subsites.[47] In addition, retrospective reviews failed to demonstrate a difference in local recurrence based on the extent of surgical excision, even when perichondrium was preserved.[48] Today, the same prognostic indicators and surgical principles of obtaining wide, clear margins for treatment of cutaneous melanoma can be applied safely to the auricle.

Surgical Management of Regional Lymph Nodes

Therapeutic Lymph Node Dissection

The most common sites for metastasis of HN cutaneous melanoma are the cervical and parotid lymph node basins.[49,50] Therapeutic lymph node dissection (TLND) is accepted universally as the treatment of choice for regional disease. The neck dissection must include all draining nodal basins as well as the intervening lymphatics between the primary tumour and the site of regional disease. The location of the primary tumour dictates the specific type of TLND, as well as the need for a superficial parotidectomy. In the absence of gross tumour involvement, or disruption from open biopsy or previous surgical dissection, concerted efforts should be made to preserve the spinal accessory nerve, internal jugular vein, and sternocleidomastoid muscle.

Melanomas of the anterolateral scalp, temple, lateral forehead, lateral cheek, and ear, arising anterior to an imaginary coronal plane through the external auditory canals (EACs), drain via the parotid nodal basin to the jugular lymph node chain.[51] For this reason, melanomas anterior to this coronal plane require a superficial parotidectomy and modified radical neck dissection (MRND). If the melanoma arises in a more inferior location, such as the chin or neck, a superficial parotidectomy is not warranted. Melanomas located on the scalp and occiput, posterior to the imaginary coronal plane through the EACs, can drain to postauricular, suboccipital, and posterior triangle lymph nodes. These nodal basins are not addressed during routine MRND. In this situation, a posterolateral neck dissection, which extends to the midline of the posterior neck, is required.[52]

Elective Lymph Node Dissection

Historically, one of the most controversial debates in melanoma surrounded treatment of regional nodal basins in the absence of clinical metastasis (prophylactic treatment of the N-zero neck). Melanomas measuring less than 1.0 mm in thickness have an excellent prognosis, with a 5-year survival rate approaching 95% to 99%. For this reason, elective treatment of the neck is considered unnecessary for the majority of thin stage I melanomas since the risk of occult nodal metastasis is less than 5%. Conversely, melanomas measuring greater than 4.0 mm in thickness have an extremely poor prognosis. The high 70% rate of systemic metastasis is thought to negate any benefit that may be gained by electively treating regional nodal basins.[53] The real controversy surrounded elective treatment of the neck for patients with intermediate thickness (1.0-3.9 mm) melanomas. Opponents of elective lymph node dissection (ELND) contended that melanoma metastasis is unpredictable. In Fisher's retrospective review of 1444 HN melanoma patients, up to 16% developed distant metastasis in the absence of regional disease.[54] The potential for haematogenous melanoma spread to bypass regional nodal basins theoretically limits the utility of an ELND. Opponents further argue that all 4 prospective, randomized trials failed to demonstrate an overall survival benefit for patients undergoing ELND in the absence of regional metastasis.[55-58]

In 1967 the WHO Melanoma Group conducted the first prospective, randomized trial (No. 1) between 1967 and 1974.[57] A total of 535 patients with stage I and II melanoma of the extremity were enrolled. No difference in survival benefit was found between patients who underwent WLE and observation, with TLND reserved for the development of gross nodal metastasis, compared with patients who underwent WLE and ELND. Similarly, surgeons at the Mayo Clinic randomized 171 patients with stage I disease to: 1) WLE and observation, 2) WLE and delayed (30-60 days) ELND, or 3) WLE with concomitant ELND.[55] ELND was not found to provide a survival benefit compared with observation.

Although both prospective trials represent pioneering research in a challenging area, both study designs have been criticized.[49] At the time of the studies, the prognostic significance of tumour thickness and ulceration was unknown. Later analysis of the WHO Melanoma Group Trial No. 1 found significant discrepancy in the distribution of tumour thickness

between the 2 treatment arms. Furthermore, 52% of lesions in the ELND group were ulcerated compared with only 19% in the observation group.[49] Subsequent re-analysis of these data with respect to tumour thickness and ulceration identified a subset of patients with a 22% improved 10-year survival in the setting of ELND. The accuracy of clinical staging within the trial was also questioned because several institutions reported a 30% rate of occult nodal metastasis. This rate is quite high compared with reports in the literature that range from 10% to 20%. Last, Balch argues that the failure to detect a survival benefit with ELND was not surprising, given that both trials included patients with an overall low risk for regional metastasis at the time of diagnosis. Approximately 85% of patients enrolled in the WHO Melanoma Group Trial No.1 were women with extremity melanomas, a group that is recognized to have a low rate of metastasis compared with other sites. In addition, the Mayo Clinic excluded patients with HN and midline trunk melanomas.

