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Surveillance of Sentinel Node-Positive Melanoma Patients with Reasons for Exclusion from MSLT-II: Multi-Institutional Propensity Score Matched Analysis

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BACKGROUND: In sentinel lymph node (SLN)-positive melanoma, two randomized trials demonstrated equivalent melanoma-specific survival with nodal surveillance vs completion lymph node dissection (CLND). Patients with microsatellites, extranodal extension (ENE) in the SLN, or >3 positive SLNs constitute a high-risk group largely excluded from the randomized trials, for whom appropriate management remains unknown.

STUDY DESIGN: SLN-positive patients with any of the three high-risk features were identified from an international cohort. CLND patients were matched 1:1 with surveillance patients using propensity scores. Risk of any-site recurrence, SLN-basin–only recurrence, and melanoma-specific mortality were compared.

RESULTS: Among 1,154 SLN-positive patients, 166 had ENE, microsatellites, and/or >3 positive SLN. At 18.5 months median follow-up, 49% had recurrence (vs 26% in patients without high-risk features, $p < 0.01$). Among high-risk patients, 52 (31%) underwent CLND and 114 (69%) received surveillance. Fifty-one CLND patients were matched to 51 surveillance patients. The matched cohort was balanced on tumor, nodal, and adjuvant treatment factors. There were no significant differences in any-site recurrence (CLND 49%, surveillance 45%, $p = 0.99$), SLN-basin–only recurrence (CLND 6%, surveillance 14%, $p = 0.20$), or melanoma-specific mortality (CLND 14%, surveillance 12%, $p = 0.86$).

CONCLUSIONS: SLN-positive patients with microsatellites, ENE, or >3 positive SLN constitute a high-risk group with a 2-fold greater recurrence risk. For those managed with nodal surveillance, SLN-basin recurrences were more frequent, but all-site recurrence and melanoma-specific mortality were comparable to patients treated with CLND. Most recurrences were outside the SLN-basin, supporting use of nodal surveillance for SLN-positive patients with microsatellites, ENE, and/or >3 positive SLN. (J Am Coll Surg 2021;232:424–431. Crown Copyright © 2020 Published by Elsevier Inc. on behalf of the American College of Surgeons. All rights reserved.)

Performance of completion lymph node dissection (CLND) for sentinel lymph node (SLN)-positive melanoma has declined substantially in the wake of the Second Multicenter Selective Lymphadenectomy Trial (MSLT-II) and the German Dermatologic Cooperative Oncology Group Selective Lymphadenectomy Trial (DeCOG-SLT), both of which demonstrated equivalent survival outcomes in patients receiving nodal basin surveillance compared with CLND.[1-3] While uptake of nodal surveillance has been enthusiastic and widespread, there are limitations of the applicability of these findings to specific high-risk patient populations who were poorly represented or not included at all in the landmark trials. More than 70% of MSLT-II participants and over 90% of DeCOG-SLT participants had only a single positive SLN; the majority had nodal tumor deposits <1 mm in greatest dimension, and both trials excluded patients with extension of tumor outside the involved node (extranodal extension [ENE]).[1,2,4] MSLT-II also excluded patients with microsatellitosis, and neither trial had more than a handful of patients with more than 3 positive sentinel nodes.[1,5]

For patients with high-risk tumor and nodal features that were not represented in these landmark trials, uncertainty remains regarding the appropriateness of nodal surveillance. Despite this, previous work demonstrated that nodal surveillance has been adopted for the majority of such patients.[3] To better inform management of SLN-positive patients who were not represented in the landmark nodal management trials, we sought to compare outcomes of CLND vs nodal surveillance for patients with these high-risk features.

