Lymph node dissection for melanoma: where do we stand?

Madalyn G Neuwirth^{*1}, Edmund K Bartlett¹ & Giorgos C Karakousis¹

Practice points

Background

- The management of regional nodal basins for melanoma has varied over time from more aggressive radical elective lymph node dissections (LND) to less morbid sentinel lymph node (SLN) biopsies with selective completion lymphadenectomy for patients harboring micrometastatic disease.
- While the standard of care remains completion LND for micrometastatic disease in the sentinel node, controversy still exists as to the precise benefit of this approach.
- Advances in ultrasound technology have allowed for earlier detection of clinically occult disease providing an alternate method of surveying the nodal basin in patients with melanoma, which may become increasingly more relevant in the future.

Elective LND

- A historical overview of elective lymphadenectomy in melanoma management is provided, with summary of salient randomized trials.
- The WHO initiative demonstrated improved survival among patients with nodal metastases in patients who underwent elective LND compared with those who underwent therapeutic LND after the development of clinically palpable nodes.
- The Intergroup Melanoma Surgical Trial identified several subsets of patients based on demographic and tumor factors with improved survival after elective LND compared with treatment of the primary tumor alone.

SLN biopsy

- SLN biopsy procedure is introduced as an important prognostic tool in management of clinically localized primary melanoma.
- Studies confirm the high sensitivity and negative predictive value of the SLN biopsy technique in staging the regional nodal basin(s).
- The MSLT-1 trial was designed to evaluate the prognostic and potential therapeutic value of the SLN biopsy.

Prognostic & potential therapeutic role of SLN biopsy for melanoma

- The MSLT-1 trial found no difference in melanoma-specific survival between the two randomized groups of SLN biopsy and clinical observation.
- Improved survival (of ~20%) was demonstrated in a subset analysis of patients with nodal metastases, favoring the group in which metastatic nodal disease was identified by SLN biopsy and who underwent immediate completion lymphadenectomy compared with the observation group who underwent delayed lymphadenectomy with the appearance of clinical nodal disease.
- A 10-year updated report of the MSLT-1 including a latent subgroup analysis found similar results to the initial report.

¹Department of Surgery, Hospital of the University of Pennsylvania, Philadelphia, PA, USA

^{*}Author for correspondence: Tel.: +1 215 531 2780; Madalyn.peters@uphs.upenn.edu

Practice points (cont.)

Completion LND

- The incidence and prognostic significance of spread of melanoma to regional nonsentinel nodes is discussed.
- The MSLT-2 trial was designed to study the benefit of performing a completion LND after a positive SLN biopsy.
- A recent small randomized German trial (Dermatologic Cooperative Oncology Group) with relatively limited follow-up and several other retrospective studies have found no significant improvement in survival outcomes with immediate completion lymphadenectomy for positive SLN biopsy.

Future perspective

- Advances in radiologic imaging with increasing sensitivity of subclinical nodal disease and blood biomarkers (e.g., circulating tumor cells/tumor material) may complement the SLN biopsy in prognostication.
- These tools may help to better risk stratify patients for enrollment in adjuvant studies with new agents and to select patients (or not) for more extensive regional surgeries.

The extent and timing of regional lymphadenectomy and its role in patients with clinically localized primary melanoma has been the subject of considerable debate. While therapeutic lymphadenectomy for clinically positive nodes is uniformly accepted, the benefit of regional lymphadenectomy in patients with clinically uninvolved lymph nodes potentially harboring micrometastatic disease is less clear. Efforts to better select patients for complete regional lymphadenectomy after sentinel lymph node biopsy are underway. The future holds the promise of more stringent selection criteria and perhaps the identification of subgroups of patients for which a therapeutic benefit may be realized. Moreover, novel sensitive radiological techniques for detecting *in vivo* micrometastatic nodal disease may improve surgical precision, further decreasing potential morbidities of lymphadenectomy.

First draft submitted: 10 June 2016; Accepted for publication: 30 September 2016; Published online: 3 March 2017

KEYWORDS

- lymphadenectomy
- lymph node dissection
- melanoma • sentinel lymph node biopsy

Lymph node dissection (LND) for patients with malignant melanoma has been extensively discussed with respect to its prognostic and therapeutic roles. Since early descriptions of metastatic spread via the lymphatic system, debate has persisted on how to best manage the regional lymph nodes in these patients. Prior to advances in imaging and introduction of the sentinel lymph node (SLN) biopsy technique, patients with clinically localized disease either underwent elective LND (ELND) – that is lymphadenectomy – before clinical nodal disease is apparent with the intent to remove occult metastatic spread, or were observed for the development of clinical metastatic disease, at which time they would typically undergo a therapeutic LND, which was defined as complete regional lymphadenectomy after development of clinically positive lymph nodes. Early studies in ELND for melanoma reported conflicting results with regard to locoregional recurrence and disease-free survival [1–8]. These studies were frequently limited by their single institution design and small sample sizes.

However, prospective randomized trials failed to demonstrate survival benefit for ELND. In the absence of a clear value, with respect to survival for ELND, concern was raised over the potential for serious morbidity associated with the procedure.

