Evolving management of positive regional lymph nodes in melanoma: Past, present and future directions

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Abstract

Sentinel lymph node (SLN) biopsy has become the standard of care for lymph node staging in melanoma and the most important predictor of survival in clinically node-negative disease. Previous guidelines recommend completion lymph node dissection (CLND) in cases of positive SLN; however, the lymph nodes recovered during CLND are only positive in a minority of these cases. Recent evidence suggests that conservative management (*i.e.* observation) has similar outcomes compared to CLND. We sought to review the most current literature regarding the management of SLN in metastatic melanoma and to discuss potential future directions.

Introduction

The management of regional lymph nodes (LNs) in melanoma has been a topic of controversy for decades. The introduction of sentinel lymph node (SLN) biopsy was a major milestone, and it became the standard of care for lesions with Breslow thickness >1 mm.[1,2] Following a positive SLN biopsy, completion lymph node dissection (CLND) was generally advocated in order to halt regional disease and to increase survival. However, recent evidence disputes these recommendations. Here, we review the most current literature regarding the management of positive SLN biopsies in patients with melanoma.

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Elective lymphadenectomy

In 1892, Snow recommended ELND for all patients with melanoma, regardless of the presence of clinical regional nodal metastases.[3] Subsequently, four randomized trials failed to demonstrate an overall survival (OS) benefit for ELND.[4-7] In two of these, the WHO (World Health Organization) ELND Trial and the Intergroup Melanoma Trial, select subgroups of patients with clinically negative LNs who underwent ELND did have better outcomes than wide local excision (WLE) alone.[6,7] These subgroups included patients with primary tumors without ulceration or with thickness between 1 and 2 mm (*vs*. thicker tumors), patients with extremity (*vs*. truncal) location and patients younger than 60 years old.[7] With the introduction of the SLN biopsy technique, ELND has largely been replaced.

Sentinel lymph node biopsy-based management

SLN biopsy with lymphatic mapping was introduced for individualized management of regional LNs.[8] Most experts advocate the triple technique, which consists of preoperative lymphoscintigraphy, perioperative injection of blue dye (isosulfan blue or methylene blue) and intraoperative gamma-probe detection.[8,9] The sensitivity of this technique is approximately 99%.[8]

The overall incidence of positive SLNs in patients undergoing SLN biopsy ranges from 15 to 20%. The rate depends on the primary tumor thickness: 35-40% of T4 tumors and 5-7.8% for T1 lesions.[10-12] Several other prognostic factors are associated with increased risk of SLN-positivity, including Breslow tumor thickness, ulceration, high mitotic rate, young age, lymphovascular invasion and tumor location, especially truncal.[13-18]

According to the American Joint Committee on Cancer (AJCC) 8th edition staging manual and 2018 National Comprehensive Cancer Network (NCCN) guidelines, SLN biopsy should be considered in all melanoma patients with stage T1b (<0.8 mm with ulceration or 0.8-1 mm with or without ulceration) or greater.[19,20] A consensus for which patients with T1a melanomas (<0.8 mm without ulceration) should undergo SLN biopsy has not yet been established. Several experts advocate that SLN positivity rates in T1a lesions are sufficient to justify consideration of SLN biopsy.[21] NCCN guidelines recommend

that the decision to perform SLN biopsy in these patients should be based on specific tumor characteristics.[20] The role of SLN biopsy in thick melanoma is also controversial, considering the substantial risk for distant metastases regardless of LN involvement. Additionally, no therapeutic benefit from SLN biopsy-based management in these patients has yet been shown.[22] However, positive SLN status can be used as eligibility criteria for adjuvant therapy in specific subgroups of patients, such as those with stage 3 BRAF-mutant melanoma. Without a known SLN status, these patients could be ineligible for additional therapeutic options.[23]

In 2018, the Society of Surgical Oncology (SSO) released updated guidelines for the management of SLN in melanoma.[24] These new guidelines mandate that routine SLNB is not recommended for patients with thin melanomas that are T1a (non-ulcerated <0.8 mm in Breslow thickness) and may be a consideration for thin melanomas that are T1b (0.8-1.0mm Breslow thickness or 0.8 mm Breslow thickness with ulceration) with sufficient patient counseling. SLN biopsy is recommended for all intermediate-thickness (T2 or T3, Breslow thickness 1.0-4.0 mm) and may be recommended for thick melanomas (T4, >4.0 mm Breslow thickness) with patient counseling about potential risks and benefits.[24]

