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REVIEW

Clinical utilities and biological characteristics of melanoma sentinel lymph nodes

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Abstract

An estimated 73870 people will be diagnosed with melanoma in the United States in 2015, resulting in 9940 deaths. The majority of patients with cutaneous melanomas are cured with wide local excision. However, current evidence supports the use of sentinel lymph node biopsy (SLNB) given the 15%-20% of patients who harbor regional node metastasis. More importantly, the presence or absence of nodal micrometastases has been found to be the most important prognostic factor in early-stage melanoma, particularly in intermediate thickness melanoma. This review examines the development of SLNB for melanoma as a means to determine a patient's nodal status, the efficacy of SLNB in patients with melanoma, and the biology of melanoma metastatic to sentinel lymph nodes. Prospective randomized trials have guided the development of practice guidelines for use of SLNB for melanoma and have shown the prognostic value of SLNB. Given the rapidly advancing molecular and surgical technologies, the technical aspects of diagnosis, identification, and management of regional lymph nodes in melanoma continues to evolve and to improve. Additionally, there is ongoing research examining both the role of SLNB for specific clinical scenarios and the ways to identify patients who may benefit from completion lymphadenectomy for a positive SLN. Until further data provides sufficient evidence to alter national consensus-based guidelines, SLNB with completion lymphadenectomy remains the standard of care for clinically node-negative patients found to have a positive SLN.

Key words: Melanoma; Metastasis; Review; Biologic characteristics; Sentinel lymph node; Sentinel lymph node biopsy

Core tip: This review examines the development of sentinel lymph node biopsy for melanoma as the quintessential technique for determining a patient's nodal status, the efficacy of sentinel lymph node biopsy in patients with melanoma, and the biology of melanoma metastatic to sentinel lymph nodes.

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INTRODUCTION

An estimated 73870 people will be diagnosed with melanoma in the United States in 2015, resulting in 9940 deaths from the disease[1]. The treatment for localized primary cutaneous melanoma is wide local excision (WLE) with dedicated 1-2 cm margins depending on the depth of the melanoma. WLE is curative in the majority of patients when melanoma is found and treated at an early stage. However, 15%-20% of melanoma patients develop nodal metastasis, which portends a significantly worse prognosis[2,3]. Lymph node basins are the most common site of melanoma metastasis and is often the first site involved with metastatic disease[4,5]. The presence of nodal disease, even at the microscopic level, predicts worse melanoma-specific survival (MSS), and nodal status comprises an important component of the 7th edition American Joint Committee on Cancer staging system for melanoma[2].

In particular, the presence or absence of nodal micrometastases is the most important prognostic factor in early-stage melanoma, particularly in intermediate thickness melanoma, and as such, evaluation of regional lymph nodes and detection of nodal metastasis provides powerful staging data[3,6]. Furthermore, clinically undetectable melanoma micrometastasis in the lymph nodes, which if left untreated, may develop into macrometastases which ultimately and theoretically may promote the development of metastatic distant disease[7,8]. Therefore, early detection of melanoma metastasis to the lymph nodes allows for early control of regional disease. Because of the prognostic value of nodal status in patients with melanoma, there has been extensive work over the past several decades into the development of surgical methods to ascertain nodal status in clinically node-negative patients with melanoma. This review specifically examines the development of sentinel lymph node biopsy (SLNB) for melanoma as the quintessential technique for determining a patient's nodal status, the efficacy of SLNB in patients with melanoma, and the biology of melanoma metastatic to sentinel nodes.

SENTINEL LYMPH NODE BIOPSY

Development and validation

Prior to SLNB, the management of clinically negative nodes in patients with melanoma was accomplished by means of either nodal observation alone or elective lymph node dissection (ELND) of the draining nodal basin. Although nodal observation after wide excision avoided unnecessary ELND at the index operation, patients who recurred with macroscopic nodal disease would require a delayed therapeutic lymph node dissection when these nodes became clinically evident, sometimes as long as 8-10 years later[8,9]. Prior to the introduction of SLNB, ELND at the time of WLE was the only available method to identify nodal micrometastases. The practice of ELND was challenged by prospective randomized trials that demonstrated no survival benefit over nodal observation. In addition, ELND exposed patients to increased morbidity in a group where up to 80% or more of patients were found to have no lymph node metastases after ELND[10-12]. Because staging of lymph nodes plays an important role in overall melanoma prognosis, SLNB was developed as a technique to determine the biology of the lymph node basin with significantly lower morbidity. Subsequently, ultrasound evaluation of the lymph node basin has been studied for determination of nodal metastases that can be confirmed by fine needle aspiration[13]. Although ultrasound is shown to be useful when compared with physical examination in the diagnosis of regional melanoma recurrences, the evidence for preoperative use of ultrasound in lieu of SLNB is lacking and is limited by the fact that relatively large metastatic deposits in the lymph node need to be present for visualization by ultrasound[14,15].