With the advent of the SLN biopsy technique, surgeons were able to accurately characterize the status of the regional nodal basin(s) in patients using a more selective and limited lymph node surgery. The MSLT-1 trial, a large multicenter, international randomized trial, confirmed the tremendous prognostic value of the SLN biopsy [9]. While the trial did not demonstrate a survival advantage overall for the group randomized to SLN biopsy, with completion lymphadenectomy for patients with a positive SLN (defined immediate lymphadenectomy of remaining lymph nodes in the regional nodal basin) compared with the nodal observation group, among patients harboring nodal metastases, there was an improved survival of approximately 20% noted in the SLN group. Whether the addition of immediate

completion LND contributed to the reported survival advantage of the SLN biopsy group, or the SLN biopsy itself was primarily responsible for the apparent therapeutic effect, is the basis of the MSLT-2 trial, whose patient accrual has been completed. Results of this trial will further inform on the value of completion lymphadenectomy for patients with positive SLN versus close surveillance of the nodal basin with ultrasound.

Increasingly, there has been a trend to more selective and precise surgery in multiple tumor types, with melanoma being no exception. This article provides a brief historical overview of the management of regional nodes for patients with melanoma from past to present highlighting current controversies, with a glimpse of possible future directions.

Elective LND

Lymphatic drainage from the primary tumor in melanoma has long been recognized as the most common initial route of metastatic spread, with the first site of metastasis identified as the draining nodal basin. Not surprisingly, removal of these nodes became one of the first approaches to try to control the spread of disease. As lymphatic drainage to associated lymph node basins became widely recognized, options for regional nodal basin management were considered. In addition to wide local excision (WLE) of the primary tumor, early studies suggested that LND could improve prognostication for the disease and potentially improve overall survival outcomes when compared with WLE alone [1]. This led to interest in prophylactic or ELND, which was based on the notion that further metastatic spread could be prevented or halted, at the level of the regional lymph nodes before more disseminated disease was allowed to develop.

Several studies supported this hypothesis [10]. In one study from the late 1950s, a small cohort of patients who underwent ELND was found to have superior 5-year survival rates with nodes which were microscopically positive (60%) compared with a group of patients who underwent therapeutic LND for clinically positive lymph nodes (10%) [2]. A few years later, Southwick *et al.* published on a series of 142 patients, 75 of whom underwent WLE with ELND, reporting 5-year survival rates at 80% for patients with clinically negative lymph nodes compared with 32.4% for those who underwent only WLE with observation (40.9% of the observation group required therapeutic LND and had a 5-year survival rate

of 26.5%) [3]. Gumpert and Harris had similar findings in 1974 and also evaluated rates of concordance of clinical exam to pathological nodal status, reporting an overall 'error' rate (discordance of negative exam and positive pathology) of 18% [4]. Patients who were clinically and pathologically negative had a 5-year survival rate of 56%, compared with 30% for those who were clinically negative but microscopically positive and 13% for those who were clinically and pathologically positive. Additionally, a group at Massachusetts General Hospital reported a retrospective series of 427 patients with 5-year survival rates for clinically and pathologically negative, clinically negative and pathologically positive, and clinically positive nodes of 77, 59 and 22%, respectively [5]. These studies in aggregate suggested that removal of clinically occult disease was associated with improved outcomes.

Critics of prophylactic LND cautioned against subjecting patients to the morbidities from the procedure including risk of lymphedema and complications from wound healing with unclear benefit. Furthermore, there was concern raised for affecting the protective immune response to metastatic disease by removal of unaffected regional lymph nodes [7,11,12]. Several studies served to strengthen these arguments by finding no significant improvements in overall survival with ELND. Bodenham *et al.* compared prophylactic LND with no LND for clinically negative nodes, showing no difference in 5-year survival rates. Furthermore, patients undergoing therapeutic LND for clinically positive nodes had significantly decreased survival (20%) compared with patients with clinically negative nodes (73%), suggesting little efficacy in improving survival by LND alone [6,7]. Conrad *et al.* also reported no significant difference between WLE alone and WLE with LND with 80 versus 88% 5-year survival, respectively in primary tumors of the extremity with invasion to the level of dermis and/or subcutaneous tissue [8].

With conflicting evidence regarding the value of elective lymphadenectomy, four notable large randomized trials were undertaken (Table 1). In 1978, Sim *et al.* published a prospective randomized study for localized stage I melanoma, with three study arms: observation with therapeutic LND for development of clinically positive nodes; immediate LND; and delayed LND (performed 2–4 months after WLE of the primary tumor). They found no significant differences in recurrence or disease-free

Table 1. Randomized trials for elective lymph node dissections.

Study (year)	n	Thickness (mm)	Median follow-up (years)	5-year OS: WLE	5-year OS: WLE + ELND	p-value
Sim <i>et al.</i> (1978)	173	Any	NR	85	85	NS
Veronesi <i>et al.</i> (WHO) (1982)	553	Any	8.2	72	74	NS
Cascinelli <i>et al.</i> (WHO) (1998)	240	>1.5	11	51	62	0.09
Intergroup (1996)	740	1–4	7.4	82	86	0.25
Intergroup follow-up (2000)	–	–	10	73 [†]	77 [†]	0.12

[†]OS reported was for a 10-year follow-up period.
ELND: Elective lymph node dissection; NR: Not reported; NS: Not significant; OS: Overall survival; WLE: Wide local excision.

survival across all groups [13]. Similarly in the early 1980s, the WHO sponsored a randomized prospective trial for melanoma patients with T1–4cN0M0 disease. The trial found that delayed LND, in this study defined as lymphadenectomy performed at the time of clinically detectable disease, had similar outcomes compared with immediate LND following WLE [14]. Cascinelli *et al.* continued the WHO initiative in the 1990s randomizing patients to immediate LND following WLE or clinical observation with LND indicated only for development of clinically positive disease [15]. The study found no statistically significant differences in survival between the immediate and delayed lymphadenectomy groups. However, it did identify that patients with microscopic metastasis to the lymph nodes in the ELND group had improved survival rates when compared with those who underwent therapeutic LND after developing palpable nodes. This was the first suggestion of a potential survival advantage associated with early resection of nodal metastases in a randomized trial.