SLN status is important to ascertain because it is one of the most significant clinicopathological prognostic factor to determine survival in patients with melanoma. The 5-year melanoma-specific survival (MSS) rate is 73% for positive SLNs compared with 97% for patients with negative nodal disease.[25] While the prognostic strength of SLN status is less in thin and thick melanomas than intermediate-thickness, it is still widely regarded as the standard of care in these patients.[22]

Pathological assessment of sentinel lymph node

The pathological assessment of a SLN biopsy provides information to guide management on an individualized basis. Several studies have proposed different methods and protocols for SLN detection. The European Organization of Research and Treatment of Cancer (EORTC) Melanoma Group has developed specific recommendations to standardize the pathological assessment of SLN disease.[26,27]

According to their recommendations, the description of a positive SLN should encompass i) the microanatomic location based on the Dewar classification;[28] ii) the tumor burden according to the Rotterdam criteria[29] for the maximum diameter of the largest lesion; and iii) the SLN tumor burden stratified per category; <0.1 mm, 0.1-1.0 mm, or >1.0 mm.

Dewar *et al.* defined the different microanatomic locations of a metastatic lesion within the sentinel node. The location can be defined by one of five descriptors: subscapsular, parenchymal, combined, multifocal, and extensive, which is defined by any metastasis larger than 5 mm or any lesion with extracapsular spread. Patients with SLN metastases that are defined as subcapsular have been found to have an extremely low probability of non-SLN involvement, and as such could potentially be managed without further surgical intervention.[28]

The Rotterdam Criteria classify the maximum diameter of the largest lesion in the SLN into three categories: <0.1 mm, 0.1-1 mm and >1 mm.[29] This classification has been validated by several studies.[29-31] Patients with minimal SLN tumor burden (<0.1 mm) have similar prognostic factors and outcomes as SLN-negative patients.[30] Five-year survival rates in lesions <0.1 mm are between 90-100%, and rates of non-SLN-positivity are approximately 0-12%.[29-31] Some experts believe that these microscopic lesions should be treated conservatively.

More recently, molecular detection of malignant cells using reverse transcriptase polymerase chain reaction (RT-PCR) has been proposed to decrease false negative rates associated with pathological evaluation using conventional staining and immunohistochemistry.[32] RT-PCR is proposed as a means of increasing the sensitivity of traditional histology and immunohistochemistry but is not itself considered superior to immunohistologic examination.

Sentinel lymph node biopsy-based management vs observation

The Multicenter Selective Lymphadenectomy Trial-I (MSLT-I) was a prospective, international, randomized trial which was designed to determine the survival advantage of early nodal intervention (SLNB plus CLND if positive) *vs* observation for patients with primary cutaneous melanomas with Breslow thickness of 1.2-3.5 mm or those with any Breslow thickness with Clark level IV and V.[2,33,34] The trial also intended to determine whether SLN biopsy could be used to identify patients with clinically occult nodal metastases and whether immediate CLND yielded better outcomes than lymphadenectomy performed only when nodal recurrence was revealed during observation. The results of this trial showed that the pathologic status of the SLN was an important prognostic factor in melanoma. All patients who underwent SLN biopsy and subsequent CLND experienced prolonged 10-year disease-free survival (DFS) as compared to observation alone (intermediate-thickness melanomas, 71.3±1.8% *vs* 64.7±2.3% and thick melanomas, 50.7±4.0% *vs* 40.5±4.7%). Patients with nodal metastases from intermediate-thickness melanomas also experienced prolonged 10-year DFS and MSS.[33] The MSLT-I helped establish SLN biopsy as the gold standard staging technique, and it is currently widely accepted as such in the guidelines of most national and professional organizations.[34-37]

Management of sentinel lymph node-positive melanoma

Completion lymphadenectomy

A survey-based study in 2012 demonstrated that the majority of surgeons (91.8%) perform CLND after positive SLN.[38] Despite its popularity, however, the complications after CLND are considerable and include events such as wound infection, dehiscence, and lymphedema. Morbidity rates associated with CLND are reported up to 20-50% for axillary dissections and 17-90% for inguinal dissections.[22,39] Furthermore, only 12-25% of specimens from CLND contain additional nodes (non-SLN) with metastatic disease.[18,40-42] This finding implies that more than two-thirds of patients have metastatic disease only in SLNs, and would derive no clinical benefit from CLND. Therefore, the identification of low-risk patients with positive SLNs who could be treated conservatively was warranted to reduce unnecessary surgery and its associated morbidity.

