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ORIGINAL ARTICLE – MELANOMAS

Observation After a Positive Sentinel Lymph Node Biopsy in Patients with Melanoma

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ABSTRACT

Background. The benefit of completion lymph node dissection (CLND) in melanoma patients with a positive sentinel lymph node (SLN) remains unknown.

Methods. We identified patients with a positive SLN from 1994 to 2012. Patient and tumor characteristics, reasons for not undergoing CLND, patterns of recurrence, and melanoma-specific survival data were analyzed.

Results. Of 4,310 patients undergoing SLN biopsy (SLNB), 495 (11 %) had a positive SLN—167 (34 %) patients underwent nodal observation and 328 (66 %) had immediate CLND. Patients in the no-CLND group were older (66 vs. 56 years; $p < 0.001$) and more likely to have lower extremity lesions (57 vs. 42 %; $p = 0.006$). There were no differences in tumor thickness, Clark level of invasion, ulceration, or SLN tumor burden. Median follow-up was 23 and 80 months for the no-CLND and CLND groups, respectively, and median time to recurrence was similar at 9 and 12 months, respectively ($p = 0.48$). There was no difference in local and in transit recurrence rates between groups (16 %, no CLND, and 18 %, CLND; $p = 0.48$). Nodal disease as a site of first recurrence occurred in 15 % of patients in the no-CLND group and 6 % of CLND patients ($p = 0.002$). In contrast, systemic recurrences occurred in 8 % of no-CLND patients compared with 27 % of CLND patients ($p < 0.001$). While median recurrence-free survival was higher after CLND (34.5 vs. 20.9 months; $p = 0.02$), melanoma-specific survival was similar (not reached, no CLND vs. 110 months, CLND; $p = 0.09$).

Conclusions. Immediate CLND after a positive SLNB is associated with fewer initial nodal basin recurrences but similar melanoma-specific survival. These results support ongoing equipoise in the Multicenter Selective Lymphadenectomy Trial II (MSLT-II).

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The incidence of invasive melanoma in the US continues to rise.[1] With widespread adoption of sentinel lymph node (SLN) biopsy (SLNB) for staging patients with primary melanomas >1 mm in depth, the number of patients with stage III disease has increased considerably.[2,3] Completion lymph node dissection (CLND) after a positive SLNB evolved as the standard approach for patients with invasive melanoma. National Comprehensive Cancer Network (NCCN) guidelines for patients with positive SLNB recommend options of either immediate CLND or enrollment in a clinical trial investigating alternatives such as close observation.[4] Despite these recommendations, a recent review of the National Cancer Database showed that only 50 % of patients with a positive SLNB underwent CLND.[5] This disparity highlights the ongoing debate surrounding the merits of CLND.

The presence of disease within the non-SLNs (NSLN) is the most important predictor of poor survival in patients with a positive SLN undergoing CLND.[3,6] Clearance of the regional lymph node basin with CLND may also cure a subset of patients with positive SLNs.[2] However, most patients do not harbor metastatic disease in the NSLN[2,7] and yet are still at risk of developing distant disease. This would be another potential argument against routine CLND in these patients. Coupled with the morbidity of CLND, lack of effective adjuvant therapy, and absence of prospective, randomized data on the role of CLND in improving survival, the argument for nodal observation in patients with positive SLNs persists.

In a multi-institutional study by Wong et al.[8] 134 patients with a positive SLNB underwent nodal observation. When

compared with a contemporary group of 164 patients undergoing immediate CLND, there was no difference in melanoma-specific survival [74 % 3-year disease-specific survival (DSS) for CLND vs. 80 % for no CLND; $p = 0.65$]. Only patient age and thickness of the primary tumor were predictive of survival on multivariate analysis. Limitations of this study include short median follow-up (20 months), small sample size ($n = 134$), and significantly less tumor ulceration in the observation group. A subsequent single institution study by Kingham et al.[9] included 37 patients undergoing nodal observation with longer follow-up (median of 32 months). The authors found no differences in DSS or recurrence-free survival (RFS) when compared with 271 patients undergoing immediate CLND. With 15–20 % of patients expected to harbor metastatic disease in the NSLN,[2] the low number of patients in the nodal observation arm limited the power of this study.