Initiated in the 1980s, the Intergroup Melanoma Surgical Trial, a prospective multi-institutional international randomized trial, also addressed the role of ELND in patients with clinically localized intermediate thickness (1–4 mm) melanoma [16]. The study found no significant difference in 5- and 10-year survival rates between the ELND and nodal observation groups (77 vs 73%; $p = 0.12$) [17]. However, survival rates were improved among certain subgroups of patients after ELND based on clinical and pathologic factors. Specifically, in patients with age <60 years, extremity tumor location, primary tumors without ulceration or tumor thickness of 1–2 mm, survival was greater in the ELND versus nodal observation group.

SLN biopsy

Without substantive evidence showing a survival benefit to routine prophylactic LND for early-stage melanoma patients with clinically localized disease, attention turned toward developing methods for selective lymphadenectomy. This could obviate perhaps some of the morbidity of the surgery while still affording the at least prognostic value of nodal assessment. The concept of the SLN, the first draining node(s) of the tumor site, was championed for use in melanoma by DL Morton in the late 1980s and early 1990s, building on older lymphoscintigraphy studies. Potential benefits of this procedure included accurate staging of the regional nodal basin through a less invasive and morbid surgery, and selection of patients for complete lymphadenectomy who were found to have nodal metastases. Morton *et al.* described their early experience with the sentinel node biopsy in 237 patients using technetium-labeled dextran for intraoperative localization of the SLN and Patent Blue V or isosulfan blue dye [18]. Among the patients in whom sentinel nodes were identified prior to formal lymphadenectomy (81.8%), 40 (21%) had nodal involvement; of which 95% were detected within the sentinel node, reflecting the high sensitivity and negative predictive value of the technique. A second study further reinforced the value of the SLN biopsy reporting a detection rate of nodal metastasis at 95% [19].

As support for SLN biopsy grew, a higher-powered prospective study was warranted to further investigate its benefit. The MSLT-1 study was designed in the early 1990s in order to assess the validity of the sentinel node biopsy with regard to its prognostic and therapeutic value. Patients with clinically localized melanoma (thickness 1.2–3.5 mm) were randomized to WLE alone with clinical observation and therapeutic

lymphadenectomy for patients who developed nodal disease versus WLE with sentinel node biopsy and immediate completion LND for patients with micrometastases, in other words, clinically occult nodal metastasis detected by SLN biopsy [9]. The objective of this trial was to evaluate the value of SLN biopsy in detecting nodal involvement in clinically negative regional nodal basins, as well as assess the impact on survival for early completion lymphadenectomy in patients with positive sentinel node biopsies. The primary end point was melanoma-specific survival, with secondary end points including disease-free survival, survival comparisons between negative and positive sentinel node patients within the SLN biopsy group, incidence of nodal metastasis among the observation group and SLB biopsy group (including false negative biopsies), and survival with or without nodal metastases among observation and SLN biopsy groups.

Prognostic & potential therapeutic role of SLN biopsy for melanoma

The MSLT-1 trial reported on recurrence-free and melanoma-specific survival outcomes with its primary cohort of patients having intermediate thickness melanoma (1.2–3.5 mm) randomized 40:60 to the two major groups of nodal observation versus sentinel node biopsy, summarized in [Table 2](#) [20]. A total of 1347 patients were enrolled and randomized for the trial between the years 1994 and 2002 from North America, Europe and Australia, with 19 patients dropping out and one deemed ineligible due to clinically positive nodes; the final analysis was conducted on 1327 patients. It confirmed the already known tremendous prognostic value of

the SLN technique, with 5-year survival rates in the SLN positive group being significantly worse than the SLN negative group (72.3 vs 90.2%; $p < 0.001$). Not surprisingly, it also found recurrence-free survival was improved in the SLN group versus the nodal observation group. With regard to a primary end point of the study, however, there was no difference in 5-year melanoma-specific survival rates between the two randomized groups (87.1 and 86.6% for SLN biopsy vs observation groups, respectively). Interestingly, in a subgroup analysis of patients with nodal metastases, those patients in the SLN arm who underwent immediate LND for positive nodes did demonstrate an improved survival (72.3%) compared with those in the observation arm who underwent delayed lymphadenectomy for clinical nodal disease (52.4%; $p = 0.004$). Importantly, both groups had a similar (but not identical) rate of nodal disease with an incidence of 16.0% micrometastases in the SLN group and 15.6% clinical nodal disease rate in the observation group with median time to clinical detection at 1.33 years (95% CI: 1.02–1.76). However, those with negative SLN biopsies had a nodal recurrence rate of 3.4% ($n = 26$) with median follow-up time of 59.8 months. In taking these false-negative cases into consideration, the rate of nodal involvement in the biopsy group increases to 19.4%. With longer term follow-up including the patients with false negative, the rate of nodal mets in the two groups were 20% biopsy group versus 17.4% in the observational group among intermediate thickness patients (1.2–3.5 mm) and 39.9 versus 37.6% among thick melanoma patients (derived from supplemental appendix) [21]. However,

Table 2. Summarization of randomized trials evaluating the role of completion lymphadenectomy following sentinel lymph node biopsy.