METHODS

The study cohort included adult patients with SLN-positive cutaneous melanoma who were treated at 1 of 21 international centers in the 2 years after the June 2017 publication of MSLT-II (June 1, 2017 to June 30, 2019). Patients were excluded from the main study cohort if they had regional or distant metastases identified on staging studies conducted before or soon after the sentinel node biopsy, a previous melanoma, or concurrent (second primary) melanoma. Decisions regarding CLND vs nodal surveillance were at the discretion of treating clinicians and patients. Study data had been collected during standard of care evaluation and management, and were abstracted independently by providers at each institution. De-identified datasets were received and compiled by the

Abbreviations and Acronyms

AJCC = American Joint Committee on Cancer
CLND = completion lymph node dissection
DeCOG-SLT = Dermatologic Cooperative Oncology Group Trial
ENE = extranodal extension
MSLT-II = Second Multicenter Selective Lymphadenectomy Trial
RFS = recurrence-free survival
SLN = sentinel lymph node

central coordinating center, Moffitt Cancer Center, in compliance with Institutional Review Board/Ethics Committee-approved protocols and negotiated Data Use Agreements.

This study focused on a sub-population of patients within this main cohort who had high-risk disease, defined as extranodal extension, microsatellitosis, and/or more than 3 positive sentinel lymph nodes. Outcomes were compared for patients with and without these criteria to provide context, but the primary analysis was restricted to patients with high-risk characteristics because appropriate management for such patients was not adequately addressed by MSLT-II or DeCOG-SLT.

The primary study outcome was recurrence-free survival (RFS), which was defined as time to recurrence at any site, with patients censored at death or end of follow-up. Secondary outcomes included recurrence limited to the sentinel node basin (SLN-basin only recurrence), distant metastasis, and death due to melanoma. A propensity score matched analysis was performed to compare similar groups of patients with high-risk characteristics based on whether they were managed with CLND or nodal surveillance. Factors associated with performance of CLND vs nodal surveillance were determined using a stepwise logistic regression that included patient age, sex, primary site, tumor depth, presence of ulceration, number of positive sentinel lymph nodes, maximum dimension of nodal tumor deposit, American Joint Committee on Cancer (AJCC) 8th edition stage, receipt of adjuvant systemic therapy, and follow-up time. Variables achieving a p value of 0.30 were included in the regression model to calculate a propensity score for each patient. The propensity score corresponded to the likelihood of nodal management with CLND vs nodal surveillance. Patients were matched 1:1 on the propensity score using the nearest neighbor method with a caliper width of 0.30. The associations between nodal management (CLND vs nodal surveillance) and each survival outcome were compared using Kaplan-Meier curves with log rank tests. Statistical analyses were performed using Stata 15.1.[6]

Table 1. Characteristics of High-Risk Patients in this Study

High-risk criteria	N (%)
Extranodal extension, n (%)	56 (34)
Microsatellite, n (%)	80 (48)
>3 positive sentinel lymph nodes, n (%)	11 (7)
Extranodal extension and microsatellite, n (%)	17 (10)
Extranodal extension and >3 positive sentinel lymph nodes, n (%)	2 (1)
Total, n	166

RESULTS

Comparison of patients with and without high-risk characteristics

There were 1,154 patients in the multi-institutional cohort. Among these, 166 had high-risk characteristics including 56 with extranodal extension, 80 with microsatellites, 11 with more than 3 positive SLNs, 17 with both extranodal extension and microsatellites, and 2 with both extranodal extension and more than 3 positive SLNs (Table 1). Compared with the other patients in our cohort, these 166 patients were older, had greater Breslow depth primary tumors with more frequent ulceration and more head and neck primary tumors, were more likely to have nodal tumor deposits $\geq$1 mm, and had higher AJCC 8th edition stage (all values of $p < 0.01$) (Table 2). These patients were also more likely to have received adjuvant systemic therapy (51% vs 42%, $p = 0.04$), the most common adjuvant regimens received being anti-PD-1 immunotherapy (79%), BRAF/MEK inhibitor therapy (7%), and combination immunotherapy (3%).

A greater proportion of high-risk patients underwent CLND (52 of 166, 31%) than among patients without any of these characteristics (CLND 141 of 988, 14%). Of high-risk patients undergoing CLND, 54% had a positive non-SLN (28 of 52) compared with 18% of patients without any of these characteristics (26 of 141). Recurrence occurred in 49% of high-risk patients (81 of 166) at a median follow-up of 18.5 months, compared with only 26% of patients (260 of 988) without any of these characteristics (Table 2). Recurrences limited to the SLN-positive basin occurred in 11% of high-risk patients (18 of 166) compared to 8% without any of these characteristics (78 of 988). By the time of database lock, 12% (20 of 166) of high-risk patients had died due to melanoma vs only 4% without any of these characteristics (35 of 988).

