Lymph nodes and the melanoma surgeon: re-defining a long-term relationship

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Practice points

- In the history of the surgical treatment of melanoma, emphasis was placed on lymphatic drainage and radical surgical lymphadenectomy. The era of retrospective review as evidence of benefit followed, until prospective randomized trials called pre-emptive regional lymphadenectomy into question.
- These trials resulted in the adoption of wide excision as the standard treatment for patients with clinically localized melanoma. Sentinel lymph node (SLN) mapping was developed as a means of identifying patients for staging and pre-emptive (prophylactic) regional lymphadenectomy.
- Level one medical evidence demonstrates that SLN biopsy is a diagnostic procedure as opposed to a therapeutic procedure with regard to melanoma-specific survival.
- The value of completion of lymph node dissection in SLN (+) patients is increasingly being questioned as retrospective studies (and one interim report of a prospective randomized trial) demonstrates no difference in survival between SLN (+) patients who undergo completion of lymph node dissection and those that do not.

Surgeons now have an enhanced ability to stage patients with clinically localized cutaneous melanoma using sentinel lymph node biopsy. Despite this, the weight of clinical evidence is tilting in favor of a measured approach to pre-emptive lymph node removal. Careful consideration of whether traditional surgical approaches to the regional nodes, whether done in the name of 'staging' or pre-emptive removal of a potential site of relapse, really 'benefit' the patient is paramount for optimal care.

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Exciting progress in the nonoperative management of recurrent melanoma has been made, with the introduction of Braf inhibitors for patients with mutated Braf, MEK inhibitors, ipilimumab and anti-PD-1 for patients with stage IV and unresectable stage III melanoma. The availability of these agents diminishes the potential, albeit unproven value, of pre-emptive removal of regional nodal disease.

No one has focused on the regional lymph node quite like the surgical oncologist. Pursuit of the regional node is a 'raison d'être', a justification for a significant portion of surgical oncology training and the subject of endless debates, journal clubs and symposia. But like an old friend, perhaps it is time to recognize that the relationship of the surgical oncologist to the regional draining lymph node from a melanoma has changed. Much has been learned about the significance of the regional lymph nodes in the last 20 years, and it behooves the surgeon caring for melanoma patients to develop a measured approach to surgical removal of nodes, based on this knowledge. The morbidity of lymph node removal has been more precisely defined. Patients are involved in the decision-making process

KEYWORDS

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as never before, and are increasingly concerned about the potential risks of removal of lymph nodes compared with the proposed benefit. In addition, the tremendous allocation of limited resources to surgical removal of nodes, in the absence of strong data in support of benefit, must factor into the decision.

For the last several decades, surgeons (mea culpa) have viewed the regional nodes in melanoma patients in a fairly simplistic way. A highly accurate and sensitive way to identify microscopic regional nodal disease, namely sentinel lymph node (SLN) biopsy, has been developed, providing a means of identifying patients with regional tumor spread. This solved what was perceived to be the reason that prospective randomized trials (PRTs) had not demonstrated a benefit to pre-emptive lymph node removal, the fact that only 20% of patients were determined to have melanoma in their lymph nodes at 'elective' lymph node dissection (ELND). The idea that this 20% of patients could be cured by ELND was based on several firmly held beliefs and assumptions:

- Melanoma begins as a localized process and spreads sequentially, usually spreading first to the regional nodes before traveling to distant sites;
- Surgical interruption of this metastatic cascade will prevent spread of tumor to distant sites;
- Microscopic nodal disease becomes macroscopic nodal disease.

Historically, the surgical treatment of melanoma was characterized by the importance of radical surgical lymphadenectomy

Surgical focus on the regional nodes peaked in the mid 20th century, when radical lymphadenectomy for soft tissue tumors such as melanoma and breast cancer was heralded as the only hope for cure. At that time, adjuvant therapy for patients with breast cancer and melanoma was considered ineffective. Removal of regional nodes was based on the belief that interruption of the spread of tumor when localized to the primary site or regional nodes would prevent distant disease (by a 'next step' phenomenon). Indeed, the observation that melanoma traveled via the lymphatics to the regional draining nodes was one of the seminal oncologic observations of the early 20th century and led to the brief popularity

of the 'in continuity' lymphadenectomy for cutaneous melanoma.