Study (year)	Randomized groups	Patient eligibility	n	Outcomes	p-value
MSLT-1 (NCT00275496) (2006, 2014)	SLNB vs nodal observation	Clark level III and Breslow thickness ≥ 1.00 mm	1616	No significant difference in melanoma-specific survival in intermediate or thick melanoma treatment groups [†]	0.18 (int.); 0.56 (thick)
DeCOG-SLT (NCT02434107) (2013)	Completion LND vs nodal observation	Primary melanoma ≥ 1.00 mm of torso or extremity and +SLNB	473	No difference in distant met-free survival or recur-free survival at 3-year follow-up	0.43 (met-free); 0.83 (recur-free)
MSLT-2 (NCT00297895) (2006–present)	Completion LND for +SLNB vs nodal observation with ultrasound	+ SLNB for primary melanoma with at least Clark level III or Breslow thickness ≥ 1.20 mm	1925	Currently awaiting results of trial	NA

[†]Among patients with nodal metastases in the intermediate thickness group, melanoma-specific survival was significantly increased in the biopsy group compared with the observation group ($p = 0.04$).

int.: Intermediate thickness; LND: Lymph node dissection; met: Metastases; NA: Not applicable; recur: Recurrence; SLNB: Sentinel lymph node biopsy.

because the statistically significant difference in survival found between nodal metastatic groups came out of a subgroup analysis, the question is whether the patients with microscopic disease in essence represent the same patients as those who go on to develop macroscopic disease, or whether there is a different biology at play. This concept was described by Thomas in 2008 as prognostic false-positivity, in other words, micrometastatic disease in SLN that is essentially clinically and prognostically insignificant [22]. In truth, there is no easy way to answer this question; ideally a randomized study of patients with high risk of harboring nodal micrometastases could be developed and perhaps provide the necessary power to identify a difference between early and late nodal intervention groups without invoking a subgroup analysis. Of course, identifying a population enriched for such nodal disease (e.g., thicker primaries, among others) would likely entail enrolling a study population with higher risk for hematogenous metastases, which could very well obviate any benefit of early intervention at the nodal level. In fact, in the subsequent reporting of the MSLT-1 trial, earlier nodal intervention on patients with thick melanomas appeared to confer no survival benefit [21]. With more sensitive imaging modalities, perhaps microscopic disease could be identified without need for surgical biopsy and a study could be designed using a population of patients with identified microscopic disease by imaging. Such a study though, if feasible, would no doubt raise ethical concerns if the nodal disease is the only site of identified metastasis and a group were to be randomized to observation of this disease. In the end, the MSLT-1, despite its high quality design, has been subjected to some of the same criticisms of the ELND trials, which identified no overall difference in survival between early and delayed intervention but found subgroups for whom there appeared to be a survival advantage.

In 2014, an update was published of the MSLT-1 trial, with 10-year survival rates being no different between the two randomized groups; the significant findings of the subgroup analysis among patients with nodal metastases favoring the SLN group persisted [21]. Disease-free survival at 10 years was increased for the sentinel node biopsy group compared with the observation group for intermediate thickness melanomas; 1.20–3.50 mm (71.3 vs 64.7%), as well as for thick melanomas >3.50 mm (50.7 vs 40.5%). Presence of nodal metastases

was associated with decreased survival in both the intermediate and thick melanoma groups (suggesting prognostic value even in the latter group). Among patients with nodal metastases and melanomas of intermediate thickness, early nodal intervention was associated with prolonged distant disease-free survival (62 vs 41%) and melanoma-specific survival (56 vs 41%). An accelerated failure time latent subgroup analysis was performed to account for the difference in time at which nodal status was known and even with these analyses, the survival difference persisted. The difference in 10-year survival rates was not significant however, between treatment groups with thick melanomas and nodal involvement (48.0 vs 45.8% for early vs late nodal intervention, respectively). This suggests that in patients with high risk for hematogenous or distant metastases, timing of nodal intervention may be less likely to alter the natural history of disease.

Ultimately, again the debate centers less on if to intervene in instances of nodal disease but rather, when to intervene, in other words, what is the time cost of waiting for subclinical disease to become clinically apparent? Conceptually, when melanoma metastasizes to the lymph node, there may be a couple of scenarios that may exist, elaborating on old concepts and the ‘incubator versus marker hypothesis’ described by Morton [23]: first, the lymph node metastasis may occur and remain in the lymph node for some finite period before further metastasizing to distant sites prior to it becoming clinically apparent; second, the lymph node metastasis may occur and remain indolent not further metastasizing to distant sites until well after it is clinically apparent or and last, the lymphatic metastasis may occur nearly synchronously with metastasis to other distant sites. In all but the first scenario, it is difficult to see how early nodal intervention can impact on the natural history of the disease (Table 3). Even so, there may be a subset of patients for which that scenario applies and efforts to identify that population would be useful to selectively offering regional therapy and justifying the morbidity of the procedure.

Completion LND

The survival advantage identified through subgroup analysis in the MSLT-1 trial still leaves open the question of whether completion or immediate lymphadenectomy for patients with

Table 3. Schematic description of various clinical scenarios of melanoma metastases to regional lymph nodes, distant sites and potential benefit of performing early lymphadenectomy.