Several studies attempted to identify patient, tumor and SLN characteristics associated with non-SLN-positivity.[43-49] Breslow thickness, presence or absence of ulceration, and SLN tumor burden correlate with the likelihood of additional non-SLN-positivity.[45-49] A large multicenter retrospective series suggests that patients with SLN sub-micrometastasis (<0.1 mm in maximum diameter) have an identical 5-year survival rate as SLN-negative patients with low risk to develop nodal recurrence.[27] This group of

patients could also potentially be spared from a CLND and instead might undergo other adjuvant therapy regimens.

Nine retrospective studies compared SLN-positive patients who underwent CLND versus observation alone[50-60] (Table 1). Despite minor variations, all but one[55] failed to demonstrate improvement in MSS in patients undergoing CLND. Recently, the MSLT-II, an international, multicenter, randomized phase III trial assessed the usefulness of CLND in patients with melanoma and positive SLN metastases.[59] It consisted of a screening phase in which patients were enrolled before SLN biopsy and a randomization phase in which CLND was compared with observation and nodal ultrasonography. The final analysis is expected to be published in 2022, but initial findings have demonstrated that immediate CLND increased the 3-year DFS (68±1.7% *vs* 63±1.7%) and the rate of regional disease control at 3 years (92±1.0% *vs* 77±1.5%) but did not increase 3-year MSS (86±1.3% and 86±1.2%) among these patients with melanoma and SLN metastases.[59] It is noteworthy that most patients in the trial had a low-volume nodal tumor burden. Some subjects had only molecular indications of melanoma in the SLN, determined by PCR (12% of the randomized study population). Therefore, it is possible that these patients may have had better outcomes than those in retrospective studies due to a lower SLN tumor burden. Patients with a larger SLN burden are more likely to have non-SLN metastases than patients with a smaller tumor burden.

The MSLT-II also confirmed that the pathologic status of non-SLN has independent prognostic value, while the number of involved SLN was not significantly related to MSS. In this trial, non-SLN metastases were identified in the observation group via ultrasound or physical exam and were present at higher rates than the dissection group at both 3- and 5-year follow-up (22.9% *vs* 17.9% at 3-years, 26.1% *vs* 19.9% at 5-years). For patients who undergo observation rather than lymphadenectomy, lack of a non-SLN status may prevent appropriate risk stratification and selection of adjuvant therapy.

The findings of MSLT-II are congruent with those from another trial, DeCOG-SLT.[61] This study included 483 patients with positive SLN who were randomized to CLND or nodal observation. The results demonstrate that there is no significant difference in the 3-year distant DFS (77% in CLND arm *vs* 77% in observation arm), a dramatic shift from previous school of thought and practice, as described above. However, it is important to note that this study was underpowered due to lower than expected event rate and more patients with smaller metastases than previously reported.[61] The Sunbelt Melanoma Trial compared observation *vs* CLND in 214 melanoma patients with tumor-negative SLN by conventional

Table 1. Summary of studies comparing CLND and observation after positive SLNB.