In this early surgical procedure for melanoma, the primary lesion was resected with wide margins and the lymphatics between the primary and regional nodes were removed with the bridge of soft tissue between the two sites [1].

In continuity, lymphadenectomy was eventually modified, and the era of ELND for cutaneous melanoma began (roughly 1964–1985) for patients with clinically localized melanoma and no palpable evidence of regional nodal disease (Figure 1). Wide excision (WE) and ELND was less morbid than the 'in continuity' dissection, which was abandoned. The primary melanoma was removed with wide empiric margins and the draining regional lymph nodes were removed. This approach was based on the belief that removal of microscopic regional nodal metastasis interrupted the orderly spread of disease to distant sites.

Enter the era of retrospective review as evidence of benefit

Surgeons embraced ELND for patients with intermediate risk of melanoma in the second half of the 20th century, up until about 1988. The reason for this was that retrospective data supported a survival benefit for lymph node (+) patients if their nodes were removed early, compared with patients whose regional nodes were removed when they became clinically enlarged ('therapeutic' lymph node dissection, TLND). The survival advantage at 5 years was approximately 20%, a significant advantage for the patients having early node removal [2]. The assumption was that patients with microscopic disease would progress to clinically apparent disease, and, indeed, the fact that approximately 20% of patients were found to have (+) nodes at ELND and approximately 20% of patients undergoing WE alone developed clinically apparent regional nodal metastasis was cited as evidence to support this assumption. Unfortunately, chronic lymphedema was a common complication of this approach. Subsequent experience has provided a more accurate prediction of lymphedema risk. This varies widely and can be reasonably estimated based on patient factors (age, body habitus, anatomic location of draining lymph nodes) as well as disease stage (microscopic vs macroscopic vs bulky nodal disease) and postoperative treatment (radiation). The definitions commonly used

Figure 1. Timeline of lymph node management in patients with clinically localized melanoma.

CLND: Completion lymphadenectomy; ELND: Elective lymphadenectomy; LND: Lymph node dissection; SLN: Sentinel lymph node; WE: Wide excision.

to describe surgical removal of regional nodes under varying clinical conditions are listed in [Box 1](#).

Prospective clinical trials & the difficulty of proving a benefit for pre-emptive (elective) regional lymph lymphadenectomy

The era of ELND was followed by a period of time that can be considered the ‘golden age’ PRTs led by surgeons. It was a time of great controversy, with heated debate about the ethical validity of the trials being conducted by Bernard Fisher in breast cancer and whether it was appropriate to randomize patients with melanoma to a ‘narrow’ margin of excision or to no regional nodal dissection. Umberto Veronesi initiated the first PRT trial evaluating the extent of radial margins for melanoma excisions, asking whether a 1 cm versus a 3 cm margin was adequate for melanoma ≤ 2 mm in depth [3]. Subsequently, the question of whether ELND did, indeed, offer a survival advantage to patients with clinically localized melanoma compared with WE alone was asked in the context of a PRT by several groups. These studies are listed in [Table 1](#). Importantly, none of them demonstrated an overall survival advantage

favoring ELND. During this period of time, many surgeons continued to perform ELND, however, stating that there were methodologic flaws associated with the trials. They (we) argued that the trials were underpowered to detect a small but significant survival advantage to ELND because most patients (80%) had negative regional nodes. In addition, inclusion criteria were criticized for each trial. In all of the trials, the patients randomized had relatively early melanoma, so that the incidence of regional nodal metastasis was low. In the Intergroup trial, patients were not stratified based on age, ulceration of the primary tumor, primary site or Breslow depth category. In subgroup posthoc analysis, an advantage to ELND was reported for patients with nonulcerated melanoma, those with melanoma between 1 and 2 mm, and those with extremity melanoma [4]. These posthoc analyses were cited as reasons to continue to perform ELND in subgroups of patients with melanoma. The tide finally began to turn, however, in the early 1990s, when most surgeons accepted that without a single PRT demonstrating a survival advantage, continuing to electively remove the regional nodes was difficult to justify.