Herein, we report the largest single institution experience to date comparing outcomes in patients undergoing nodal observation versus those having immediate CLND following positive SLNB. The aims of our study are to (i) characterize the populations undergoing nodal observation (no CLND) and CLND; (ii) determine the pattern of initial recurrence between the no-CLND and CLND groups; (iii) determine melanoma-specific survival of both patient groups; (iv) characterize the outcome of no-CLND patients who experience a subsequent isolated nodal recurrence.

METHODS

A prospectively maintained melanoma database was used to identify patients undergoing SLNB. All patients underwent preoperative lymphoscintigraphy with intradermal injection of 99 mTc-sulfur colloid (400 mCi) on the day of surgery and intraoperative intradermal injection of 1 % isosulfan blue dye. The sentinel node(s) were identified during surgery with the use of a gamma probe and visual identification of blue nodes in the nodal basin identified on lymphoscintigraphy. All blue nodes and/or those with a high count were considered sentinel nodes. When the nodal basin count was less than 10 % of the count of the hottest node removed, the sentinel lymphadenectomy was concluded. The technique of histologic evaluation of the SLN includes a period of fixation, bisection through the longest meridian, and hematoxylin and eosin (H&E)-stained sections from each half. If the H&E is negative, then two additional H&E sections are analyzed. If all H&E are negative, immunohistochemistry is performed on two serial sections (250 μm) with staining for HMB45 and S100. Histologic evaluation after nodal clearance includes a similar H&E evaluation of each resected node as described above. Tumor burden within the SLN was measured and categorized as <0.1, 0.1–1, or >1 mm according to the Rotterdam criteria.[10] If multiple lesions were present, the largest lesion was recorded. Patients with metastatic disease within the SLN were divided into two groups. One group underwent CLND and the other nodal observation. The reasons for nodal observation were captured from the electronic medical record and categorized as previously described.[9] Those in the no-CLND group who went on to develop nodal recurrence without distant metastatic disease underwent salvage lymphadenectomy. These patients were included in the no-CLND group for analyses. Patients with stage IV disease on extent of disease work-up and those undergoing nodal observation under the Multicenter Selective Lymphadenectomy Trial II (MSLT-II) were excluded. Demographic characteristics, clinicopathologic findings, and follow-up status were recorded. Recurrences were categorized as nodal, regional (local and in-transit disease) or systemic and were identified during follow-up visits consistent with NCCN guidelines. Access to patient information was approved by the Memorial Sloan-Kettering Cancer Center Institutional Review and Privacy Board.

Clinical variables for the CLND and no-CLND groups were analyzed using Fisher's exact test for categorical variables and the Kruskal–Wallis test for continuous variables. Survival rates were calculated by the Kaplan–Meier method. A p value <0.05 was considered statistically significant. Statistical analyses were performed using R (R Development Core Team 2011), including the 'survival' package.

RESULTS

Of 4,310 patients undergoing wide local excision with SLNB, 495 (11 %) were found to have a positive SLN. One hundred and sixty-seven patients underwent nodal observation (34 %) and 328 had an immediate CLND (66 %). Patient and primary tumor characteristics are shown in Table 1. Patients in the no-CLND group were significantly older than those undergoing CLND (66 vs. 56 years; $p < 0.001$). Although males were more likely to harbor a positive SLN, there were no differences in gender distribution between the groups. Median tumor thickness was similar between groups (2.8 mm) but tumor location varied. Patients in the no-CLND group were more likely to have lower extremity primary lesions (57 vs. 42 %) and had less truncal involvement (28 vs. 42 %; $p = 0.006$). There were no differences in the rate of tumor ulceration (46 vs. 44 % no-CLND; $p = 0.84$) or Clark level of invasion between groups.

TABLE 1 Patient and primary tumor characteristics

Characteristic	No CLND ($N = 167$)	CLND ($N = 328$)	p value
Age [years; median (range)]	66 (8–95)	56 (7–90)	<0.001
Sex [n (%)]			1.00
Male	105 (63)	205 (63)	
Female	62 (37)	123 (37)	
Tumor thickness [mm; median (range)]	2.8 (0.7–18)	2.8 (0.7–38)	0.97
Location [n (%)]			0.007
Upper extremity	23 (14)	33 (10)	
Lower extremity	71 (43)	104 (32)	
Head/neck	21 (13)	37 (11)	
Trunk	46 (28)	136 (42)	
Unknown/other	5 (3)	18 (5)	
Clark Level [n (%)]			0.58
II	1 (0.6)	0 (0)	
III	8 (5)	20 (6)	
IV	127 (76)	241 (74)	
V	21 (13)	40 (13)	
Unknown/NA	10 (6)	27 (8)	
Ulceration [n (%)]			0.84
Present	77 (46)	141 (44)	
Absent	84 (50)	144 (44)	
Unknown	6 (4)	43 (13)	