Pathway of melanoma metastases		Outcome of early selective lymph node dissection
Lymphatic involvement		
Metastases to lymph nodes (short latency period)		Possible benefit
Metastases to lymph nodes (long latency period) with macroscopic lymph node involvement and distant metastases		Unlikely benefit
Metastases to lymph nodes and distant organs (nearly synchronous)		Unlikely benefit
Non-lymphatic involvement		
Metastases to distant organs		Unlikely benefit

a positive SLN is necessary. There are two issues that become relevant to this discussion: there is a large majority of patients (80–85%) who are not found to have any additional disease in their nonsentinel nodes on completion dissection after positive SLN biopsy; and patients with non-SLN disease may have a worse prognosis, in other words, the very patients who we would look to be improving survival by performing a more extensive lymphadenectomy surgery may be those at greatest risk for having disease not limited to the regional nodal basin. To the second point, a retrospective study from Memorial Sloan Kettering Cancer Center suggested that patients with nonsentinel node positive disease had a significantly worse prognosis than those with disease confined only to the SLNs – and this difference persisted even when adjusting for total nodal disease burden [24]. Other investigators have similarly reported the negative prognostic value of non-SLN disease [25–27]. As such, the MSLT-2 trial aims to try to identify the value of completion LND in patients with melanoma and a positive SLN

(Table 2) [28]. In this trial, which has completed accrual, patients who underwent SLN biopsies with evidence of micrometastasis are randomized to either completion lymphadenectomy as described or clinical observation with surveillance interval nodal ultrasounds. The primary outcome is melanoma-specific survival and secondary outcomes are recurrence and disease-free survival.

Several retrospective studies have been reported to address the value of completion LND in anticipation of the randomized trial results [27,29]. A multi-institutional retrospective study from Memorial Sloan–Kettering Cancer Center, investigated the utilization of completion LND among patients with sentinel node drainage to more than one nodal basin and subsequent survival outcomes [30]. Median overall survival was 45 versus 30 months among the patients who underwent completion LND for positive sentinel nodes in multiple basins versus those who did not, which was not statistically different ($p = 0.6$). Another large retrospective European Organization for Research

and Treatment of Cancer study found no association of completion LND with disease-specific survival by univariate or multivariate analyses [31].

Results of a multi-institutional randomized Phase III trial from the German Dermatologic Cooperative Oncology Group with similar design to the MSLT-2 were recently published, as shown in Table 2 [32]. Patients with melanoma of the trunk or extremities, primary tumor thickness of at least 1.0 mm and a positive sentinel node were randomized to observation, including physical exam, regional sonography and periodic cross-sectional imaging or completion LND [32,33]. The study found no significant difference in distant metastasis-free survival or overall survival between the randomized groups, with median follow-up time of 35 months. In the intention-to-treat analysis, the distant metastasis free survival at 3 years was 77% in the observation group and 74.9% in the completion LND group ($p = 0.87$). The study had several noted limitations including poor accrual resulting in early closure with a smaller than anticipated sample size of the study and relatively short follow-up (which will be extended), as well as exclusion of head and neck patients. As such, it has not resulted in a paradigm shift in the routine management of the nodal basin in patients with positive SLNs.

While the results of the MSLT-2 are awaited, several efforts are being made to better select patients with a positive SLN for completion LND, and at the same time to try to mitigate the morbidity of the lymphadenectomy procedure (particularly for groin lymphadenectomy). Rotterdam–Dewar criteria involving the location, size and nature of sentinel nodal metastases (e.g., unifocal or multifocal) have been proposed as a way of predicting the presence of nonsentinel node disease [25,34–35]. Using these criteria, patients with SLN metastasis present only in the subcapsular location and with metastasis <0.1 mm have a low likelihood of having additional nodal disease found on completion lymphadenectomy (2%), and this may represent a group that could be reasonably spared the morbidity of the additional surgery [26]. In fact, the survival of this group was found to be 95% at 5 years. The Minitub registry (European Organization for Research and Treatment of Cancer 1208), will continue to offer valuable information with respect to these patients with low SLN burden [36].

Unfortunately, only a very small proportion of patients fall into this subgroup and the assumption that rates of regional nodal recurrence will reflect that of nodal positivity on completion dissection must be approached with caution since the level of histologic scrutiny of the non-SLN may be less rigorous than that of the SLN. Moreover, for most other combinations of size or nodal location of the micrometastasis, the risk of non-SLN metastasis approaches that of the overall risk quoted to patients irrespective of the features of the micrometastasis.

At the same time, as more selective offering of the procedure is investigated, efforts are underway to reduce the morbidity of the lymphadenectomy surgery. A minimally invasive LND approach has shown early promising results in potentially reducing wound complications for groin dissections [37].

Conclusion

Management of the regional lymph nodes for melanoma has evolved significantly over time, generally moving in the direction of less extensive or radical surgery, paralleling initiatives to the primary tumor, which also witnessed a shift to more narrow margins compared to historical approaches. From routine elective lymphadenectomies, to selective SLN biopsy based on thickness and consideration of other pathologic (and clinical) variables, there has been a paradigm shift which ultimately reflects a better understanding of melanoma tumor biology. Current nodal management for melanoma seeks to strike the balance of obtaining important prognostics/staging information and regional control of disease on the one hand with surgical morbidity on the other. While SLN biopsy has become entrenched as a valuable staging tool, the relative value of completion lymph node dissection among patients harboring metastases in the sentinel nodes is less clear and is the subject of ongoing clinical investigation (the MSLT2 trial whose results are pending). With the advent of novel targeted and immunotherapies for melanoma, the role of surgical management of regional nodes for melanoma also confer survival advantages to patients not witnessed before with the introduction of these agents to the adjuvant setting (in fact, this has already been seen with adjuvant anti-CTLA4 therapy). Progress in diagnostic imaging and genetic testing of primary tumors will also likely modify the role of

surgery on the regional nodes for melanoma, particularly with regards to patient selection. Nodal management for melanoma has come a long way, but will no doubt continue to evolve to more precise and selective surgery, with efforts aimed at optimizing therapeutic value while minimizing morbidity.