Study	Year	Countries	Design	Name of Trial	Disease-Free Survival				Melanoma-Specific Survival			
					3-year		5-year		3-year		5-year	
					CLND	no CLND	CLND	no CLND	CLND	no CLND	CLND	no CLND
	3-year											
Wong[50]	2006	United States, Australia, Israel, Netherlands	Retrospective		88%	80%			74%	80%		
van der Ploeg[51]	2009	Netherlands	Retrospective		60%	83%			80%	100%		
Leiter[61]	2016	Germany	Randomized clinical trial	DeCOG-SLT	72.3%	69.7%						
Faries[59]	2017	United States Australia, Italy, Netherlands, United Kingdom, Sweden, Switzerland, Canada, Germany, Israel, Spain	Randomized clinical trial	MSLT-II	68%	63%			86%	86%		
	5-year											
Kingham[52]	2010	United States	Retrospective				40%	45%			58%	68%
van der Ploeg[58]	2012	Netherlands, Poland, United Kingdom, Italy, Belgium, France	Retrospective								67%	66%
Satzger[53]	2014	Germany	Retrospective				57%	70%			67%	82%
Bamboat[54]	2014	United States	Retrospective				40%	28%			60%	68%
McMasters[62]	2016	United States	Randomized Clinical Trial	Sunbelt Melanoma Trial			84%	79%				
Lee[55]	2016	United States	Retrospective				55%	48%			73.7%	65.5%
Mosquera[56]	2017	United States	Retrospective								72.2%	70.4%
Melstrom[57]	2014	United States, Australia	Retrospective									

Adapted from Macedo *et al.*[60]

pathology but who had melanoma detected in the SLN by RT-PCR. In this analysis, there was improved DFS (84.0% in CLND arm *vs* 79.4% in observation arm) but not OS (85.9% in CLND arm *vs* 85.5% in observation arm). An important limitation of this study is that only patients with conventionally SLN-negative but RT-PCR-positive were included.[62]

The newest SSO guidelines for management of positive SLNB reflect these findings. The recommendation for the role of CLND is that CLND or careful observation are both options for patients with low-risk micrometastatic disease, based on consideration of clinicopathologic factors. A number of important high-risk features are those of patients who were not included in the trial criteria of MSLT-II, including extracapsular spread or extension, concomitant microsatellitosis of the primary tumor, more than 3 involved nodes, more than 2 involved nodal basins and immunosuppression. For these patients, observation is only a consideration after thorough patient discussion and counseling regarding potential risks and benefits of foregoing CLND.[24] However, most patients with positive SLNB, including those with intermediate thickness (1.5-3.50 mm) primary tumors or with 2 or 3 involved lymph nodes in the SLN are still *high-risk*. It is important to note that these patients were included in the trial results of MSLT-II, and subgroup analysis for patients with greater disease burden in the SLN and with intermediate thickness still did not indicate a significant benefit from CLND. It is also important to note that the observation groups in MSLT-II and DeCOG-SLT underwent frequent follow-up, and thus this should be recommended to patients who ultimately undergo observation instead of intervention with CLND. These recommendations may not be applicable to patients who are unable to obtain follow-up at an institution with access to high-quality nodal ultrasonography.[24] These new guidelines reflect a shift from the previous dogma, where CLND was thought of by many as the appropriate next step in management for positive SLN in melanoma.

Immunotherapy

Oncolytic immunotherapy is an area of growing interest in the management of advanced melanoma. Immune checkpoint inhibitors are a new class of targeted agents, which re-orient the immune system, CTLA-4 and PD-1 receptors in particular, to attack tumor cells. They include ipilimumab, pembrolizumab, and nivolumab. Ipilimumab, a CTLA-4 inhibitor, was studied in patients with stage III nodal metastatic melanoma after CLND and was found to significantly improve recurrence free survival compared to placebo.[63] Several phase III studies have confirmed improved response rates with the anti-PD1 inhibitors nivolumab and pembrolizumab in advanced melanoma.[64-66] Pembrolizumab was recently associated with improved rates of progression-free survival compared with ipilimumab in patients with advanced stage III or IV melanoma.[66] It has also been identified that a combination of targeted agents may have a synergistic benefit in the management of advanced regional or distant melanoma. Patients receiving both ipilimumab and nivolumab had enhanced progression-free survival as compared to monotherapy or placebo, but at the cost of a higher incidence of severe adverse effects.[67,68] The role of immune therapy in the neoadjuvant setting of advanced melanoma has yet to be determined, and is only currently appropriate in the setting of clinical trials.[69]