CLND completion lymph node dissection, *NA* not applicable

TABLE 2 Nodal basin and SLN characteristics

Characteristic	No CLND ($n = 167$)	CLND ($n = 328$)	p value
Nodal basin [n (%)]			
Axilla	48 (29)	136 (42)	0.03
Groin	72 (43)	117 (36)	
Neck	20 (12)	40 (12)	
Popliteal	1 (0.6)	0 (0)	
Other	1 (0.6)	1 (0.3)	
>1 nodal basin [n (%)]	24 (14)	33 (10)	
Axilla as component of draining basin	16	25	
Groin as component of draining basin	7	5	
Neck as component of draining basin	1	2	
Popliteal as component of draining basin	0	1	
Median number of LNs examined with SLNB (range)	2 (1–15)	2 (1–14)	0.17
Patients with single positive SLN [n (%)]	134 (80)	246 (75)	0.23
Patients with positive non-SLN [n (%)]	NA	53 (16)	
If non-SLN positive, median number of additional positive nodes (range)	NA	1 (1–8)	
Sentinel lymph node tumor diameter [n (%)][a] (mm)			0.23
<0.1	50 (30)	75 (23)	
0.1–1	52 (31)	53 (16)	
>1	34 (20)	54 (16)	

SLN sentinel lymph node, *CLND* completion lymph node dissection, *LNs* lymph nodes, *SLNB* sentinel lymph node biopsy, *NA* not applicable

[a] Includes only patients in whom SLN tumor diameter was recorded (no CLND, N = 136; CLND, N = 182)

As expected, based on the differences in location of primary tumors between groups, the distribution of involved nodal basins also differed (Table 2). The no-CLND group had a greater percentage of patients with groin node involvement (43 vs. 36 %; $p = 0.03$) and fewer with axillary basin involvement (29 vs. 42 %; $p = 0.03$). Fourteen percent of patients in the no-CLND group had more than one nodal basin involved compared with 10 % in the CLND group. There were no differences in the median number of lymph nodes examined (two for both groups; $p = 0.17$) or the percentage of patients with a single positive SLN (80 % no-CLND vs. 75 % CLND; $p = 0.23$). The degree of SLN tumor burden was similar between groups.

In 66 % of the no-CLND cohort, the reason for not undergoing CLND was patient decision. Physician decision was the second most common reason, documented in 22 % of cases. Patient co-morbidities was a cited reason in the minority of cases (4 % patients).

Median follow-up was 23 and 80 months for the no-CLND and CLND groups, respectively (Table 3). Eighty-one patients (49 %) recurred in the no-CLND group, with a median time to recurrence of 9 months. Similarly, 179 patients (55 %) undergoing CLND recurred, with a median time of 12 months ($p = 0.46$). When considering sites of first recurrence, there were no differences in regional recurrence rates between groups (16 % no CLND vs. 18 % CLND; $p = 0.58$). In contrast, nodal only (15 % no CLND vs. 6 % CLND; $p = 0.002$) and systemic only (8 % no CLND vs. 27 % CLND; $p < 0.001$) recurrences differed considerably. Among the patients who recurred systemically, median time to recurrence was 9 months in the no-CLND group and 18 months in the CLND group.

Of the 25 patients in the no-CLND group who developed nodal basin-only recurrence, 18 (72 %) underwent salvage lymphadenectomy. On last evaluation of these 18 patients (median follow-up time of 18 months), 2 (11 %) died of disease, 12 (67 %) remain free of disease, and 4 (22 %) are alive with disease. The reasons for forgoing

TABLE 3 Patterns of first recurrence

	No CLND ($n = 167$)	CLND ($n = 328$)	p value
Median follow-up (months)	23	80	
Recurrence [n (%)]	81 (49)	179 (55)	
Time to first recurrence (months)	9	12	0.46
Site of first recurrence [n (%)]			
Regional recurrence only	26 (16)	59 (18)	0.58
Nodal recurrence only	25 (15)	20 (6)	0.002
Systemic recurrence only	13 (8)	89 (27)	<0.001
Regional disease as component of recurrence	34 (20)	65 (20)	
Nodal disease as component of recurrence	26 (16)	23 (7)	
Systemic disease as component of recurrence	21 (13)	90 (27)	