To address these concerns, the Intergroup Melanoma Surgical Trial (IMST) was initiated.[58] The IMST was a prospective, multi-institutional study of 740 patients with intermediate tumour thickness (1-4 mm) melanomas of the trunk, extremity, and HN region. Patients were once again randomized to WLE and observation vs. WLE and ELND. Cox regression analysis identified ulceration, site, tumour thickness, and age as independent markers for survival. Overall 5-year survival rates were not found to be different between the 2 treatment groups. However, a significant survival benefit was found in patients 60 years of age and younger who underwent ELND, especially if their tumour was non-ulcerated or measured 1 to 2 mm in thickness. Although this subgroup analysis is subject to the shortcomings of retrospective review, and it is criticized because patients were not randomized on age, patients were randomized prospectively on tumour thickness and ulceration.

The fourth prospective trial was initiated in 1982 by the WHO Melanoma Group (No. 14). In an attempt to study patients truly at high risk for occult nodal metastasis, 240 patients with trunk melanomas measuring greater than 1.5 mm in thickness were enrolled.[56] A difference in survival was not observed between patients randomized to observation vs. ELND. In a multivariate analysis including sex, age, tumour thickness, and treatment, only sex and tumour thickness were found to have a significant impact on survival. However, this study did identify a statistically significant 5-year survival difference for patients with micrometastasis identified during ELND (47%) compared with patients in the observation arm who underwent TLND only after the development of gross nodal disease (27%). For this reason, the WHO Melanoma Group advocated early detection of nodal metastasis using procedures such as SLNB.

Statistical power remains 1 of the greatest challenges in investigating the survival benefits of ELND and early detection of nodal disease.[59] Only 20% of melanoma patients presenting with localized disease actually harbor occult nodal metastasis. It is only this 20% who would potentially benefit from early removal of nodal basins. Adjuvant melanoma therapy imparts a survival benefit in 25% to 50% of cases. If a similar survival benefit is applied to the ELND group, 25% to 50% of the 20% of patients with occult disease should benefit. In other words, only 5% to 10% of patients undergoing ELND are expected to experience a survival advantage. Detecting this small difference requires extremely large clinical trial enrolment, numbering in the thousands. McMasters and colleagues point out that the IMST, WHO, and Mayo Clinic trials lacked adequate statistical power to detect this small survival benefit. For this reason, the group concluded that the 4% survival benefit observed in the elective lymph node dissection (ELND) group of the IMST study is clinically significant, despite the fact that statistical significance was not reached. In summary, numerous prospective, randomized trials have failed to demonstrate an overall survival benefit for patients undergoing ELND.[55-62] Therefore, routine ELND is no longer advocated for melanoma. Instead, the procedure has been replaced by SLNB.

Sentinel Lymph Node Biopsy

Sentinel lymph node biopsy represents a minimally invasive, cost-effective, and efficient means of screening patients for regional metastasis. Nodal status is currently recognized as the single most important prognostic factor for melanoma patients.[63] Ten percent to 20% of individuals harbour occult, microscopic nodal disease. In an attempt to identify this small group of patients who warranted TLND, while sparing the remaining 80% of patients without regional disease the morbidity associated with a neck dissection, Morton and colleagues introduced SLNB for the evaluation of patients with trunk and extremity cutaneous melanoma.[62] These investigators demonstrated that the status of the SLN accurately represented the status of the entire nodal basin from which it was obtained. SLNB is the best staging modality for regional disease, with the highest sensitivity and specificity of any modality currently available. Among major melanoma cancer centers across the world, it is now accepted as the standard of care.[64-66]

Success of SLNB hinges on appropriate patient selection. Patients presenting with palpable regional disease or distant metastasis are not candidates for SLNB because additional prognostic information will not be gained. In addition, patients who have undergone previous neck dissection or resection of the primary site with wide margins are not deemed candidates due to lack of accuracy. The SLN technique has evolved to include preoperative lymphoscintigraphy by nuclear medicine.[67] Approximately 2 to 4 hours before surgery, patients undergo intradermal injection of a radioactive colloid into the 4 quadrants surrounding the primary melanoma

tumour. Lymphoscintigraphy is then performed to guide the surgeon in determining the number, location, and laterality of nodal basins at risk for metastatic disease. It is particularly helpful in the setting of midline HN melanomas that have the potential for bilateral lymphatic drainage. Once under anaesthesia, intraoperative lymphatic mapping with isosulfan blue dye (Lymphazurin 1%, Hirsch Industries, Inc., Richmond, VA) is performed.[62] Approximately 1 mL of dye is injected into the intradermal layer surrounding the primary melanoma lesion. Unlike melanoma of the trunk and extremity, the primary tumour and draining lymphatics are in close proximity within the HN region. Therefore, WLE of the primary tumour is performed first to reduce radioactive "shine-through," which will render the intraoperative gamma probe useless in identifying SLNs.