Morton *et al*[16] first developed the technique of intraoperative identification of the sentinel lymph nodes by taking advantage of the orderly draining pattern of lymph nodes surrounding a cutaneous melanoma. They postulated that migrating tumor cells from a primary lesion would first metastasize to a single node, or a select few nodes, before continuing on to the rest of the nodal basin and beyond. Thus, by examining the SLN for metastatic disease, one could infer that if the sentinel node is negative for malignant cells, the remaining nodes of the basin are as well. Since the first description in 1992, several studies have confirmed this theory and demonstrated that a negative SLN predicts the negative status of the remaining nodes in at least 96% of cases[17-20]. Conversely, when a SLN contains micrometastases, approximately 20% of positive SLN cases will have additional nodes beyond the sentinel node which also contain metastatic melanoma[21,22]. It should be emphasized that SLNB is not a simple biopsy procedure and it requires coordination between Nuclear Medicine

physicians to perform preoperative lymphoscintigraphy to localize the sentinel lymph nodes, surgeons to identify and resect the sentinel lymph nodes and pathologists to identify micrometastasis in the sentinel lymph nodes. Therefore, it is more appropriate to use the terminology of selective sentinel lymph node dissection. However, SLNB has been widely used in the literature, therefore, we use SLNB throughout this review.

Morton *et al*[16] first published on SLNB in 1992 and subsequently validated the role of this technique in the treatment of melanoma patients through the groundbreaking Multicenter Selective Lymphadenectomy Trial-Ⅰ (MSLT-Ⅰ). MSLT-Ⅰ was a prospective, randomized trial designed to determine whether SLNB performed in newly diagnosed, clinically lymph node negative melanoma patients conferred a survival advantage compared with observation alone of the draining nodal basins. The trial commenced in 1994 with a primary study population of patients with intermediate-thickness melanomas (the trial was subsequently expanded to include patients with thick melanomas and thin melanomas). The final analysis examined 2001 randomized patients (1347 intermediate thickness, 340 thin, and 314 thick melanomas) and was reported in 2014.

The final report of MSLT-Ⅰ demonstrated in the intermediate thickness group that the positive SLN rate was 16%. Furthermore, 10-year disease-free survival (DFS) rates were significantly higher in the SLNB arm when compared with the nodal observation arm (71.3% ± 1.8% *vs* 64.7% ± 2.3%, respectively; HR = 0.76; 95%CI: 0.62-0.94; *P* = 0.01), but no significant differences in 10-year MSS or overall survival (OS) were found between the SLNB arm and the nodal observation arm. In the thick melanoma group, the positive SLN rate was 32.9%, and a significant difference in 10-year DFS between the SLNB arm and the nodal observation arm was also seen (50.7% ± 4.0% *vs* 40.5% ± 4.7%, respectively; HR = 0.70; 95%CI: 0.50-0.96; *P* = 0.03), although again there were no significant differences in MSS and OS between the SLNB and nodal observation arms[3,20]. Due to a low number of patients, survival analyses could not be performed in patients with thin melanoma. Although a significant difference in DFS was found in MSLT-Ⅰ, it must be remembered that the primary endpoint of MSLT-Ⅰ was to determine if there was a difference in MSS between the two treatment arms (WLE with nodal observation *vs* WLE with SLNB). Unfortunately, due to the low event rate, the study proved to be underpowered to determine whether SLNB had an impact on OS or MSS.

The most critical analysis that came out of MSLT-Ⅰ was determining the prognostic value of SLN status. The study confirmed the value of SLN status as the most important prognostic factor for survival in patients with localized melanoma. Patients with a positive SLN had a significantly lower 10-year MSS (62.1% ± 4.8%) when compared with negative SLN patients (85.1% ± 1.5%; HR = 3.09; 95%CI: 2.12-4.49; *P* < 0.001). Furthermore, multivariate analysis found that SLN status was the most important prognostic predictor for melanoma recurrence and melanoma-specific death in the intermediate thickness group. The prognostic value of SLN status and the significant difference in 10-year MSS based on SLN status was also seen in patients with thick melanomas (48.0% ± 7.0% for positive SLN *vs* 64.6% ± 4.9% for negative SLN; HR = 1.75; 95%CI: 1.07-2.87; *P* = 0.03). Therefore, the status of a patient's SLN provides powerful prognostic information in patients with intermediate thickness and thick melanomas, although it is unknown if removal of microscopic disease confined to lymph nodes through SLNB has a therapeutic effect on survival.

In addition to demonstrating the prognostic significance of SLN status, MSLT-Ⅰ also showed that SLNB correctly identified patients who would later develop macroscopic nodal disease. This was shown by comparing the total rate of nodal disease that developed in both the SLNB arm and the nodal observation arm. In the intermediate thickness group, the total rate of nodal disease in the SLNB arm (positive SLN and nodal recurrence in negative SLNB patients) was 21.9% which was similar to the nodal recurrence rate of 19.5% in the nodal observation arm. Similarly, in the thick melanoma group, the total rate of nodal disease was 42% in the SLNB arm which again was similar to the nodal recurrence rate of 41.4% in the nodal observation arm. These results demonstrate that SLNB identifies the vast majority of patients with nodal micrometastases who would ultimately later develop macroscopic nodal recurrences. This allows for surgical intervention at a point when there is a lower burden of disease and when surgery may technically be less challenging.