CLND completion lymph node dissection

salvage lymphadenectomy in the remaining seven patients include patient refusal ($n = 2$), lost to follow-up ($n = 1$), prohibitive co-morbidities ($n = 1$), development of concurrent stage IV breast cancer ($n = 1$), patient/doctor decision to pursue systemic treatment due to location and pathologic features of the primary tumor ($n = 2$). Specifically, there were no cases in which the decision to forgo salvage lymphadenectomy was due to documented distant metastatic melanoma. At last evaluation (median follow-up of 18 months), two of these seven (29 %) patients are alive with disease and the remaining five (71 %) had died (three died of other causes, and two died of disease).

Survival

Median DSS was similar between groups (not reached for no CLND vs. 110 months CLND; $p = 0.09$; Fig. 1a). However, RFS was significantly higher in the CLND group (34.5 vs. 21 months; $p = 0.02$; Fig. 1b). Median DSS of patients who developed systemic disease at first recurrence was 46 months for the no-CLND group and 35 months for the CLND group ($p = 0.98$). We next compared DSS in patients undergoing immediate CLND with a positive NSLN ($n = 59$) with those in the no-CLND group who developed node-only recurrence and went on to salvage lymphadenectomy ($n = 19$; Fig. 1c). Interestingly, we found a melanoma-specific survival advantage favoring the salvage lymphadenectomy group (median DSS 36.5 months CLND vs. not reached for salvage LND; $p = 0.005$).

On univariate analysis, increasing age, tumor thickness, and the presence of ulceration were associated with higher melanoma-specific mortality (Table 4). Because it was a major factor of interest in this study and there was a statistically insignificant trend towards worse DSS with CLND ($p = 0.09$), it was included in the multivariate model. Factors associated with higher melanoma-specific mortality on multivariable analysis included increasing age ($p = 0.006$), tumor thickness ($p = 0.001$), and ulceration ($p < 0.001$; Table 4).

DISCUSSION

In the absence of data from prospective randomized trials, the therapeutic value of CLND in the management of melanoma patients with positive SLNs is still debated. The potential merits of CLND include improved staging and regional lymph node control. In addition, a subset of the 16 % of patients who harbor metastatic disease in the NSLNs are rendered disease-free and potentially cured. In contrast, the majority of patients undergoing CLND do so at the cost of its associated morbidity and are unlikely to receive any therapeutic benefit as disease is either limited to the SLN or has already spread beyond the nodal basin. Our inability to determine whether NSLN disease is a predictor or determinant of non-nodal failure forms the basis of the CLND debate.

In over 2,000 patients treated in the Sunbelt melanoma trial, major complications occurred in 23 % of patients after CLND compared with 4.6 % after SLNB.[11] In a report by De Vries et al.[12] 50 % of patients undergoing CLND experienced a complication compared with 6 % after SLNB. Quality of life has also shown to be worse in those who underwent CLND versus patients who had SLNB alone.[13] The higher morbidity and poorer quality of life associated with inguinal lymphadenectomy may in part explain why a greater percentage of patients in the no-CLND group had lower extremity lesions and positive SLNs in the inguinal basin.

The present study showed that immediate CLND after a positive SLNB is associated with a decreased rate of nodal basin recurrence. Our rates of nodal recurrence (16 % no CLND and 6 % CLND) are consistent with published reports.[2,14] Importantly, there were no cases of patients developing uncontrolled nodal disease in the observation arm. Interestingly, systemic disease as a site of first recurrence differed among groups (8 % no CLND vs. 27 % CLND). Possible explanations include patient selection bias and differences in follow-up time between groups. Similarities in tumor depth, Clark level, ulceration, and SLN tumor burden between groups would argue against selection bias, but due to the retrospective nature of this study it was not possible to determine exactly which clinicopathologic factors influenced surgeons' decisions to forgo CLND. Another possibility is that follow-up time for the no-CLND group was