Evaluating recurrence patterns based on the specific high-risk characteristics, rates of SLN-basin only and all-site recurrence were 13% and 47%, respectively, for patients with extranodal extension, 8% and 52%, respectively, for patients with microsatellites, and 15% and

Table 2. Comparison of Sentinel Lymph Node Positive Patients With and Without High-Risk Characteristics*

Variable	No high-risk characteristic	High-risk characteristic present	p Value
Patients, n	988	166	
Patient and disease characteristic			
Sex, m, n (%)	594 (60)	103 (62)	0.64
Age, y, median (25^{th}–75^{th} percentile)	60 (48–69)	68 (57–75)	<0.01†
Tumor location, n (%)			0.04†
Head and neck	127 (13)	27 (16)	
Trunk	394 (40)	49 (30)	
Extremity	467 (47)	90 (54)	
Breslow depth, mm, median (25^{th}–75^{th} percentile)	2.3 (1.4–4.0)	3.9 (2.7–6.0)	<0.01†
Ulceration, n (%)	377 (38)	92 (55)	<0.01†
Number of positive SLN, n (%)			<0.01†
1	782 (79)	94 (57)	
2–3	203 (21)	54 (33)	
4 or more	3 (<1)	18 (11)	
AJCC 8^{th} edition stage, n (%)			<0.01†
IIIA	315 (37)	9 (6)	
IIIB	203 (24)	14 (9)	
IIIC	342 (40)	118 (75)	
IIID	5 (<1)	17 (11)	
Treatment, n (%)			
Completion lymph node dissection	141 (14)	52 (31)	<0.01†
Adjuvant systemic therapy	414 (42)	84 (51)	0.04†
Outcome, n (%)			
Recurrence (any site)	260 (26)	81 (49)	<0.01†
SLN-basin only recurrence	78 (8)	18 (11)	0.20
Death due to melanoma	35 (4)	20 (12)	<0.01†

*Microsatellites, extranodal extension, and/or >3 positive sentinel nodes.
†Statistically significant.
AJCC, American Joint Committee on Cancer; SLN, sentinel lymph node.

54%, respectively, for patients with >3 positive SLNs (p = not significant for all comparisons).

Propensity-score matched analysis among patients with high-risk characteristics

In patients with 1 or more of the 3 high-risk characteristics, there were significant differences in propensity for CLND vs nodal surveillance based on patient and melanoma-specific factors, supporting the use of a propensity score matched analysis (Table 3). Using propensity scores, 51 of 52 CLND patients were matched to 51 nodal surveillance patients. The matched cohort was balanced with respect to patient, tumor, nodal, and adjuvant treatment factors (Table 3). Of CLND patients, 49% recurred (25 of 51) vs 45% of matched patients receiving nodal observation (23 of 51), with no difference in RFS (log rank 0.99) (Table 4, Fig. 1). Twelve-month RFS was 59% for CLND patients and 60% for surveillance patients. At 18 months, RFS was 40% for CLND patients and 46% for surveillance patients. Additionally, no statistically significant differences were observed in SLN-basin only recurrence (CLND 6% vs surveillance 14%, SLN-basin only RFS log rank p = 0.20), distant metastasis (CLND 33% vs surveillance 24%, distant metastasis-free survival log rank p = 0.68), or death due to melanoma (CLND 14% vs surveillance 12%, melanoma-specific survival log rank p = 0.86) (Table 4).