Another observation that came from MSLT-Ⅰ is the suggestion that treatment of nodal disease at the microscopic level may impart a survival advantage compared with treatment of nodal disease at the macroscopic, clinically palpable level. This was based on the finding that 10-year MSS was significantly higher at 62.1% ± 4.8% in the SLNB group, in which a completion lymph node dissection (CLND) was performed immediately for microscopic nodal disease, *vs* 41.5% ± 5.6% in the nodal observation group, where a nodal dissection was performed for a macroscopic and clinically evident or palpable nodal recurrence (HR = 0.56; 95%CI: 0.37-0.84; *P* = 0.006). This difference remained significant even after accounting for false-negative results in the SLNB arm. However, this same significant difference was not seen in the thick melanoma group. These data potentially support findings of prior studies demonstrating an improvement in survival for immediate lymphadenectomy when compared with delayed lymphadenectomy. The potential survival advantage of early CLND after a positive SLNB is still controversial and may be due to lead time bias, but it is undeniably a prognostic marker and leads to improved local control[10,23].

These findings have been confirmed by a large, retrospective examination of 5840 patients from the Melanoma Institute Australia database[24]. In that large

study, DFS and regional recurrence-free survival were significantly improved in patients who had WLE with SLNB compared with patients who only had WLE, although MSS was not significantly different between these same two groups. However, for patients with melanomas >1-4 mm in thickness, MSS was significantly improved on univariate analysis for patients who had a SLNB, and distant metastasis-free survival was also significantly improved in patients who had a WLE with SLNB compared with patients who only had WLE.

There have also been studies that have investigated prognostic factors that predict the presence of SLN micrometastases in patients with melanomas 1.0 mm thickness. These factors help to guide selection of patients with melanoma who are most likely to benefit from SLNB, although current guidelines generally recommend SLNB for patients with intermediate thickness and thick melanomas who are clinically node-negative and medically fit for the procedure. The Sunbelt Melanoma Trial was a prospective, randomized trial designed to evaluate the role of high-dose interferon therapy in patients found to be SLN positive. In addition, it also provided a nonrandomized evaluation of SLNB[25]. A positive SLN was seen in 19.8% of patients, and in their population of 961 patients with melanomas of 1.0 mm thickness who underwent SLNB, multivariate analysis identified decreasing age, increasing Breslow thickness, Clark level, and ulceration as being significantly associated with a positive SLN.

Multiple prior studies also identified increasing Breslow thickness and decreasing age, as well as a high mitotic rate and lymphovascular invasion as predictors of a positive SLN in patients undergoing SLNB for melanoma[26-29]. The presence of ulceration is found to independently predict SLN status in many studies and, in fact, is included in current staging system because of its association with survival[19,26,29-32]. Other clinicopathologic factors have been evaluated, but the results of studies analyzing regression and tumor infiltrating lymphocytes as prognostic markers for SLN status have been mixed and inconsistent[33-37]. In 2011, a large study by the Sentinel Lymph Node Working Group, analyzing 3463 patients, confirmed many of these independent predictive factors for a positive SLN, including Breslow thickness, age, and lymphovascular invasion[37].

Technical aspects of sentinel node biopsy

The initial technique reported for SLNB made use of vital blue dye alone infiltrated into the skin at the site of the primary lesion. The blue colored draining lymphatic channel was traced to the blue sentinel node in the associated nodal basin. In the initial report, Morton *et al*[16] reported that the SLN was successfully identified in 82% of cases. Subsequently, radiolabeled colloid, which was also infiltrated at the primary lesion site in the same manner, was then utilized to aid in the detection of sentinel nodes. Furthermore, use of radiotracer introduced the use of lymphoscintigraphy, which allowed for preoperative identification of draining sentinel nodes, in addition to allowing for intraoperative identification of sentinel nodes using a handheld gamma probe. Use of both vital blue dye and radiotracer increased the identification of sentinel nodes to 97% to 99%[17,38,39]. Importantly, several studies also highlighted the importance of harvesting not only the SLN with the highest radiotracer count, but also nodes with lower counts, so as to not miss associated sentinel nodes that may be positive for melanoma micrometastases. The current literature supports the "10% rule", which entails removing all sentinel nodes with ≥ 10% radioactivity of the highest count node in order to optimize the detection of nodal metastases[25,38,40].

Morton's original description of SLNB utilized an isosulfan blue dye (lymphazurin), which was found to have adequate lymphatic uptake with a particle size large enough to become trapped in the SLN without readily traveling beyond[41,42]. Lymphazurin was found to be safe in the MLST-I trial, being associated with a very low complication rate, however subsequent studies cited an increased risk of anaphylactic reaction. Specifically, the use of lymphazurin was associated with a 1% risk for an anaphylactic reaction while other milder adverse allergic reactions included pruritis and localized swelling[43]. Methylene blue dye was used as a substitute when lymphazurin was in short supply nationally, and was found to be equally as effective in SLN identification and less expensive. However, controversy still exists over the use of lymphazurin compared with methylene blue, with studies conflicting in their efficacy and safety[44-46].