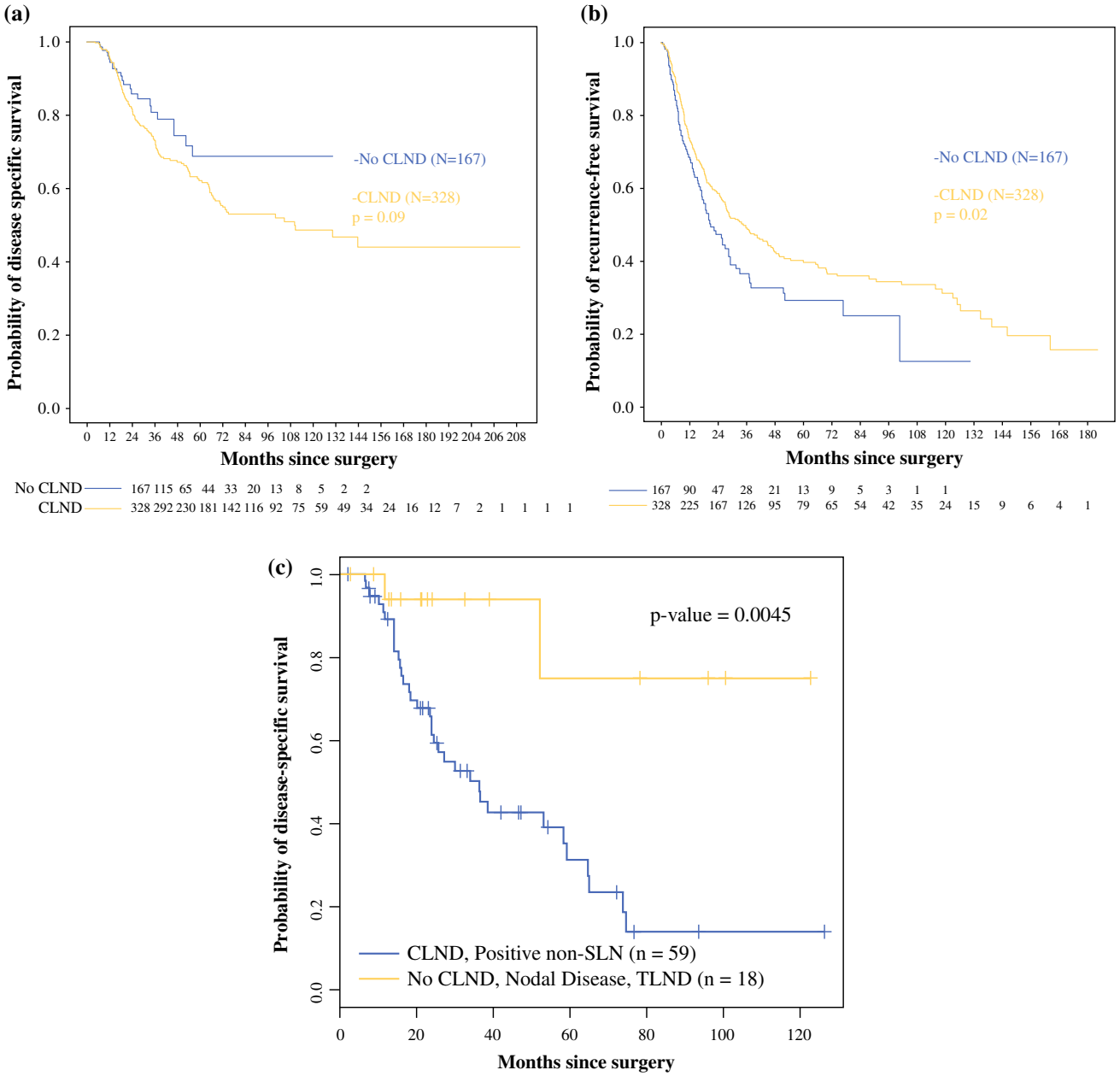

FIG. 1 Outcome in melanoma patients with a positive SLN selected for nodal basin observation; (**a**) Disease-specific survival of patients selected for nodal basin observation (*N*-Ã=-Ã167) vs. those who underwent CLND (*N*-Ã=-Ã328); (**b**) Recurrence-free survival of patients selected for nodal basin observation (*N*-Ã=-Ã167) vs. those who underwent CLND (*N*-Ã=-Ã328);(**c**) Disease-specific survival of patients selected for initial nodal basin observation who developed nodal basin recurrence only and who went on to therapeutic LND (*N*-Ã=-Ã18) vs. those who had a positive non-sentinel node at initial CLND (*N*-Ã=-Ã59)

shorter (23 vs. 80 months) and therefore a smaller proportion of all systemic recurrences had been detected in the no-CLND group. This factor may be particularly pertinent as patients with thin melanomas (0.75–1 mm) were also included in this study. Although only 4 % of our patient cohort had primary lesions <1 mm thick and a positive SLN, sufficient follow-up time to detect all potential recurrences is a limitation of our study. Although the median time to systemic recurrence in the no CLND is in line with other reports,[15] with longer follow-up we expect median time to systemic recurrence would increase.