DISCUSSION

Although the paradigm-changing findings of MSLT-II and DeCOG-SLT have shaped treatment for the majority of SLN-positive melanoma patients, the appropriateness of nodal surveillance has remained unclear for the SLN-positive patients who were under-represented or excluded from these trials. This analysis of SLN-positive patients who were treated at major melanoma centers worldwide since MSLT-II publication confirmed that patients with

Table 3. Characteristics of Unmatched and Propensity-Score Matched Sentinel Lymph Node-Positive Patients with Extranodal Extension, Microsatellites, or More Than 3 Positive Nodes Based on Nodal Management with Surveillance vs Completion Lymph Node Dissection

	Unmatched patients			Matched* cohort		
Characteristic	**Surveillance**	**CLND**	**p Value**	**Surveillance**	**CLND**	**p Value**
No. of patients	114	52		51	51	
Sex, m, n (%)	72 (63)	31 (60)	0.66	29 (57)	30 (59)	0.84
Age, y, median (25^{th}–75^{th} percentile)	70 (58–76)	63 (55–74)	0.15†	68 (57–76)	64 (56–74)	0.24
Primary site, n (%)			0.76			0.81
Head and neck	18 (16)	9 (17)		9 (18)	8 (16)	
Trunk	32 (28)	17 (33)		14 (27)	17 (33)	
Extremity	64 (56)	26 (50)		28 (55)	26 (51)	
Breslow depth, mm, median (25^{th}–75^{th} percentile)	3.9 (2.8–5.8)	3.5 (2.7–6.0)	0.49	3.9 (2.8–5.1)	3.6 (2.7–6.0)	1.00
Ulceration, n (%)	60 (53)	32 (62)	0.28	29 (57)	32 (63)	0.54
Microsatellites, n (%)	70 (61)	27 (52)	0.25	26 (51)	26 (51)	1.00
Extranodal extension, n (%)	51 (45)	24 (46)	0.86	29 (57)	24 (47)	0.32
Number of positive SLN, n (%)			0.03†			0.50
1	71 (62)	23 (44)		24 (47)	23 (45)	
2–3	35 (31)	19 (37)		22 (43)	19 (37)	
≥4	8 (7)	10 (19)		5 (10)	9 (18)	
Size of nodal tumor, n (%)			0.02†			0.25
<1 mm	34 (30)	10 (19)		15 (29)	10 (20)	
≥1 mm	70 (61)	42 (81)		36 (71)	41 (80)	
Unknown	10 (9)	0 (0)		0 (0)	0 (0)	
Any positive non–SLN, n (%)	N/A	28 (54)	N/A	N/A	28 (55)	N/A
AJCC 8^{th} edition stage						
IIIA	6 (6)	3 (6)	0.10†	1 (2)	3 (6)	0.10
IIIB	11 (10)	3 (6)		6 (12)	3 (6)	
IIIC	82 (77)	36 (69)		41 (80)	35 (69)	
IIID	7 (7)	10 (19)		3 (6)	10 (20)	
Adjuvant therapy, n (%)	55 (48)	29 (56)	0.37	28 (55)	28 (55)	1.00
Follow-up, d, median (25^{th}–75^{th} percentile)	337 (203–784)	360 (57–769)	0.13	454 (57–643)	377 (56–779)	0.63

*Propensity score for CLND vs surveillance determined using stepwise logistic regression, including variables with p value ≥0.30; patients were matched 1:1 on the propensity score using the nearest neighbor method with a caliper width of 0.30.
†Statistically significant.
AJCC, American Joint Committee on Cancer; CLND, completion lymph node dissection; SLN, sentinel lymph node.

extranodal extension, microsatellites, and more than 3 positive sentinel nodes have significantly higher risk of all-site and nodal basin recurrence, as well as death due to melanoma. Patients with extranodal extension were excluded from both MSLT-II and DeCOG-SLT, and while patients with >3 positive SLNs were allowed,

Table 4. Time-to-Event Outcomes with Nodal Surveillance vs Completion Lymph Node Dissection in Matched Cohort of Patients with Extranodal Extension, Microsatellites, or More Than 3 Positive Nodes