Box 1. The most common terminology for operative resection of regional nodes is displayed.**Terminology used for surgical nodal procedures**

- ELND: elective lymph node dissection. Prophylactic or pre-emptive removal of regional nodes without clinical or radiologic evidence of disease
- TLND: therapeutic lymph node dissection. Removal of regional nodes with clinical or radiologic evidence of melanoma
- SLN biopsy/sentinel lymphadenectomy: removal of nodes identified using radio colloid or blue dye or both as the first draining regional nodes
- CLND: completion lymph node dissection. Removal of the remaining (nonsentinel nodes) in patients with microscopic disease in the sentinel lymph node

Wide excision was the standard treatment for patients with clinically localized melanoma prior to SLN mapping

Enthusiasm for ELND waned. This fact is forgotten by many who now claim that SLN staging allows the surgeon to identify the 20% of patients with regional nodal disease and the remaining 80% of patients can be spared a regional lymphadenectomy. In the years between ELND for most patients and the widespread adoption of SLN mapping, the standard treatment for patients with clinically localized melanoma and nonpalpable regional nodes was a WE of the primary and clinical surveillance of the nodal basin.

Sentinel lymph node mapping: finally, the answer to patient selection for radical lymph node surgery

The concept of a 'sentinel node' was first proposed by Cabanas in penile cancer [8] and later taken up by D Morton and his group and applied to patients with melanoma [9]. Morton and colleagues used radio colloid to identify the regional nodal basin, followed by the injection of blue dye to assist with visual identification of the draining blue channel leading to the SLN. Further refinement of the technique by D Krag led to widespread use and quick adoption by many surgeons who found that using an intra-operative handheld gamma probe minimized the time required to learn how to identify the SLN in breast cancer and melanoma and successfully stage the nodal basin [10,11]. This led to a revolution in the surgical management of patients with cutaneous melanoma. Patients who had previously undergone a WE and observation were offered regional nodal staging via SLN mapping and biopsy. Completion lymph node dissection (CLND) in SLN(+) patients was considered 'standard'. In a sense, it was 'back to the future'.

It is important to remember that 40% of patients who develop recurrence after treatment for clinically localized melanoma will recur at sites other than the regional nodes [12]. These data were published by the Sydney Melanoma Unit (now the Melanoma Institute of Australia, Sydney, Australia) in a retrospective analysis of patients accrued to a prospective institutional database (Figure 2A). Even if SLN mapping identified 100% of those who will recur first in regional nodes (which it clearly does not), it can only be 60% accurate in predicting any recurrence because the regional nodes are the site of first recurrence in only 6/10 patients who develop recurrent disease [12]. These data also demonstrate that pre-emptive removal of regional nodes prevents relapse in regional nodes (Figure 2B). This approach has the potential to improve disease-free survival (DFS) because the most common site of failure has been surgically removed. This observation was confirmed by the improvement in relapse-free survival (a secondary end point) reported for patients undergoing SLN/CLND in the MSLT I trial [13]. The validity of this secondary end point, has, justifiably, been questioned [14].

Determination of the utility of SLN mapping depends on how 'failure' is defined, and how the goal of the procedure is articulated. If the goal is accurate regional basin staging then one must determine the number of patients who have a (-) SLN removed, then undergo an immediate CLND and no other nodes contain disease. This study was performed by Morton and colleagues, in 2003, less than 1% of patients were found to have non-SLN metastasis, demonstrating that the procedure is highly accurate for pathologic staging of the regional nodal basin [15].

Another method of assessing clinical utility depends on determining how often a (-) SLN precedes clinical nodal basin failure, representing a pathologic 'false-negative' staging procedure.

This assumes that micrometastatic disease was present in the regional nodes at the time of SLN mapping procedure. It is equally plausible that the nodal basin metastasis was a later event in the disease course, and that the initial SLN staging was accurate. This number, as determined by the MSLT1 group, is 4% [16].

Certainly the most important definition for patients depends on the ability of the procedure to predict survival. In other words, how often do patients with a (-) SLN die of melanoma? As previously stated, only 60% of recurrences will occur first in the regional nodes, so that 40% of patients who recur will do so at other sites [12]. In patients with clinically localized melanoma and a (-) SLN, approximately 15% will die of melanoma by 10 years [13]. So from the patient's perspective, the procedure provides false reassurance in 15% of patients.