Future perspective

Looking ahead, the MSLT-2 trial will further inform whether a completion LND should be the standard recommendation for patients with melanoma and a positive SLN or whether close observation with ultrasound surveillance can yield similar outcomes. In fact, practice trends have already demonstrated that a significant proportion of patients do not undergo a completion LND in the USA. In one study of national practice patterns, approximately 50% of patients did not undergo completion LND (many presumably undergoing imaging surveillance) [38]. A more recent rationale for completion LND has been eligibility for adjuvant trials using newer targeted therapy and immune checkpoint inhibitors, which have shown significant response rates in the stage IV setting. These eligibility criteria may of course change, pending the results of the MSLT-2 trial. If no significant differences are observed, this trial may propose a paradigm shift in clinical management of the regional nodal basin. This would also have implications of pathologic staging of stage III patients (with respect to N stage).

Ultrasound techniques have advanced over the years to detect earlier evidence of nodal disease, far superior than physical exam alone [39,40], and no doubt if the MSLT-2 trial is a negative trial, these technologies will likely continue to be refined. In addition to advanced ultrasonography, the future holds the promise for further technological developments in detecting micrometastatic disease. Novel intra-operative 3D imaging has been described for minimally invasive identification of regional nodes for sentinel node biopsies [41]. Similarly, single proton emission CT/CT imaging has been employed for preoperative localization of SLN [42]. Ultrasound-guided fine needle aspiration cytology for suspicious lymph nodes identified by specific ultrasound morphology criteria has been employed recently as an adjunct for minimally invasive means of detecting clinically occult nodal disease [43,44].

The possibility of noninvasive characterization of regional lymph nodes is also coming to realization. With the use of photoacoustic ultrasound imaging, identification of melanoma micrometastases, in other words, clinically negative nodes that are found to have metastatic disease within the lymph nodes on histopathologic evaluation, can be accomplished by identifying changes in ultrasonic signals produced from thermo-electric conversion of absorbed laser light to heat by tumor-containing tissue, which has already been evidenced in preclinical studies [45,46]. With the addition of near-IR fluorophore indocyanine green, this imaging modality can be further enhanced to characterize the SLN status with increased sensitivity and specificity [47]. These and other methods, perhaps combined with molecularly targeted imaging, may eventually be able to distinguish abnormal or suspicious lymph nodes from metastatic disease prior to biopsy, as has already been witnessed in preliminary preclinical investigations for other cancers [48,49]. This not only may obviate the need for performing an SLN procedure for most patients for which there is no nodal disease identified, but may in fact limit the surgical lymphadenectomy to only those nodes harboring metastatic disease, thus eliminating the need for consideration of full LND. Circulating melanoma cells and serological tumor markers have begun to be developed as 'liquid biopsy' indicators of metastatic melanoma progression [50–52]. Perhaps in the future, the sensitivity of these assays to not only predict tumor burden but also the compartmentalization of disease (e.g., lymphatic or extra-lymphatic) will allow for more rationale for pursuing aggressive regional surgeries or not. Clearly, the future is bright with several exciting technological prospects, and the role of surgery on lymph nodes and other sites for melanoma will no doubt continue to evolve as novel systemic therapies continue to develop.

Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.

References

Papers of special note have been highlighted as:

• of interest

- 1 Balch CM, Soong SJ, Murad TM, Ingalls AL, Maddox WA. A multifactorial analysis of melanoma. II. Prognostic factors in patients with stage I (localized) melanoma. *Surgery* 86(2), 343–351 (1979).
- 2 Lane N, Lattes R, Malm J. Clinicopathological correlations in a series of 117 malignant melanomas of the skin of adults. *Cancer* 11(5), 1025–1043 (1958).
- 3 Southwick HW, Slaughter DP, Hinkamp JF, Johnson FE. The role of regional node dissection in the treatment of malignant melanoma. *Arch. Surg.* 85, 63–69 (1962).
- 4 Gumpert SL, Harris MN. Results of regional lymph node dissection for melanoma. *Ann. Surg.* 179(1), 105–108 (1974).
- 5 Mundth ED, Guralnick EA, Raker JW. Malignant melanoma: a clinical study of 427 cases. *Ann. Surg.* 162, 15–28 (1965).
- 6 Bodenham DC. A study of 650 observed malignant melanomas in the South-West region. *Ann. R. Coll. Surg. Engl.* 43(4), 218–239 (1968).
- 7 Bodenham DC. Malignant melanoma: the problem of lymph-node metastases. *Proc. R. Soc. Med.* 62(11 Part 1), 1090–1092 (1969).
- 8 Conrad FG. Treatment of malignant melanoma: wide excision alone vs lymphadenectomy. *Arch. Surg.* 104(4), 587–593 (1972).
- 9 Morton DL, Thompson JF, Essner R *et al.* Validation of the accuracy of intraoperative lymphatic mapping and sentinel lymphadenectomy for early-stage melanoma: a multicenter trial. Multicenter Selective Lymphadenectomy Trial Group. *Ann. Surg.* 230(4), 453–463; discussion 463–455 (1999).
- 10 Fortner JG, Woodruff J, Schottenfeld D, Maclean B. Biostatistical basis of elective node dissection for malignant melanoma. *Ann. Surg.* 186(1), 101–103 (1977).
- 11 Baum M. Should lymphadenectomy be discarded? I. Immunological considerations. *Surgeon* 18(6), 351–356 (1973).
- 12 Clark WH Jr, From L, Bernardino EA, Mihm MC. The histogenesis and biologic behavior of primary human malignant melanomas of the skin. *Cancer Res.* 29(3), 705–727 (1969).
- 13 Sim FH, Taylor WF, Ivins JC, Pritchard DJ, Soule EH. A prospective randomized study of the efficacy of routine elective lymphadenectomy in management of malignant melanoma. Preliminary results. *Cancer* 41(3), 948–956 (1978).
- 14 Veronesi U, Adamus J, Bandiera DC *et al.* Delayed regional lymph node dissection in stage I melanoma of the skin of the lower extremities. *Cancer* 49(11), 2420–2430 (1982).
- 15 Cascinelli N, Morabito A, Santinami M, Mackie RM, Belli F. Immediate or delayed dissection of regional nodes in patients with melanoma of the trunk: a randomised trial. WHO Melanoma Programme. *Lancet* 351(9105), 793–796 (1998).
- 16 Balch CM, Soong SJ, Bartolucci AA *et al.* Efficacy of an elective regional lymph node dissection of 1 to 4 mm thick melanomas for patients 60 years of age and younger. *Ann. Surg.* 224(3), 255–263; discussion 263–256 (1996).
- 17 Balch CM, Soong S, Ross MI *et al.* Long-term results of a multi-institutional randomized trial comparing prognostic factors and surgical results for intermediate thickness melanomas (1.0 to 4.0 mm). Intergroup Melanoma Surgical Trial. *Ann. Surg. Oncol.* 7(2), 87–97 (2000).
- 18 Morton DL, Wen DR, Wong JH *et al.* Technical details of intraoperative lymphatic mapping for early stage melanoma. *Arch. Surg.* 127(4), 392–399 (1992).
- 19 Ross MI, Reintgen D, Balch CM. Selective lymphadenectomy: emerging role for lymphatic mapping and sentinel node biopsy in the management of early stage melanoma. *Semin. Surg. Oncol.* 9(3), 219–223 (1993).
- 20 Morton DL, Thompson JF, Cochran AJ *et al.* Sentinel-node biopsy or nodal observation in melanoma. *N. Engl. J. Med.* 355(13), 1307–1317 (2006).
- 21 Morton DL, Thompson JF, Cochran AJ *et al.* Final trial report of sentinel-node biopsy versus nodal observation in melanoma. *N. Engl. J. Med.* 370(7), 599–609 (2014).
- Long-term follow-up of large prospective multicentered randomized trial, demonstrating improvement in disease-free survival for patients managed with sentinel lymph node (SLN) biopsy.
- 22 Thomas JM. Prognostic false-positivity of the sentinel node in melanoma. *Nat. Clin. Pract. Oncol.* 5(1), 18–23 (2008).
- 23 Morton DL. Overview and update of the Phase III Multicenter Selective Lymphadenectomy Trials (MSLT-I and MSLT-II) in melanoma. *Clin. Exp. Metastasis* 29(7), 699–706 (2012).
- 24 Gyorki DE, Boyle JO, Ganly I *et al.* Incidence and location of positive nonsentinel lymph nodes in head and neck melanoma. *Eur. J. Surg. Oncol.* 40(3), 305–31 (2014).
- 25 Dewar DJ, Newell B, Green MA, Topping AP, Powell BW, Cook MG. The microanatomic location of metastatic melanoma in sentinel lymph nodes predicts nonsentinel lymph node involvement. *J. Clin. Oncol.* 22(16), 3345–3349 (2004).
- 26 van der Ploeg AP, van Akkooi AC, Rutkowski P *et al.* Prognosis in patients with sentinel node-positive melanoma is accurately defined by the combined Rotterdam tumor load and Dewar topography criteria. *J. Clin. Oncol.* 29(16), 2206–2214 (2011).
- The Rotterdam–Dewar Combined Criteria is identified as a strong prognostic parameter for survival in the European Organisation for Research and Treatment of Cancer melanoma group center review.
- 27 Ariyan C, Brady MS, Gonen M, Busam K, Coit D. Positive nonsentinel node status predicts mortality in patients with cutaneous melanoma. *Ann. Surg. Oncol.* 16(1), 186–190 (2009).
- 28 ClinicalTrials.gov ID: NCT00297895. <https://clinicaltrials.gov/ct2/show>
- 29 Wong SL, Morton DL, Thompson JF *et al.* Melanoma patients with positive sentinel nodes who did not undergo completion lymphadenectomy: a multi-institutional study. *Ann. Surg. Oncol.* 13(6), 809–816 (2006).
- 30 Melstrom LG, Taylor E, Kuk D *et al.* International multi-institutional management and outcome of melanoma patients with positive sentinel lymph nodes in more than one nodal basin. *Ann. Surg. Oncol.* 21(13), 4324–4329 (2014).
- 31 van der Ploeg AP, van Akkooi AC, Rutkowski P *et al.* Prognosis in patients with sentinel node-positive melanoma without immediate completion lymph node dissection. *Br. J. Surg.* 99(10), 1396–1405 (2012).
- 32 Leiter U, Stadler R, Mauch C *et al.* Complete lymph node dissection versus no dissection in patients with sentinel lymph node biopsy positive melanoma (DeCOG-SLT): a multicentre, randomised, Phase III trial. *Lancet Oncol.* 17(6), 757–767 (2016).
- 33 Leiter URS, Cornelia Mauch, Werner Hohenberger *et al.* Survival of SLNB-positive melanoma patients with and without complete lymph node dissection: a multicenter, randomized DECOG trial. *J. Clin. Oncol.* 33 (2013).
- Multicenter randomized trial to evaluate potential survival benefit of SLN biopsy in patients with head and neck melanoma,