	Entire follow-up period			12 months		18 months	
	Event			(95% CI)		(95% CI)	
Variable	**Surveillance**	**CLND**	**p Value***	**Surveillance**	**CLND**	**Surveillance**	**CLND**
Any site recurrence-free survival	23	25	0.99	60 (43–73)	59 (43–73)	46 (27–58)	40 (23–55)
SLN-basin only recurrence-free survival	7	3	0.20	88 (70–95)	94 (78–98)	78 (59–89)	90 (73–97)
Distant metastasis-free survival	12	17	0.68	78 (60–98)	78 (61–88)	74 (56–86)	57 (38–72)
Melanoma-specific survival	6	7	0.86	88 (71–95)	90 (72–97)	88 (71–95)	86 (67–69)

*Survival curves compared using log rank tests.
CLND, completion lymph node dissection; SLN, sentinel lymph node.

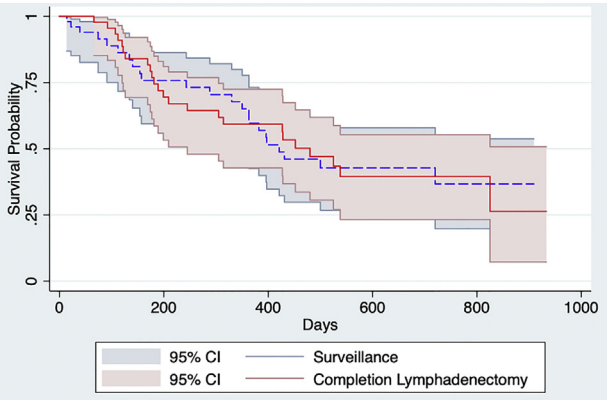

Figure 1. All-site recurrence-free survival for matched cohort of high-risk sentinel node-positive patients based on nodal management with surveillance vs completion lymph node dissection.

they constituted less than 1% of patients on MSLT-II and an unspecified but very low number of patients on DeCOG-SLT (only 8% of patients had 2 or more positive nodes). Nevertheless, within matched groups of patients who all had at least 1 of these characteristics, the central findings of MSLT-II and DeCOG-SLT were reproduced. While numerically fewer CLND patients had isolated nodal recurrences (although not statistically different in this small matched cohort), the majority of recurrences in this high-risk group of patients occurred outside the nodal basin. Accordingly, nodal management with surveillance vs CLND resulted in comparable all-site recurrence-free, distant metastasis-free, and melanoma-specific survival.

A principal rationale for conducting MSLT-II was the observation that in the majority of SLN-positive patients, the SLN(s) is/are the only positive nodes, with no additional nodal metastases identified in most completion dissection specimens.[1] By design, MSLT-II and DeCOG-SLT excluded patients whose disease characteristics portended a heightened risk of non-SLN metastases.[1,2] Previous studies have demonstrated positive non-SLNs in more than one-third of patients with extracapsular extension and more than half of patients with satellite foci.[7] Risk of non-SLN positivity also increases with number of positive SLNs.[7-10] This study validates these findings. In patients with any combination of extracapsular extension, microsatellites, or numerous positive SLNs, who did undergo CLND, 54% had additional non-SLN metastases, compared with 18% in patients without these features.

Among patients with 1 or more of these high-risk characteristics, a randomized controlled trial of nodal surveillance vs CLND is unlikely to ever be performed, so alternative strategies are needed to guide the selection of CLND vs nodal surveillance for such patients. The propensity-score matched analysis used in this study of exclusion patients was critical to mitigate selection bias and enabled comparison of nodal management strategies in similar groups of patients by matching patient, disease, and treatment factors, including the receipt of adjuvant systemic therapy.