Following WLE of the primary melanoma, nodal basins at risk for metastasis are evaluated for increased radioactivity using a handheld gamma probe. A 1- to 3-cm incision is made overlying the areas of increased radioactivity. A preauricular incision is recommended for SLNB in the parotid region. Facial nerve monitoring is also recommended in this setting. SLNs are then identified using a combination of the gamma probe and visual cues from the blue dye. Each SLN is individually dissected from surrounding tissue. Within the parotid bed, gentle dissection in the anticipated direction of the facial nerve is imperative. The staging procedure is considered complete when all nodal basins demonstrate minimal background radioactivity (< 10%) relative to the primary lesion and sentinel nodes.

Histopathologic protocols for SLN evaluation vary from institution to institution. As reported by Morton et al,[68] at the University of Michigan, all SLNs are sent for histologic evaluation using permanent sections. Morton et al recommend not to use frozen sections, stating that this practice is less reliable, carrying a false negative rate between 5% to 10%.[68] Their evaluation includes serial sectioning (5-µm thick sections) and staining with haematoxylin and eosin (H&E). All SLNs negative on H&E staining are then subjected to melanoma-specific immunohistochemical staining (IHCS) for S-100 and Melan-A (MART- 1). This panel was chosen after pathologic evaluation of 99 positive SLNs from 72 patients treated at their institution.[69] The sensitivities for S-100, Melan-A, and HMB-45 were found to be 97%, 96%, and 75%, respectively. In addition, they found that HMB-45 stained a smaller percentage of cells (25% to 75%), with weaker intensity compared with S-100 and Melan-A. For this reason, they no longer routinely stain for HMB-45. Patients with a positive SLN return to the operating room within 2 weeks of diagnosis for definitive TLND. Patients with a negative biopsy are followed clinically. An alternative to this 2-staged technique is immediate TLND based on frozen section evaluation of the SLNs. However, it is important to realize that the reliability of frozen sections for melanoma analysis has been questioned[68,70] and permanent sections remain the "gold" standard.

The pathologist plays an extremely critical role in the success of the SLNB. Occult lymphatic metastasis from cutaneous melanoma can be difficult to detect, with tumour cells occupying less than 2% of the entire lymph node volume.[68] Therefore, rigorous pathological analysis including serial sectioning, special immunohistochemical study when indicated, and interpretation by an experienced pathologist is necessary. Wagner and colleagues reported the mean tumour volume in positive SLNs to be only 4.7 mm^3.[71] Joseph and colleagues reported identification of only 73% of metastatic SLNs using standard H&E staining alone.[72] In a study by Karimipour et al, 20 of the 97 positive SLNs (21%) were negative on initial H&E staining.[69] This high false negative rate highlights the importance of IHCS for accurate diagnosis of occult nodal disease. From a practical standpoint, the histologic analysis of SLNs is more thorough, cost-effective, and complete compared with traditional evaluation of the entire lymphadenectomy specimen because the technique provides the pathologist with a limited number of nodes to evaluate thoroughly.[73]

In an effort to further increase SLNB sensitivity, Haigh et al.[74] investigated the utility of carbon dye as a mapping adjunct. Unlike isosulfan blue dye, the carbon remains as a permanent marker to aid the pathologist in identifying the specific intranodal site of lymphatic drainage, which is the most likely area for occult metastatic disease.[74] Su et al suggest SLNB to be particularly helpful in the diagnosis of occult desmoplastic melanoma/desmoplastic neurotropic melanoma (DM/DNM). Here, a focused histopathologic evaluation is particularly important because the microscopic features of metastatic DM/DMN are quite variable, often lack resemblance of the primary tumour, are limited to a paucity of tumour cells, and demonstrate inconsistencies on HMB-45 and Melan-A staining.[75]