Talimogene laherparepvec (T-VEC) is an intralesional oncolytic immunotherapy recently approved by the U.S. Food and Drug Administration (FDA) for the treatment of stages IIIB, IIIC, or IVM1a melanoma.[70] T-VEC improves the durable response rate compared with subcutaneous granulocyte-macrophage colony-stimulating factor (GM-CSF).[70] The injections are generally well tolerated, with the majority (89%) of adverse events being grade 1 or 2. Preliminary clinical data suggest that the combination of T-VEC with ipilimumab or pembrolizumab is well tolerated and more efficacious than treatment with single therapies.[71,72]

Targeted therapy

Melanomas are often associated with somatic mutations, most frequently BRAF, with mutations seen in up to 30.4-66.0% of cutaneous melanomas.[73,74] The significance of BRAF in the pathogenesis of melanoma is that RAF proteins regulate the ERK MAP kinase cascade. Activation of RAF kinase phosphorylates MEK1 and MEK2, which regulate cell proliferation. Thus, inhibiting RAF proteins, like BRAF, or MEK activity leads to significant clinical response in melanomas.[75] These small molecule inhibitors have been studied as adjuvant therapy for stage IV metastatic melanoma, and new studies examining these drugs as adjuvant and neoadjuvant therapy for stage III melanoma are currently underway.

There are three BRAF inhibitors that have been studied as targeted treatment for melanoma: vemurafenib, dabrafenib and encorafenib. Vemurafenib was the first to be approved by the Food and Drug Administration (FDA) in 2011 for metastatic melanoma with the BRAF V600E mutation.[76] In clinical trials, progression free survival (PFS) and median OS were significantly higher for vemurafenib compared to chemotherapy (PFS 6.9 months *vs* 1.6 months, median OS 13.6 months *vs* 9.7 months for vemurafenib *vs* chemotherapy, respectively).[77] Then, in 2013, dabrafenib was FDA approved for the same indication and demonstrated PFS of 5.1 months compared to 2.7 months with chemotherapy.[78] In 2018, encorafenib was approved in combination with MEK inhibitor binimetinib for metastatic melanoma.[79]

Unfortunately, development of drug resistance to BRAF inhibitor monotherapy occurs relatively quickly, as almost all patients develop tumor relapse within one year of therapy.[80] Thus, BRAF inhibitors are often combined with MEK inhibitors like trametinib, binimetinib and cobimetinib.[76] There are three FDA-approved combinations of BRAF and MEK inhibitor combination therapy: dabrafenib plus trametinib, vemurafenib plus cobimetinib, and encorafenib plus binimetinib. All approved combinations have superior survival rates compared to BRAF or MEK inhibitor monotherapy.[81-84]

The most common adverse events (AEs) with BRAF inhibitors are skin toxicities, pyrexia and fatigue. Photosensitivity is a particular concern with vemurafenib therapy while pyrexia is more commonly seen with dabrafenib. With MEK inhibitors, common AEs include cutaneous reactions, fatigue, mylgia and cardiovascular toxicities. With combination therapy, the most common AEs are pyrexia, chills and fatigue.[76] With these promising clinical results for stage IV metastatic melanoma, these small molecule inhibitors may play an important future role as adjuvant or neoadjuvant therapy for advanced stage III melanoma.

High-dose interferon

Prior to the introduction of immune therapy, HDI alfa-2b was a mainstay of treatment in the setting of adjuvant therapy in high-risk melanoma. ECOG conducted three major intergroup trials: ECOG E1684, ECOG E1690, and ECOG E1694.[85-87] In the former, which was conducted in the pre-SLN biopsy era, HDI improved both DFS and OS in high-risk patients with palpable lymphadenopathy.[85] In ECOG E1690, HDI was compared with low-dose interferon and demonstrated superior DFS.[86] The latter revealed that HDI was superior to ganglioside vaccine.[87] More recently, the Sunbelt Melanoma Trial demonstrated no improvement in DFS and OS in patients with nodal disease undergoing

CLND or adjuvant HDI compared with observation.[62] However, this trial was not adequately powered to detect small differences in DFS or OS. Still, due to a high toxicity profile, lack of substantial benefit and advent of newer immune-targeting agents, HDI is no longer advocated as an adjuvant therapy.[69]