Today, the majority of sentinel nodes are identified using intraoperative radiotracer detection with or without the use of vital blue dyes, with a reported proportion of successfully mapped sentinel nodes ranging from 87% to 100%[38,47]. New radiotracers are being studied that have specific radioactive properties and that bind to specific receptors within lymph nodes. These newer radiotracers are being developed for use in both lymphoscintigraphy and intraoperative SLN detection[48,49]. Specifically, Tilmanocept was developed as a radiotracer which binds tightly not only to technetium, but more importantly, to mannose receptors *via* its attached mannose molecules. Mannose receptors are expressed in reticuloendothelial cells that are present in lymph nodes, and Tilmanocept is readily picked up and retained in these draining lymph nodes. A phase Ⅲ study demonstrated the efficacy of Tilmanocept during SLNB for melanoma patients and showed that Tilmanocept identified more sentinel nodes in more patients and also identified more sentinel nodes with melanoma when compared with vital blue dye[48]. Several additional technologies are in development, including indocyanine green (ICG) conjugated with human serum albumin, ICG labeled with Technetium-99m, and superparamagnetic iron oxide tracer[50-52].

Given the often complicated lymphatic drainage patterns, particularly of the head and neck, single photon emission computed tomography with integrated computed tomography (SPECT/CT) has been investigated as an additional modality to identify sentinel nodes.

Radiotracer is injected up to 24 h preoperatively and the sentinel nodes are then identified using SPECT. The integration of CT allows for identification of the anatomic location of the sentinel nodes. Several studies demonstrate a potential benefit of using SPECT/CT for preoperative planning and intraoperative decision making[53-56].

False negative rate of sentinel node biopsy

SLNB is a valuable staging and prognostic tool in patients with melanoma, however the efficacy of any test is in part dependent on the number of positive cases missed by a test or the false-negative rate (FNR) of that test. True positives are patients with metastatic disease in a SLN that has been verified on pathology. False-negatives are the number of patients with a negative SLNB who later develop a nodal recurrence in the dissected nodal basin due to missed microscopic nodal disease. The FNR is calculated as the number of false-negatives divided by the total number of true positives plus false negatives multiplied by 100 [false negatives/(true positives + false negatives) × 100]. There is some variation in the reported FNR across studies published since the introduction of SLNB in the early 1990's. However, the largest meta-analysis on SLNB to date by Valsecchi *et al*[47] reports data from 71 studies and includes over 25000 patients. These data demonstrated a FNR ranging from 0% to 34%, with a weighted summary estimate of 12.5%. The FNR was inversely associated with patients who underwent successful SLN mapping using lymphoscintigraphy with or without the use of dyes. This meta-analysis also demonstrated an additional association of FNR with an increasing length of follow-up and studies found to be of higher quality.

Complications from sentinel node biopsy

SLNB is a less morbid procedure when compared with CLND, which is the standard of care for patients with melanoma nodal metastasis. Prior studies describe the morbidity associated with CLND, including wound separation, cellulitis, hematoma/seroma, lymphedema, and nerve injury, with some studies citing a complication rate as high as 65%[57-59]. The Sunbelt melanoma trial reported on the complications seen in patients undergoing SLNB alone *vs* patients who underwent a SLNB followed by CLND for a positive SLN[60]. The overall complication rate in the SLNB alone group was approximately 5% and the most frequent complications were hematoma/seroma and wound infection. The most frequent complications in the group that had SLNB followed by CLND included lymphedema, wound infection, hematoma/seroma formation, and sensory nerve injury, with a total complication rate of 23.2%. The difference in complications was particularly pronounced for patients undergoing inguinal CLND (31.5%) compared with patients undergoing axillary CLND (4.6%). MSLT-Ⅰ also reported on the complication rate seen in patients having SLNB. When all of the various complications are totaled for patients who had SLNB alone, the complication rate was approximately 12% to 13% compared with the nearly 40% rate of complications seen in patients who also had CLND for a positive SLN.

SPECIFIC CLINICAL SCENARIOS

Thin melanoma

In the United States, the majority (> 70%) of patients who present with melanoma are diagnosed with thin melanomas (up to 1 mm in Breslow thickness)[61]. Patients with thin melanomas have a low risk of harboring a lymph node metastasis due to their early diagnosis[29]. The role of SLNB in thin melanoma patients is not clearly defined and current guidelines do not recommend its routine use, but rather recommend discussion at the individual patient level[6,62]. The risk of SLN metastases in thin melanoma patients is reported to range from as low as 1% to up to 18%, however the majority of these studies report a positive SLN in approximately 5% to 10% of thin melanoma cases[29,37,63-66]. Despite many studies describing independent predictive markers for a positive SLN in thin melanoma patients, there has been no consensus reached over which factors to utilize, and the factors found to be significant vary from study to study[29,65-69]. Additionally, there are inconsistent results when reporting the significance of SLN status in thin melanoma patients[29,64]. The most frequently associated risk factors for SLN metastases in patients with thin melanoma are Breslow thickness, Clark level, ulceration, mitotic rate, and younger age[29,63-66,69,70].