Prospective clinical trials & the difficulty of proving what we thought we knew

As previously stated, the development of SLN mapping and biopsy radically changed the surgical management of melanoma patients with intermediate risk disease. There was so much enthusiasm for this 'minimally invasive' highly accurate (with regard to pathologic staging of the regional nodes) test, however, that it began to be used in patients with very early melanoma and those with deep primaries. Largely as a result of this, more and more surgeons began to question the role of the procedure in these subgroups of patients less likely to 'benefit' from pre-emptive node removal, and to ask, perhaps more importantly, whether patients should always undergo a CLND following a (+) SLN biopsy. Underlying these issues was the fundamental question of whether the SLN biopsy (with CLND in node (+) patients) was a diagnostic or therapeutic procedure.

This question was addressed by D Morton and colleagues in a PRT, MSLT I (Figure 3). This was a large, international trial in which patients

with clinically localized melanoma were randomized to WE versus WE and SLN mapping. Patients with (+) SLNs underwent a CLND and those randomized to WE were closely observed. If they developed evidence of enlarged regional nodes, they underwent a TLND. The primary end point of the trial was disease-specific survival (DSS). The first trial results were reported in 2006, and demonstrated no difference in DSS between patients undergoing SLN biopsy compared with those managed with WE and nodal basin observation [16]. The final report confirmed no survival difference between the two groups with regard to the primary end point, melanoma-specific survival [13]. There was a difference in DFS, although this was a secondary objective of the trial, favoring patients undergoing SLN staging.

Following the initial report of MSLT I, the necessity of CLND began to be called into question. Many continued to advocate that SLN biopsy/CLND improved DFS, a valid end point in other therapeutic cancer trials. It must be kept in mind, however, that DFS was a secondary end point of the trial. Pre-emptive surgical removal of the most common site of relapse can, potentially, lengthen disease free survival. Melanoma-specific survival would not be improved if the regional recurrence was a predictor but not a determinant of death from disease. Because the goal of MSLT1 was to determine if SLN biopsy was a therapeutic procedure (i.e., its use increased the number of patients cured of the disease), and improvement in DFS but not MSS would be of less interest. Other arguments against viewing the SLN biopsy as a therapeutic procedure based on this trial have been articulated, including the high incidence of false positives and questions about the validity of posthoc statistical analysis on interim data [17].

If there is no melanoma-specific survival benefit to SLN biopsy, then how likely is it that CLND in SLN (+) patients improves survival? Additionally, several retrospective reports of SLN (+) patients

Table 1. Prospective randomized trials demonstrating no impact of elective node dissection on survival.

Investigator (year)	Patients (n)	Site of primary	Sponsor	Findings	Ref.
Veronesi <i>et al.</i> (1982)	553	Extremity	WHO	NS	[5]
Sim <i>et al.</i> (1986)	209	All sites	Mayo Clinic	NS	[6]
Cascinelli <i>et al.</i> (1998)	252	Trunk	WHO	NS	[7]
Balch <i>et al.</i> (1996)	740	All sites	Intergroup	NS	[4]

NS: Nonsignificant.

Figure 2. The most common sites of first recurrence, for patients with recurrent melanoma following wide excision only, are illustrated. (A) The frequency of nodal, regional and visceral as a percentage of recurrences is shown by depth category of the primary lesion (x-axis). Most patients who were initially treated with wide excision only who developed recurrent melanoma (60%) did so first in the regional lymph nodes. **(B)** Site of first recurrence (proportion of bar) in patients with melanoma who underwent elective regional node resection, illustrated by depth category of the primary lesion (x-axis), who developed recurrent melanoma. Regional node recurrence was uncommon. Most patients recurred at visceral sites. Adapted with permission from [12].

who elected observation, and appeared to have a similar outcome as those treated by CLND, have been published and support a measured approach to additional nodal resection [18,19].

In an attempt to find a happy middle ground, several groups have tried to identify ‘low risk’ stage IIIA and B patients, those with a level of tumor burden in the SLN below which a CLND dissection is unnecessary. Factors used have included the diameter of the tumor deposit, whether the tumor cells were visualized

by routine methodology or special stains, the number of (+) SLNs, the site of the tumor cells within the SLN (subcapsular vs parenchymal) and the depth of the primary tumor. A recent meta-analysis [20] of these studies demonstrated considerable variability with regard to additional nodal disease at CLND. Unfortunately, until the question regarding the necessity for CLND can be definitely resolved (MSLT II and EORTC mini-TUB trial), either observation or CLND must be considered a ‘reasonable clinical option’.