- finding improved recurrence-free survival, regional and distant metastases-free survival in patients undergoing SLN biopsy directed management.
- 34 van Akkooi AC, de Wilt JH, Verhoef C *et al.* Clinical relevance of melanoma micrometastases (<0.1 mm) in sentinel nodes: are these nodes to be considered negative? *Ann. Oncol.* 17(10), 1578–1585 (2006).
 - 35 van Akkooi AC, Nowecki ZI, Voit C *et al.* Sentinel node tumor burden according to the Rotterdam criteria is the most important prognostic factor for survival in melanoma patients: a multicenter study in 388 patients with positive sentinel nodes. *Ann. Surg.* 248(6), 949–955 (2008).
 - 36 van Akkooi AC. Minitub: Prospective registry of sentinel node (sn) positive melanoma patients with minimal SN tumor burden who undergo completion lymph node dissection (CLND) or nodal observation 2009–2016. <http://www.eortc.org/sites/default/files>
 - 37 Jakub JW, Terando AM, Sarnaik A *et al.* Safety and feasibility of minimally invasive inguinal lymph node dissection in patients with melanoma (SAFE-MILND): report of a prospective multi-institutional trial. *Ann. Surg.* 265(1), 192–196 (2016).
 - 38 Bilimoria KY, Balch CM, Bentrem DJ *et al.* Complete lymph node dissection for sentinel node-positive melanoma: assessment of practice patterns in the United States. *Ann. Surg. Oncol.* 15(6), 1566–1576 (2008).
 - 39 Prayer L, Winkelbauer H, Gritzmann N, Winkelbauer F, Helmer M, Pehamberger H. Sonography versus palpation in the detection of regional lymph-node metastases in patients with malignant melanoma. *Eur. J. Cancer.* 26(7), 827–830 (1990).
 - 40 Rossi CR, Seno A, Vecchiato A *et al.* The impact of ultrasound scanning in the staging and follow-up of patients with clinical stage I cutaneous melanoma. *Eur. J. Cancer.* 33(2), 200–203 (1997).
 - 41 Sulzbacher L, Klinger M, Scheurecker C *et al.* Clinical usefulness of a novel freehand 3D imaging device for radio-guided intraoperative sentinel lymph node detection in malignant melanoma. *Clin. Nucl. Med.* 40(9), e436–e440 (2015).
 - 42 Ozguven S, Gungor S, Aras M, Sacak B, Dede F. Clinical impact of preoperative sentinel lymph node imaging with SPECT/CT in the management of interscapular malignant melanoma. *Clin. Nucl. Med.* 40(9), 762–763 (2015).
 - 43 Voit CA, Gooskens SL, Siegel P *et al.* Ultrasound-guided fine needle aspiration cytology as an addendum to sentinel lymph node biopsy can perfect the staging strategy in melanoma patients. *Eur. J. Cancer.* 50(13), 2280–2288 (2014).
 - 44 Voit CA, Oude Ophuis CM, Ulrich J, van Akkooi AC, Eggermont AM. Ultrasound of the sentinel node in melanoma patients: echo-free island is a discriminatory morphologic feature for node positivity. *Melanoma Res.* 26(3), 267–271 (2016).
 - 45 Wang Y, Xu D, Yang S, Xing D. Toward *in vivo* biopsy of melanoma based on photoacoustic and ultrasound dual imaging with an integrated detector. *Biomed. Opt. Express.* 7(2), 279–286 (2016).
 - **Employment of noninvasive photoacoustic ultrasound imaging in detecting *in vivo* melanoma and aid in detection of metastatic disease and determination of regional lymph node status.**
 - 46 Zhou Y, Li G, Zhu L, Li C, Cornelius LA, Wang LV. Handheld photoacoustic probe to detect both melanoma depth and volume at high speed *in vivo*. *J. Biophotonics* 8(11–12), 961–967 (2015).
 - 47 Stoffels I, Morscher S, Helfrich I *et al.* Metastatic status of sentinel lymph nodes in melanoma determined noninvasively with multispectral optoacoustic imaging. *Sci. Transl. Med.* 7(317), 317ra199 (2015).
 - 48 Zhang M, Kim HS, Jin T, Yi A, Moon WK. Ultrasound-guided photoacoustic imaging for the selective detection of EGFR-expressing breast cancer and lymph node metastases. *Biomed. Opt. Express.* 7(5), 1920–1931 (2016).
 - 49 Luke GP, Myers JN, Emelianov SY, Sokolov KV. Sentinel lymph node biopsy revisited: ultrasound-guided photoacoustic detection of micrometastases using molecularly targeted plasmonic nanosensors. *Cancer Res.* 74(19), 5397–5408 (2014).
 - 50 Ma J, Frank MH. Isolation of circulating melanoma cells. *Methods Mol. Biol.* doi:10.1007/7651_2015_300 (2015) (Epub ahead of print).
 - 51 Alegre E, Sammamed M, Fernandez-Landazuri S, Zubiri L, Gonzalez A. Circulating biomarkers in malignant melanoma. *Adv. Clin. Chem.* 69, 47–89 (2015).
 - 52 Xu MJ, Dorsey JF, Amaravadi R *et al.* Circulating tumor cells, DNA, and mRNA: potential for clinical utility in patients with melanoma. *Oncologist* 21(1), 84–94 (2016).