The decision to offer nodal staging depends in part on the risk threshold utilized. For SLNB, many surgeons utilize a 5% risk threshold for nodal metastasis as a criteria for potentially offering nodal staging. This is based in part on the low complication rate (approximately 5%-10%) and the low FNR (approximately 10%-15%) for SLNB. A 5% risk for a positive SLN is generally seen in melanomas with a Breslow thickness $\geqslant$ 0.75 mm and this criteria is frequently used as a threshold for offering SLNB in patients with thin melanoma. Conversely, the rate of SLN metastases in melanomas < 0.75 mm falls below 5% and the prognostic information gained from nodal staging becomes limited in these cases[29,63,64,71,72]. Clark level has also been shown to be prognostic for SLN metastasis, however it is unknown if this is a truly independent predictive marker in the face of Breslow thickness. Ulceration appears promising as a predictive marker for a positive SLN in thin melanoma patients, but ulceration is rarely seen in melanomas < 0.75 mm. More importantly, if a thickness $\geqslant$ 0.75 mm is utilized as the primary criterion for offering nodal staging, ulceration status becomes less crucial as a marker to predict SLN disease since the vast majority of ulcerated thin melanoma cases already are in melanomas $\geqslant$ 0.75 mm. Mitotic rate has also been evaluated as a potential predictive factor and has recently been incorporated into the AJCC staging system as prognostic for MSS in thin melanoma patients. However the predictive value of mitotic rate for SLN metastases is inconsistent in studies done on thin melanoma patients, possibly due to the diffe-

rences in evaluating and classifying mitotic rate across studies[29,32,63,72-77]. Based on current evidence, Breslow thickness ⩾ 0.75 mm appears to be the most consistent factor that independently predicts a > 5% risk for SLN micrometastases.

Thick melanoma

Thick melanomas (greater than 4 mm in Breslow thickness) represent approximately 5% of melanoma cases, but carries an approximately 50% survival rate in patients with thick melanoma, compared with over 90% for patients with thin melanoma[2,61]. Given that distant disease develops in a relatively high percentage of patients with thick melanoma (approximately 30% to 40% will develop distant metastasis), use of SLNB in this population is debated[78]. Indeed, many retrospective studies demonstrate that patients with thick melanoma have a dramatically increased risk of occult metastases. These studies also report variable results on the clinicopathologic factors that impact SLN positivity and on the prognostic significance of SLN status for patients with thick melanoma[20,78-85].

Approximately 25% to 40% of patients with thick melanoma will have nodal disease, and it is this population of thick melanoma patients who may potentially benefit from nodal staging. The majority of studies that have looked at SLNB in thick melanoma patients, particularly more recent studies, appear to show that SLN status is still prognostic in patients with thick melanoma. Data from the Sunbelt Melanoma Trial and the study by Gajdos *et al*[78] demonstrate that there is a significant difference in OS based on SLN status. A recent study by Yamamoto *et al*[86], the largest to date to examine SLNB in thick melanoma patients, demonstrated an overall and disease-specific advantage for patients found to be SLN negative, suggesting that SLNB offers valuable prognostic information for patients with thick melanoma. Based in part on the results of these studies, the published guidelines state that SLNB may be recommended for patients with thick melanoma to allow for accurate staging of disease[62,87].

Desmoplastic melanoma

Desmoplastic melanoma (DM) represents less than 4% of all cutaneous melanomas and is more frequently seen in older patients. It is found most commonly on the head and neck and is often a thicker tumor at presentation when compared with non-DM[88-90]. DM is divided into two histologic subtypes based on the extent of desmoplasia. Based on the Memorial Sloan Kettering Cancer Center classification system, pure DM consists of a spindle cell melanoma with ≥ 90% desmoplasia while a mixed DM has desmoplasia involving < 90% but > 10% of the spindle cell melanoma. DM is often described as being locally aggressive and having a high potential for local recurrence.

The role of SLNB in the management of DM is debated. Older studies on DM report nodal metastasis rates of approximately 30% to 40%, however contemporary single institution series demonstrate nodal metastasis rates of 9% to 18%. Furthermore, studies cite lower rates of nodal metastases for DM compared with conventional melanoma of equivalent thickness[90-95]. The positive SLN rate reported in the literature for DM ranges relatively widely from 0% to 18%[92-101]. If one excludes the small studies that report a zero rate of a positive SLN and also exclude smaller studies with less than 50 patients, the positive SLN rate for DM then ranges from 6% to 14%[92-94,96,98,101]. A large SEER database study on DM demonstrated a positive SLN rate of 2.8%[99].

In addition, clinicopathologic predictors of SLN disease in DM have also been studied. Several studies demonstrate a significantly higher SLN metastasis rate in patients with mixed DM[90,92,93,96-99,101]. The positive SLN rates in these studies for patients with mixed DM ranges from 14% to 25% while the positive SLN rate for patients with pure DM is lower at 2% to 9%. Gene expression profiling demonstrates that DM is molecularly distinct from non-DM and most closely mimics sarcomas molecularly which would explain the reason for the low incidence of lymph node metastases among patients with pure DM[102]. Again, if a 5% risk threshold for nodal disease is used as a criteria for offering nodal staging, SLNB should in general be offered to patients with mixed DM. However, controversy exists as to whether SLNB should be offered to patients with pure DM, particularly since some studies demonstrate that the SLN metastasis rate falls below 5%.