The first interim report of the DECOG trial was presented at American Society of Clinical Oncology (ASCO) 2015, and in this small PRT of CLND versus observation for SLN (+) patients, there was no difference in survival between the two arms (3-year MSS 80% in both groups) [21]. A larger ongoing prospective randomized trial evaluating the role of CLND in SLN (+) patients is currently being conducted by the MSLT II group, although the results will not be available for several more years. The primary end point of this trial is MSS, and patients are randomized 1:1 to CLND vs nodal basin observation. Again, the primary end point is DSS. If positive, this will be the first PRT to demonstrate a survival advantage to pre-emptive removal of clinically negative regional nodes.

Only 17% of patients with intermediate risk melanoma and a (+) SLN will have additional (+) nodes (NSLNs) at CLND [22]. These patients do much worse than predicted by the number of involved nodes, suggesting that the existence of 'second echelon' or 'nonsentinel' nodal disease represents particularly poor tumor biology. AJCC nodal staging is based on the number of (+) regional nodes, but Ariyan and colleagues [23] have demonstrated that a (+)

nonsentinel lymph node at CLND carries a very poor prognosis that cannot be explained by the number of positive nodes alone. These patients do worse than expected based on historical data of patients undergoing ELND found to have similar numbers of nodes, with outcome similar to patients having distant nodal disease.

Patients are not passive recipients of nodal metastasis

Young patients are more likely to have microscopic regional nodal disease but less likely to die of melanoma than older patients with microscopic regional nodal disease [24]. This suggests interplay between the patient's tumor, regional nodes and systemic immune system, favoring elimination of micrometastasis in younger patients. If the lymph node metastasis was destined to grow and become a source of inevitable tumor progression this would not be the case. The mechanism by which micrometastatic disease becomes clinically apparent is unclear, but simple progression in the passive host with a (+) SLN is unlikely to be the whole story, or even the main story. Melanoma is notorious for returning decades after potentially curative treatment, with a latency period inversely proportional to

Figure 3. Results of a prospective randomized trial of 1269 patients demonstrate no impact of SLN biopsy followed by CLND in node (+) patients on melanoma-specific survival compared with wide excision alone followed by TLND if patients developed clinically apparent regional disease. This was the primary end point of the trial.

CLND: Completion of node dissection; SLN: Sentinel lymph node; TLND: Therapeutic lymph node dissection.

Adapted with permission from [16].

the risk of the primary lesion. This suggests that micrometastatic disease is harbored at distant sites from the outset and remains dormant, to be triggered at a later time by some unknown signal or event.

Enhanced pathologic techniques demonstrate that the harder you look, the more SLNs are found to have evidence of micrometastasis. Using PCR, 25–50% of H&E-negative SLNs are positive. This certainly exceeds the percentage of patients (9–14% of SLN negative patients recur overall – of these patients about one third recur in the mapped nodal basin, i.e., 3–5%) between who progress in the regional nodal basin [25–27] (based on prospective data), suggesting that the assumption that all nodes with microscopic disease will eventually progress to macroscopic disease is unfounded. Clearly, all regional nodal disease does not become clinically apparent or the risk of nodal basin failure in patients undergoing observation would be extremely high. Regional nodal basin failure rates in the studies published to date have not been significantly higher in patients selecting observation compared with patients undergoing CLND [19]. If all microscopic nodal disease becomes macroscopic, they should be at least 15–20% higher, as this is the incidence of additional positive nodes at CLND [22].

Perhaps we should listen more carefully, or ask a different question...

Though cliché, the oft quoted saying “the definition of insanity is doing the same thing over and over and expecting a different outcome” may apply to our current surgical focus on regional lymph node removal.