Radiotherapy

RT has a role in the management of melanoma; however, the optimal regimen still remains to be determined. Adjuvant RT decreases the rate of local recurrence for patients at high risk of regional failure after CLND; however, it does not improve OS.[88] The regimen consists of 30 Gy in 5 fractions over a period of 2.5 weeks. Local control is 94% for head and neck melanoma, 87% for axilla, and 74% for ilioinguinal disease.[89-91]

Future directions

Ongoing studies

An additional randomized phase III noninferiority trial, EORTC 1208 MINITUB (Minimal SLN Tumor Burden), conducted in Germany by the Dermatologic Cooperative Oncology Group is currently ongoing. Patient enrollment will be completed in 2020 and follow up will be 10 years. (NCT01942603) The MINITUB trial focuses on patients with minimal SLN tumor burden who undergo CLND or nodal observation only. Over a 5-year period, the MINITUB expects to register 243 patients with intermediate-thickness tumors (T2-T3, Breslow thickness 1.01-4 mm) and minimal SLN tumor burden (≤0.4 mm subcapsular and/or ≤0.1 mm any location), who undergo serial nodal observation.

Advances in staging capabilities

Currently, both staging and prognosis are based on patient demographics, primary tumor histopathology, and presence of regional or distant metastasis. Recently, a transcutaneous gene expression profile (GEP) assay was introduced to add biological information to enhance staging work-up.[92,93] DecisionDx™-Melanoma (Castle Biosciences Inc, Friendswood, TX), evaluates 31 genes within the primary tumor designed to identify high-risk patients. Gerami *et al*. showed that GEP was an independent predictor for 5-year DFS (97% *vs* 31% for low- and high-risk patients, respectively).[92] The same device has since been shown to improve AJCC staging accuracy and help predict likelihood of metastasis based on particular patterns of genetic expression placing a lesion into risk-stratified categories.[94,95] This noninvasive test may serve to guide risk stratification and management of melanoma patients in the future similarly to how SLN status influences decision-making today. Currently, however, it is not recommended by any national guidelines, including NCCN and AJCC, as in its early stages of use it still remains unclear how results should influence treatment.

Combination therapies

RT in combination with immunotherapy may be beneficial in stage III and IV melanoma. RT may work synergistically with immune checkpoint inhibitors by priming the immune system to enhance the efficacy of these systemic agents. Animal models have identified PD-L1 upregulation in the tumor microenvironment following RT.[96] While the optimal radiation protocol to enhance immunogenicity remains unclear, a recent investigation included 127 patients who received ipilimumab *vs* ipilimumab-RT or ipilimumab-electrochemotherapy and showed that the addition of local RT significantly prolonged OS (93 *vs* 42 weeks) and did not increase adverse events.[97] Another study comparing ipilimumab with or without RT failed to demonstrate differences in OS and progression-free survival.[98]

Further trials investigating the role of combined, targeted molecular therapy are forthcoming. These trials include stereotactic body radiotherapy (SBRT) with concurrent anti-PD-1 (NCT 02821182, NCT02407171, NCT 02303990).[99] Preclinical evidence indicates that SBRT increases response rates and long-term survival of patients undergoing anti-PD-1 treatment by stimulating the accumulation and activation of CD8+ lymphocytes.[100]

Conclusions

Although most surgeons worldwide have adopted SLN biopsy as the gold standard for nodal staging of melanoma, CLND for positive SLN remains a topic of major debate. The two available trials comparing outcomes for SLN-positive patients, MSLT-II and DeCOG-SLT, have failed to demonstrate MSS benefit associated with CLND. However, MSLT-II showed that CLND was associated with improved DFS compared with observation at 3 years based on an increased rate of disease control. Thus, in the newest SSO guidelines, CLND is recommended for patients with high-risk clinicopathologic features, and may be weighed against observation only for low-risk patients with micrometastasis. The forthcoming results of the MINITUB trial will further assist in guiding surgical and medical oncologists towards optimal management strategies for melanoma patients with nodal metastases. Future staging techniques may be based on transcutaneous assessment of genetic profiles of melanoma, which improve accuracy of current standard of care staging guidelines and help predict tumor behavior. Next steps in the management of regional disease in melanoma may consider the use of neoadjuvant immunotherapy and combinations of surgery and RT with immune-targeted therapies, considering each patient and tumor characteristics.

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