Acral lentiginous melanoma

Acral lentiginous melanoma (ALM) is the least common of the four major histologic subtypes of cutaneous melanoma, representing approximately 2% to 10% of all cases. ALM accounts for a markedly increased proportion of melanoma cases in darker-skinned populations[103,104]. ALM is shown to exhibit more aggressive features and is associated with poorer survival when compared with non-ALM[105]. The role of SLNB in ALM is unclear, however, the three largest studies all demonstrate a survival advantage in patients with a negative SLNB at the time of resection, suggesting that SLNB plays an important prognostic role in the management of patients with ALM[105-107]. Clinicopathologic factors predictive of SLN disease in ALM have not been well studied, and no study to date has elucidated independent predictive factors.

Head and neck melanoma

Head and neck melanomas (HNM) are shown to be more aggressive and carry an increased mortality when compared with melanomas in other anatomic locations. The role of SLNB and the clinicopathologic factors that predict a positive SLN in head and neck cases are not well defined in the literature. The difficulty of SLNB in HNM is partially attributable to the inconsistent lymphatic drainage patterns of the head and neck, as well as technical and anatomic considerations. For these reasons, lymphoscintigraphy and now SPECT/CT is frequently used preoperatively for HNM[108,109]. These difficulties also likely contribute to the variation in the FNR reported for

SLNB performed for HNM[110-112].

Recent publications by Parrett *et al*[111] and Fadaki *et al*[112], which represent two of the larger studies of SLNB in HNM, confirm the predictive value of younger age, ulceration, and Breslow thickness for SLN metastasis in HNM, which is consistent with results found for melanomas at other sites. Additional findings in these two studies are lower rates of SLN metastases for HNM but worse DFS and OS, findings that are also confirmed in prior studies[25,113]. Interestingly, the lower positive SLN rate seen in some studies does not portend improved survival, as would be expected given that SLN status is shown to be the most significant prognostic indicator in melanomas of other sites[111,112]. Although the mechanism of this paradoxical finding remains unclear, the use of SLNB for HNM is still recommended. In addition, the lentigo maligna melanoma subtype frequently occurs on the sun-exposed head and neck areas of older patients and has been shown to carry an improved prognosis. However, despite the improved prognosis, lentigo maligna melanoma is treated similarly to all other melanomas of the head and neck with regard to nodal staging and SLNB is also indicated for this subtype of melanoma[114].

Truncal melanoma

Melanoma of the trunk is the most common site for melanoma in men[115,116]. While risk factors for the development of truncal melanomas have been evaluated, few studies exist assessing the value of SLNB specifically for truncal melanomas. The MSLT-Ⅰ study demonstrated that truncal melanomas predicted a worse prognosis when compared with extremity melanomas in patients who underwent SLNB (HR for death from melanoma: 1.91; 95%CI: 1.26-2.88; P = 0.002)[20]. The use of SLNB in truncal melanoma can present a particular challenge, as the draining lymph node basin and sentinel nodes may be present in more than 1 nodal basin and drainage may occur in more than one direction: Cranial or caudal, and may cross the midline, emphasizing the vital role of lymphoscintigraphy in performing SLNB in this location[117,118]. Despite these issues, guidelines recommend use of SLNB for truncal melanomas.

Extremity melanoma

The lymphatic drainage of the upper and lower extremities is typically described as more predictable, although some have described more variable drainage patterns. For instance, drainage in the upper extremities can be to the epitrochlear nodes while drainage in the lower extremities can be to the popliteal nodes. Previous studies show conflicting and inconsistent results regarding the significance of the location of a primary melanoma on SLN status and survival. Some of the larger studies to compare the prognostic value of SLNB in extremity melanoma as compared with other sites include MLST-I, the Sunbelt Melanoma trial, and the large single institution study by Fadaki *et al*[112] MSLT-Ⅰ and the Sunbelt Melanoma trial both demonstrated that location of a melanoma on the extremity was prognostic for recurrence, while Fadaki *et al*[112] showed improved MSS and OS for patients with extremity melanoma when compared with patients with truncal and head and neck melanomas[20,25,112].

IS COMPLETION LYMPHADENECTOMY INDICATED FOR ALL POSITIVE SENTINEL NODE PATIENTS?

CLND is currently recommended for all patients with a positive SLN. Nodal recurrence after a positive SLNB ranges from approximately 4% to 5% in MSLT-Ⅰ and Sunbelt Melanoma trials to 15% as reported by Wong *et al*[119]. The goal of CLND is to improve regional disease control as well as to improve survival. However, no direct evidence demonstrates that CLND definitively imparts a survival benefit, although MSLT-Ⅰ does suggest improved survival for patients who underwent CLND after a positive SLNB when compared with patients who underwent a delayed nodal dissection for a macroscopic nodal recurrence (62% *vs* 41% MSS, HR = 0.56, 95%CI: 0.37-0.84; P = 0.006)[20]. This survival benefit in MSLT-Ⅰ was seen only when all node-positive patients were compared as opposed to analyzing the entire study population. In comparing the initial treatment arms (WLE with SLNB followed by CLND for a positive SLN *vs* WLE with nodal observation followed by nodal dissection for a nodal recurrence), there was a significant difference in DFS favoring the arm treated with SLNB followed by CLND, however there was no significant difference in MSS or OS. Therefore, no definite conclusions can be made based on the results of MSLT-Ⅰ as to whether performing CLND provides a survival benefit. Because the survival benefit of CLND is controversial, the routine use of CLND has been challenged[120,121].