SLNB is a team effort involving experienced surgeons, nuclear medicine staff, and pathologists. The experience and technical skill of the surgeon is vital and may account for some of the variability observed in HN cutaneous melanoma SLN studies.[76] Morton and colleagues previously suggested a 30 case learning curve.[67] However, long-term follow- up of their international Multi-center Selective Lymphadenectomy Trial (MSLT-I) found the 30 case learning curve to be too shallow. Analysis of the first 25 cases performed at the 10 highest volume centers in the trial revealed a nodal basin recurrence rate of 10.3%.[68] This false negative rate dropped to 5.2% after 25 additional cases. The authors now conclude that a 55 case learning curve is required to achieve at least 95% accuracy with SLNB. An experienced nuclear medicine staff is necessary because inappropriate administration of the radioactive tracer can lead to "shine through" which renders the

handheld gamma probe useless in the operating room. Communication with the nuclear medicine team is critical not only in interpreting the lymphoscintigram, but also in ensuring that the appropriate lesion is mapped since patients with melanoma often present with multiple pigmented lesions and significant solar changes.

Recent multivariate analysis involving patients with stage I and II melanoma by Gershenwald and colleagues found the pathologic status (positive or negative for metastasis) of the SLN to be the most important prognostic factor for both recurrence and overall survival.[77] For stage III melanoma, a survival benefit was found in patients with occult microscopic disease compared with their counterparts who had palpable, macroscopic disease.[63] This survival benefit was so compelling that the AJCC has now incorporated SLNB into the revised staging system for cutaneous melanoma.

Although SLNB has a defined role in the evaluation of cutaneous melanoma of the trunk and extremities, several questions have been posed with respect to its application in the head and neck region.[67,78,79] The complexity of the HN lymphatic system has caused concern surrounding the reliability of the SLN to represent the status of the entire nodal basin accurately. The interlacing network of cervical lymphatic vessels is often deemed watershed in nature. The complexity of this lymphatic system was demonstrated by O'Brien and colleagues who reported 34% discordance between the clinical prediction of lymphatic drainage and lymphoscintigraphy findings in 97 cases of HN cutaneous melanoma.[80] The popularity of SLNB in the HN region has also been limited by concerns surrounding damage to vital structures such as the facial nerve,[81] technical difficulties,[78,81] and the necessity for nuclear medicine staff as well as pathologists who specialize in SLNB technique.

Schmalbach et al published their experience in 80 patients with HN cutaneous melanoma. The study demonstrated that the complexity of HN anatomy does not preclude the use of SLNB for staging of cutaneous melanoma.[76] SLNB accurately predicted the status of the nodal basin in this region. Fourteen (17.5%) of 80 patients were identified with a positive SLNB. Only 3 (4.5%) of 66 patients developed regional recurrence following a negative SLNB. The 17.5% positivity rate of SLNs and the 4.5% false negative rate both mirror the results of SLNB achieved in other anatomic sites such as the trunk and extremities.[73,82] Similar success in the application of SLNB for HN cutaneous melanoma has been reported by others,[83,84] and the technique has successfully been applied in paediatric HN cases.[85]

Approximately 25% to 30% of HN cutaneous melanomas drain to lymph nodes within the parotid bed.[76,80] Potential injury to the facial nerve from SLNB has led some surgeons to advocate superficial parotidectomy over the mapping procedure.[81] In a retrospective analysis by Schmalbach et al, 28 (93.3%) of 30 patients showing drainage to the parotid nodal basin successfully underwent staging using SLNB.[76] One patient required a superficial parotidectomy due to the location of the SLN deep to the facial nerve. A second patient experienced significant bleeding from surrounding parotid tissue, which could have placed the facial nerve at increased risk. A total of 39 nodes from 28 parotid basins were removed without facial nerve injury. Continuous facial nerve monitoring for SLNB within the parotid nodal basin can be helpful when performing the biopsy with the parotid bed. Concern has also been expressed that SLNB causes inflammation and fibrosis that could place the facial nerve at increased risk when reoperation is required to treat the parotid basin definitively in the setting of a positive SLN.[81] Ollila et al et al have shown that SLNB can be performed reliably and safely within the parotid nodal basin.[86]