Consistent with the heightened risk of residual nodal disease after positive SLN biopsy in these high-risk patients, the risk of SLN-basin–only recurrence was higher than in MSLT-II, with either nodal surveillance or CLND. While not statistically different in this study, SLN-basin–only recurrences occurred twice as often with nodal surveillance than CLND in matched high-risk patients (14% vs 6%). It is surprising that the difference was not greater, since 54% of the high-risk patients who underwent CLND were found to have positive non-SLNs compared to just 18% of patients without high-risk features. Nonetheless, in high-risk patients, nodal recurrences still accounted for the minority of recurrences, with the predominant recurrence pattern being distant or multisite disease, regardless of whether CLND was performed. Consistent with this, no difference was observed in the risk of death due to melanoma for the matched groups of high-risk patients who were managed with nodal surveillance vs CLND. These findings are comparable to those of both MSLT-II and DeCOG-SLT, in which CLND improved regional control but conferred no melanoma-specific survival benefit.[1,2,4]

More than half of our high-risk patients received adjuvant systemic therapy, differing from MSLT-II, which was conducted before widespread use of adjuvant immunotherapy or BRAF-targeted therapy. Our finding of more distant than regional recurrences aligns with recent reports of recurrence patterns in adjuvant therapy populations, which have demonstrated that distant recurrences are more common than locoregional recurrences, even among patients managed without CLND.[11,12] However, our study was not powered to address the value of adjuvant therapy in this specific patient population. It is also important to recognize that CLND does not absolve the nodal basin from future recurrence; a recent multi-institutional study of patients with recurrence treated with adjuvant anti-PD-1 therapy demonstrated that after CLND for SLN-positive disease, one-third of recurrences involved the SLN basin.[11]

Although nodal basin recurrence is a significant concern for patients with high-risk primary tumor or sentinel node features, our analysis suggests a role for deferral of regional lymphadenectomy to prioritize prompt initiation of adjuvant systemic therapy. This strategy to defer regional lymphadenectomy in these high-risk SLN-positive patients

assumes they will have appropriate surveillance to detect SLN-basin recurrences at a point when regional control can still be achieved with therapeutic lymphadenectomy. In the larger patient cohort receiving nodal surveillance, from which this study population was derived, we previously demonstrated that SLN-basin recurrences were universally salvageable.[3] Another large retrospective cohort of 370 nodal surveillance patients treated at a comprehensive cancer center had only a single patient with an unresectable isolated SLN-basin recurrence.[13] However, it is unknown whether this will be the case outside major melanoma centers, where access and attention to surveillance may differ.

The concept of deferring additional regional surgery to expedite systemic therapy is based on an as-yet unproven assumption that early initiation of adjuvant treatment confers greater benefit than waiting for the patient to recover from lymphadenectomy. Adjuvant trial protocols typically require initiation of treatment within 12 weeks of surgery. Early post-lymphadenectomy recurrence has been identified in 18% of patients in whom distant disease was excluded preoperatively and who underwent restaging before initiation of adjuvant treatment.[14] However, an impact of time to adjuvant therapy initiation on oncologic outcomes has not been formally assessed.

There may be selection bias with respect to assessment of microsatellitosis and SLN-positive disease in our study because some providers do not perform SLN biopsy in patients with microsatellitosis. The presence of microsatellitoses is an adverse prognostic feature that is considered to be commensurate with having SLN-positive disease, the basis for AJCC 8th edition staging of patients with microsatellitosis, satellites, or in-transit disease as at least IIIB.[15] At the same time, the status of SLNs in patients with microsatellitosis appears informative, with SLN-negative patients with microsatellitosis having a better prognosis than comparably staged SLN-positive patients.[16,17] While there were variable practices with respect to performance of SLN biopsy in patients with microsatellitosis across the 21 participating centers, all analyzed patients with microsatellitosis had SLN-positive disease, and patients were matched on presence of microsatellitosis, so we expect that there was little to no impact of this selection bias on the primary endpoint of recurrence-free survival.

Another limitation of this study is the relatively short median follow-up of 18.5 months, particularly with more than 50% of patients receiving adjuvant systemic therapy. Before modern adjuvant immunotherapy and BRAF-targeted therapy, the median time to nodal recurrence for SLN-positive patients managed with nodal surveillance was 9 to 12 months, a time frame that would capture the majority of recurrences in this study.[1,2,18] However, modern adjuvant therapy has lengthened this time significantly, with a recent report of SLN-positive patients receiving nodal surveillance demonstrating median RFS of 12 months with SLN-biopsy alone, and 15 and 18 months for patients receiving adjuvant immunotherapy or BRAF/MEK inhibitor therapy, respectively.[12] At the same time, our patients constitute a higher risk patient population than previously analyzed, in whom time to relapse is likely shorter, increasing the proportion of expected recurrences that have been captured during the available follow-up.