The primary reason CLND is recommended for a positive SLN is for regional disease control. Approximately 15% to 20% of patients with a positive SLN are found to have additional disease in the CLND specimen. Furthermore, results from MSLT-Ⅰ also suggest that treatment of disease at the microscopic level through CLND for a positive SLN has less morbidity, specifically less lymphedema, than a nodal dissection performed for a macroscopic nodal recurrence[80]. Possible reasons for this may be that more nodal tissue may be involved with tumor and more tissue may need to be dissected for macroscopic disease, thereby increasing the amount of lymphatics that are disrupted. However, some argue that 80% to 85% of positive SLN patients are needlessly exposed to the morbidity of CLND since no additional nodal disease is found in these cases[119,122]. There have been numerous studies evaluating clinicopathologic factors that may predict additional nodal disease after CLND[123-131]. The ability to predict which positive SLN patients are at higher risk for additional nodal disease would allow one to offer CLND to patients who may benefit the most from this procedure. However, no factors are consistently reported, and predictive markers are extensively debated.

Several classification systems to predict non-SLN disease are reported in the literature, although none are universally accepted[125,126,128-131]. The most promising factor to predict which patients may not need a CLND is a subcapsular nodal deposit in the SLN measuring < 0.1 mm in maximal diameter. This factor predicts for an approximately 5% chance for additional nodal disease, however other studies have not shown the same results[123,127,131]. Currently, there is no consensus and no reliable way to predict which patients with a positive SLN will have additional nodal disease. As a result, a blanket recommendation for CLND for all positive SLN patients is seen in current guidelines.

The MSLT-Ⅱ trial is an ongoing randomized trial, which aims to clarify the role of CLND in patients with a positive SLN. Accrual has just completed and MSLT-Ⅱ will analyze prospective survival data between patients with tumor-positive sentinel nodes who undergo CLND with those who are randomized to nodal observation. Based on the current controversy surrounding CLND, the results of MSLT-Ⅱ are eagerly awaited although it will be several years before any results are reported. Additionally, the European Organization for Research and Treatment of Cancer - Minimal Sentinel Node Tumor Burden study (EORTC - MINITUB) is also underway to evaluate survival in patients with minimal tumor burden who undergo nodal observation compared with those who undergo CLND. There has already been a similar trial known as the German Dermatologic Oncology Group (DeCOG)-SLT trial. The results of the DeCOG-SLT trial were recently presented as an abstract at the American Society of Clinical Oncology Annual Meeting in 2015. This was a phase Ⅲ study which randomized positive SLN patients to either CLND or nodal observation. The trial showed that CLND after a positive SLNB did not prolong survival in positive SLN patients when compared with nodal observation alone[132]. In addition, there were no differences in 3 and 5 year recurrence-free survival, distant metastasis-free survival (DMFS) and MSS after a median follow-up of 35 mo. However, it is important to note that the authors did not present data in terms of regional disease control. Although the authors suggest these data provide sufficient evidence to end the practice of CLND for all positive SLN patients, further data must be presented to fully interpret the findings particularly in terms of regional disease control. The clinical and pathologic characteristics of the study population must also be considered, taking into account the location of the primary melanomas, heterogeneity of micrometastases, and melanoma thickness. While it is likely that certain subgroups of patients may not benefit from CLND, caution is warranted against abandoning the standard of care until the prospective data of the MSLT-Ⅱ and DeCOG-SLT trials are fully available and critically reviewed.

BIOLOGY OF SENTINEL NODES

Morton *et al*[133] described an "incubator" model in which melanoma metastasizes in an orderly process first to the SLN, which serves as the "gateway", followed by spread to other non-sentinel nodes in the draining nodal basin. However, in approximately 15%-20% of cases, melanoma will spread to distant sites without the development of disease in the draining nodal basin[134]. This phenomenon gives credence to the "marker" model in which metastatic disease in the SLN serves as a marker of disease that has already spread microscopically to distant sites[133]. The "incubator" model of SLN disease theoretically suggests that surgical treatment of nodal metastasis can stop further spread of disease while the "marker" model suggests that systemic therapy is required to treat distant disease. It is debated as to which model accurately represents the biology of SLN metastasis, however it is likely that both models are correct and that SLN disease correlates to each model in specific subsets of patients.

As the mechanism of metastatic melanoma spread is most commonly through lymphatic flow, understanding the implications of these factors in the primary tumor and associated lymph node environment is key[135-138]. Studies evaluating patients with melanoma and breast cancer, as well as studies in animal models, demonstrate the contribution of the molecular, cellular, and anatomic aspects of tumor cells towards the development of nodal micrometastases. Several studies highlight the ability of identifying growth factor overexpression and increased tumor vascularity to predict which patients are more likely to have a positive SLN[139-143]. Increased angiogenesis and lymphangiogenesis occur both at the site of primary malignancy and in the lymph node basin *via* the release of growth factors, most notably, VEGF[140,142,144,145]. Not only does increasing the number of lymphatic vessels increase the likelihood of tumor cell delivery to lymph nodes, but recent evidence also suggests these growth factors promote tumor cell recruitment in lymph nodes and modify the local immune environment to aid in cancer cell survival[146,147]. Additionally, increased tumor cell flow towards lymph nodes has been demonstrated to be augmented by increased intratumoral interstitial fluid pressure causing widened inter-endothelial openings, thus allowing easier entry into lymphatics[136,148].