Other authors have suggested that SLNB increases the risk of in-transit metastasis (ITM), which is defined as intra-lymphatic tumour dissemination within cutaneous or subcutaneous tissue located between the primary lesion and draining nodal basin.[87-91] It is theorized that ITM develops when melanoma cells detach from the primary lesion and become lodged in the dermal plexus of lymphatics before reaching the lymph nodes. The development of ITM presents a therapeutic challenge and carries a poor prognosis as indicated by the new changes to the AJCC staging system.[63] Original reports citing increased ITM following SLNB must be viewed with caution because the studies often entailed pooled data from small cohorts and failed to control for important prognostic factors such as tumour thickness and ulceration.[87,92] A more recent prospective review comparing 4412 patients undergoing WLE alone, WLE with SLNB, and ELND identified a correlation between ITM and increasing Breslow depth, Clark level, and T stage.[92] A statistically significant difference between ITM and tumour recurrence was not found among the treatment groups, once adjustment was made for T stage, age, sex, tumour thickness, and site. Additional studies have concluded that it is the tumour biology, as opposed to the surgical procedure (SLNB; ELND), which dictates melanoma metastatic behavior.[93,94] Finally, a correlation between ITM and SLNB was not reported with MSLT-I, thus negating this concern.[68]

The impact that SLNB imparts on overall survival remains to be determined. The answer has been provided through the multi-institutional Sunbelt Melanoma Trial, which was a prospective, randomized clinical trial that used SLN staging to determine the need for adjuvant therapy.[95] The results have confirmed that SLNB accuracy and safety for head and neck lesions is acceptable and compares with that of truncal and extremity lesions.[96] McMasters and colleagues outlined 4 compelling reasons to use SLNB for accurate regional staging of cutaneous melanoma.[65] First, the SLNB technique provides important prognostic information to

the physician, patient, and family members in guiding subsequent treatment options. Second, SLNB helps identify patients harbouring nodal metastasis, who then may benefit from early TLND. Third, SLNB identifies patients who are candidates for adjuvant treatment such as interferon-α2b. Fourth, SLNB provides the most accurate means of regional staging. In doing so, the technique enables the identification of a homogeneous population of patients for enrollment into clinical trials. Regional metastasis is recognized as the most important prognostic factor in melanoma. Without accurate pathologic staging, stratification is impossible, and the results of clinical trials will remain inconsistent and difficult to interpret.

The final analysis of MSLT-I has provided additional insight into the potential therapeutic benefit of SLNB.[97] The authors concluded that biopsy-based staging of intermediate-thickness or thick primary melanomas provides important prognostic information and identifies patients with nodal metastases who may benefit from immediate complete lymphadenectomy. Also, biopsy-based management prolongs disease free survival for all patients and prolongs distant disease–free survival and melanoma-specific survival for patients with nodal metastases from intermediate-thickness melanomas.[68] Apart from this, the publication of the MSLT-I interim analysis was interesting because it was the first randomized, prospective trial to demonstrate that SLNB accurately identifies occult nodal metastasis, which will lead to advanced, palpable nodal disease if left in situ. The authors argue that there is no reason not to perform SLNB because a zero mortality rate was reported, and the complication rate of SLNB (10%) was significantly lower than for TLND (37%). Morton concluded that SLNB should be considered standard of care for regional staging of primary cutaneous melanoma—the key term being "staging." However, it should be understood that SLNB is a diagnostic tool for regional staging, not a therapeutic modality. Although it is not 100% accurate, SLNB is the most reliable means for regional staging. It is more sensitive and specific than CT, MRI, PET, ELND, and clinical examination.[98] McMasters astutely points out that we do not impart a survival benefit for any other cancer staging test, and therefore we should not ask the same of SLNB.

Non-Surgical Management

Melanoma is traditionally considered a radio-resistant tumour, though some studies support the use of hypofractionated radiation as an adjunct to surgery.[99] At this time, radiation is reserved for adjuvant treatment following definitive surgical treatment and as a primary treatment in those who are poor surgical candidates, with extensive facial lentigo maligna melanoma, neurotropic lesions, extracapsular spread, multiple node involvement (> 4), or recurrence.[100] Systemic chemotherapy or immunotherapy is reserved for those who have completed locoregional therapy and are at high risk for recurrence. These patients include those with ulcerated primary lesions, lesions greater than 4 mm in thickness, and those with in-transit, nodal, or distant metastases. Currently, systemic chemotherapy plays a principally palliative role in the treatment of melanoma. The wave of the future in systemic therapy for melanoma is immunotherapy. Immunomodulators such as interferon-alpha are already in use. These factors work by attempting to induce an immune response to the tumour leading to spontaneous regression. Meta-analysis data suggest that biochemotherapy with interferon and the cytokine interleukin-2 coupled with standard chemotherapeutic regimens may improve response rates but does not affect overall survival.[101]

CONFLICT OF INTERESTS

The author declares that there is no conflict of interests that could influence this work.

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