Recent studies in melanoma and other solid tumors have indicated that distant sites of tumor dissemination are prepared very early in the clinical course of tumor growth [28] via complex mechanisms mediated by release of tumor exosomes. These fragments of cellular membrane have been demonstrated to hone to bone marrow and ‘educate’ bone marrow progenitor cells. These then travel to potential sites of distant metastasis such as the lung, liver and bone and prepare the tissue to receive tumor deposits. Indeed, melanomas are one of the tumors most likely to utilize this mechanism to establish distant sites of metastatic spread [28]. Surgical interruption of the metastatic cascade by lymph node removal at a microscopic stage is unlikely, based on this evidence, to impact future tumor growth.

Enter the new era of melanoma therapeutics

Significant progress in the treatment of patients with recurrent melanoma and systemic disease has been made in the last 8 years with the introduction of Braf inhibitors for patients with an activating Braf mutation and ipilimumab and anti-PD-1 for patients with stage IV and unresectable stage III melanoma [29,30]. Other strategies such as Braf inhibitors in combination with Mek inhibitors have been used effectively to prolong progression-free survival (PFS) [31]. Anti-Braf therapy results in high response rates in patients whose tumors harbor the activating mutation (40–60%) and overall survival is significantly prolonged. Unfortunately, almost all patients eventually progress, with median PFS of approximately 8 months. Addition of the MEK inhibitor trametinib results in an increase in response rate at the price of increased toxicity.

Immunotherapeutics provide a more durable response, although the percentage of patients who respond is lower than those treated with Braf inhibition. Anti-CTLA4 therapy (ipilimumab) improves MSS in stage IV patients, and the drug is now US FDA approved for patients with stage IV melanoma and unresectable stage III disease. Response rates are lower (20%) but more durable, with patients who achieve a CR potentially cured. Anti-PD-1 therapy is another promising immunotherapeutic. The drug results in blockade of activated T-cell apoptosis via the programmed death (PD) receptor. Cancer cells often escape immune surveillance by expressing PD 1 ligand, resulting in apoptosis of activated T cells and downregulation of anti-tumor immunity. Response rates to anti-PD-1 are higher than those with ipilimumab. In patients with advanced melanoma, ipilimumab combined with nivolumab (anti-PD-1) results in a 53% response rate at the highest tolerated dose [32]. Nivolumab has also been approved for use in patients with recurrent melanoma who progress on ipilimumab and for use as front-line therapy.

Adjuvant therapy of high-risk patients with ipilimumab, or with Braf inhibitors such as vemurafenib or dabrafenib in patients whose tumors display a *Braf* mutation, may quickly become a new standard. Eggermont and colleagues presented the results of a prospective, randomized trial of adjuvant ipilimumab versus placebo at ASCO, in 2014, and published the results of the trial this year [33,34]. Patients

were treated with 10 mg/kg ipilimumab for up to 3 years, until relapse, toxicity or death. The primary end point of the trial was relapse-free survival (RFS). Patients with stage IIIA, IIIB, IIIC and IV disease were eligible. At a median follow-up of 2.7 years, adjuvant ipilimumab improved RFS ($p < 0.01$). Therapy was generally well tolerated, although 39% of patients discontinued treatment in the ipilimumab arm within 12 weeks, and five patients died of drug-related adverse events. Whether the drug will be approved by the FDA based on these data remains to be determined. Indeed, based on this trial, the FDA has approved adjuvant for selected patients with stage IIIA disease [35].

An ongoing international trial of adjuvant vemurafenib in patients with stage IIC and III melanoma will answer the question whether Braf inhibition in high-risk patients whose tumors harbor the activating *Braf*V600 mutation will improve DFS following surgical resection. These promising therapeutic options may soon be available to patients in whom the only potentially curative or indeed effective therapy was surgery only 5 years ago. They are currently not available outside of the context of a clinical trial for adjuvant use.

Conclusion & future perspective

The last two decades have provided surgeons with an enhanced ability to stage patients with clinically localized cutaneous melanoma. Unfortunately, this technology has advanced ahead of our capacity to understand the implications of microscopic regional node disease. Clearly the weight of clinical evidence is tilting in favor of a measured approach to pre-emptive lymph node removal. Careful consideration of whether traditional surgical approaches to the regional nodes, whether done in the name of 'staging' or pre-emptive removal of a potential site of relapse, really 'benefit' the patient is of paramount importance for optimal care of the melanoma patient.

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