Tumor infiltrating cells (TILs) are thought to be a host response to tumor cells and may play a role in controlling tumor growth in the lymph node basin[149]. Cells include tumor-specific cytotoxic T-cells and antigen-presenting dendritic cells. One mechanism of decreased TILs within the associated lymph nodes is a reduction in the number of antigen-presenting cells and activated T-cells, and an increase in the number of suppressor T-cells caused by immune suppressing cytokines originating from the primary tumor cells[150-152]. *Via* the mechanisms of increased lymph flow, these immune suppressing cytokines create a susceptible local environment in the nodal basin by inhibiting the tumor-specific cytotoxic T-cells described above. The immune suppressed environment is ideal for the growth of metastatic tumor cells[138,151,153]. The presence of increased TILs and, conversely, the

paucity of TILs in the primary melanoma have been demonstrated to be independently predictive of SLN status and also independently associated with survival in melanoma patients[34,154-156].

BIOMARKERS OF MELANOMA METASTASIS IN THE SENTINEL NODE

Advancement in the molecular understanding of melanoma and its gene expression profile has identified a variety of genetic, epigenetic, and protein biomarkers that show great promise as both predictive and prognostic markers of disease[21,157]. For example, expression levels of the NCOA3, SPP1, and RGS proteins each serve as independent predictors of SLN metastasis and DFS[158-160]. When combined as a multimarker index, the marker overexpression index is the most significant independent predictor of SLN metastases and DFS in two cohorts of melanoma patients. Such molecular markers show great promise in identifying patients who are high-risk for SLN metastases and would potentially benefit from SLNB[21,161].

Molecular evaluation of sentinel nodes at the time of SLNB also serves as a predictive indicator of disease outcomes. The use of quantitative real-time reverse transcriptase-polymerase chain reaction (qRT-PCR) assay of sentinel nodes at the time of operation can identify clinically relevant metastases that are missed by traditional histopathology[162,163]. Known as molecular upstaging, this method utilizes RNA biomarkers, and was evaluated in 214 melanoma patients with 10 years of follow-up data. Patients with qRT-PCR positive sentinel nodes had significantly worse OS and DFS compared with histopathologically negative sentinel nodes, demonstrating its potential value in detecting metastases in the sentinel nodes of patients with melanoma[163,164].

A 28-gene signature platform was developed that stratifies patient with localized cutaneous melanoma into low and high risk groups for the development of metastatic disease[165]. This study was subsequently expanded to evaluate this gene signature platform in 217 patients who had a SLNB[166]. Both the gene signature platform and SLNB were evaluated in terms of ability to predict DFS, DMFS and OS. Both the gene signature platform and SLNB were significant predictors of DFS and DMFS on multivariate analysis, while only the gene signature platform was a significant predictor of OS on multivariate analysis. Furthermore, utilizing both the SLNB results and the gene signature platform appeared to improve risk stratification. However, these results should be viewed carefully and have only been shown in a relatively limited number of patients. Further study is needed to validate the results of these studies.

Recently, the Cancer Genome Atlas Network published a framework for genomic classification of cutaneous melanoma. Four subtypes were identified based on the most significantly mutated genes in 333 melanomas: Mutant BRAF, mutant RAS, mutant NF1, and triple-wild-type. Although there was no survival association with the genomic classification, improved survival was found with samples enriched for immune gene expression associated with lymphocyte infiltration. These data support the correlation of tumor infiltration by lymphocytes and survival in melanoma patients described previously[167].

Microphthalmia transcription factor (MITF), a transcription factor involved in melanocyte differentiation and homeostasis, has been previously found to play an important role in controlling carcinogenic transformation[168,169]. Recently, Naffouje *et al*[170] demonstrated that MITF immunostaining in the primary tumor is associated with SLN status, suggesting its potential as a predictor of occult lymph node metastases. In addition, increased MITF expression was a significant prognosticator of DFS and OS in this study of 94 melanoma patients.

SUMMARY

The majority of patients with cutaneous melanomas are cured with WLE, however current evidence supports the use of SLNB given that 15% to 20% of patients will develop regional node metastasis. The results of prospective, randomized trials have clearly demonstrated the prognostic value of SLNB and have guided practice away from more invasive nodal staging techniques. Use of SLNB for melanoma is now standard of care, and given the rapid advancement in molecular and surgical technologies, the technical aspects of diagnosis, identification, and management of regional lymph nodes in melanoma will continue to evolve and to improve, particularly in identifying patients who should and should not be offered SLNB in specific clinical situations. Additionally, with ongoing high-quality trials examining the role of SLNB in melanoma, patients may be identified who may specifically benefit from CLND or who may undergo nodal observation for a positive SLN. Until further data provide sufficient evidence to alter consensus-based practice guidelines, SLNB with CLND remains the standard of care for clinically node-negative melanoma patients. Future histologic and molecular studies of the primary melanoma microenvironment and SLN micrometastasis may yield new insight into the molecular mechanisms that promote spread of melanoma cells to sentinel lymph nodes and beyond.

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