CONCLUSIONS

Disease recurrence was twice as frequent in SLN-positive patients with high-risk characteristics including extranodal extension, microsatellitosis, and/or more than 3 positive sentinel nodes. Our propensity-score matched analysis of these patients demonstrated that while SLN-basin only recurrences were higher with surveillance only, all-site recurrence and melanoma-specific mortality were comparable, whether or not CLND was performed. Because most recurrences were outside the SLN-positive basin, initiation of adjuvant systemic therapy might be prioritized over CLND in these high-risk patients.

Author Contributions

Study conception and design: Broman, Dossett, Zager
Acquisition of data: All authors
Analysis and interpretation of data: Broman, Dossett, Sun, Kirichenko, Bartlett, Nijuis, Thompson, Zager
Drafting of manuscript: Broman, Zager
Critical revision: All authors

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Invited Commentary

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The authors and the International High-Risk Melanoma Consortium have followed the natural course of academic inquiry that would follow publication of the Multicenter Selective Lymphadenectomy Trial-2 (MSLT-2) and the German Dermatologic Cooperative Oncology Group Trial (DeCOG-SLT) studies by asking if the published results could be expanded to include essentially any patients with microscopic nodal metastases from melanoma. This study[1] reviews outcomes from patients with higher risk stage III disease than what was originally included in the 2 prospective randomized trials. Their discussion is extensive and explores the questions that most of us would have about the importance of these data. I do believe that there are some opportunities to explore additional questions. Their analysis is sound, though it is limited by 2 significant challenges: it is retrospective in nature and the overall follow-up time is limited, especially when one considers patients who have recurrence in their nodal basin after observation.

Why did this study include microsatellitosis, a high-risk characteristic of the primary tumor, when the question actually focuses on nodal disease and management of the lymph node basin? Presumably, the study seeks to analyze outcomes of patients with all higher risk stage III patients. The confounding aspect of inclusion of these patients is that they are not necessarily associated with a higher risk of nodal disease, but are certainly associated with a higher risk of systemic disease. The analysis does not discern what percentage of these patients contributed to the systemic disease failures, but may skew the results to disproportionately affect the outcomes that demonstrate that most of the recurrences in this study are distant rather than regional.

Approximately 50% of patients received adjuvant therapy. Do the authors believe that systemic therapy has the same efficacy in the nodal basin as it does in hematogenous metastases? In my (anecdotal) experience, current systemic therapy options do not appear as effective in the nodal basin as they are for systemic metastases. Whether this affects survival or not is critical to decision-making around the nodal basin, but regardless, it is important to note that we still do not have truly long-term follow-up on patients undergoing systemic therapy without completion lymph node dissection (CLND). As we gain more experience with this approach to nodal disease, we will be able to make better assessments for patients and provide counsel on the role of CLND in the small subset of patients with a high risk of nonsentinel lymph node metastases.

Were all patients surveilled with ultrasound and if not, is there any evidence that ultrasound surveillance has any impact on outcome or earlier detection of disease? If we are to accept the premise that metastases are effectively treated with systemic therapy regardless of burden of disease, then the role for routine ultrasound surveillance becomes less significant. If we believe that nodal disease appears to have a differing response to systemic therapy than hematogenous metastases, then this is another argument that ultrasound surveillance is less impactful because the role of detection becomes less significant. Finally, if detection of disease is, in fact, earlier with ultrasound, then such detection would need to be early enough to improve outcomes from systemic therapy, which is highly unlikely, especially since, in this extremely high-risk patient population, most patients had recurrence outside the nodal basin, thereby making ultrasound surveillance of the nodal basin unnecessary anyway. While the focus of this study is not on the role of ultrasound surveillance, it may prompt us to consider whether it should be routinely used or not.

As noted by the authors in their discussion and in my second point above, the follow-up of patients with nodal basin recurrence