Melanoma-specific survival after salvage lymphadenectomy was improved when compared with patients with positive NSLN having immediate CLND. We are cautious in drawing any conclusions on the survival advantage of salvage lymphadenectomy as the numbers of patients at risk are small (n = 18), follow-up is limited, and the observed findings may simply reflect patient selection bias.

TABLE 4 Univariate and multivariate survival analysis for disease-specific mortality

Characteristic	Univariate analysis			Multivariate analysis			
	N	No. of patients who died of disease	*p* value	HR	95% lower limit	95% upper limit	*p* value
All patients	495	147					
CLND			0.09	CLND (Y vs. N)			
No	167	23		1.51	0.94	2.42	0.09
Yes	328	124					
Age (continuous)	494	147	0.01	1.01	1.00	1.03	0.006
Sex			0.17				
Male	310	98					
Female	185	49					
Tumor thickness (mm; median)	480	141	<0.001	1.08	1.03	1.13	0.001
Location			0.46				
Extremity	231	63					
Head/neck	58	19					
Trunk	182	56					
Unknown/other	23	9					
Clark level			0.21				
II	1	0					
III	28	10					
IV	368	96					
V	61	22					
Ulceration			<0.001	Ulceration (present vs. absent)			
Present	218	84		2.06	1.38	3.08	<0.001
Absent	228	38					
Sentinel lymph node tumor diameter (mm)			0.25				
<0.1	125	28					
0.1–1	105	11					
>1	88	17					

Including variables with a *p* value <0.1 on univariate analysis

HR hazard ratio, *CLND* completion lymph node dissection

The current study represents the largest experience on the natural history of nodal observation after a positive SLNB in melanoma. In contrast to prior studies,[8,9] we were able to measure SLN tumor burden in most patients. Efforts to identify which patients may benefit from CLND have studied SLN tumor burden in order to predict the likelihood of harboring positive NSLN. Starz et al.[16] found that invasion deeper than 1 mm below the SLN capsule yielded a survival similar to that of patients undergoing a therapeutic lymph node dissection, and was a powerful predictor of NSLN positivity. A recent validation study showed that a metastatic deposit smaller than 0.1 mm and with a maximal depth of invasion less than 0.3 mm yielded a very low probability (0–5 %) of further NSLN metastases.[17] Dewar and colleagues found that micrometastases confined to the subcapsular space ($n = 38$) had the most favorable prognosis as none of these patients had disease in the NSLN.[18] The selection bias in these retrospective series are important to note and the techniques of measuring SLN tumor burden are highly variable and not standardized. In a recent publication by van der Ploeg and colleagues, SLN tumor burden was extensively characterized in 61 patients undergoing nodal observation who were matched with a cohort undergoing immediate CLND.[19] Multivariate analysis failed to show a DSS advantage for immediate CLND. Moreover, a subgroup analysis that stratified patients by the degree of SLN tumor burden also failed to show a benefit for immediate CLND. Veenstra et al.[20] reported 5-year follow-up of 16 melanoma patients with a positive SLN ($\leq$0.3 mm tumor depth below the SLN capsule) in whom CLND was omitted.

With a median follow-up of 66 months, no patients developed a nodal recurrence. Local recurrence occurred in one patient and satellite metastases occurred in another. Albeit a small sample size of highly selected patients, these data suggest that nodal observation in certain patients with a positive SLN could be considered.

CONCLUSIONS

Selection criteria to forgo CLND remain undefined. Patient age, comorbidities, pathologic features of the primary, and measurements of tumor burden within the SLN may play an important role in selection. Our data do not support routine CLND in all patients with a positive SLNB. Importantly, the observed difference in RFS favoring CLND did not translate to a difference in melanoma-specific survival between groups. With pre-randomization stratification, MSLT II and the European MINITUB study will clarify some of these issues.

DISCLOSURES None.

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