Preoperative Ultrasound Assessment of Regional Lymph Nodes in Melanoma Patients Does not Provide Reliable Nodal Staging

Results from a Large Multicenter Trial

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Objective: To assess whether preoperative ultrasound (US) assessment of regional lymph nodes in patients who present with primary cutaneous melanoma provides accurate staging.

Background: It has been suggested that preoperative US could avoid the need for sentinel node (SN) biopsy, but in most single-institution reports, the sensitivity of preoperative US has been low.

Methods: Preoperative US data and SNB results were analyzed for patients enrolled at 20 centers participating in the screening phase of the second Multicenter Selective Lymphadenectomy Trial. Excised SNs were histopathologically assessed and considered positive if any melanoma was seen.

Results: SNs were identified and removed from 2859 patients who had preoperative US evaluation. Among those patients, 548 had SN metastases. US was positive (abnormal) in 87 patients (3.0%). Among SN-positive patients, 39 (7.1%) had an abnormal US. When analyzed by lymph node basin, 3302 basins were evaluated, and 38 were true positive (1.2%). By basin, the sensitivity of US was 6.6% (95% confidence interval: 4.6–8.7) and the specificity 98.0% (95% CI: 97.5–98.5). Median cross-sectional area of all SN metastases was 0.13 mm^2; in US true-positive nodes, it was 6.8 mm^2. US sensitivity increased with increasing Breslow thickness of the primary melanoma (0% for ≤1 mm thickness, 11.9% for >4 mm thickness). US sensitivity was not significantly greater with higher trial center volume or with pre-US lymphoscintigraphy.

Conclusion: In the MSLT-II screening phase population, SN tumor volume was usually too small to be reliably detected by US. For accurate nodal staging to guide the management of melanoma patients, US is not an effective substitute for SN biopsy.

Keywords: melanoma, staging, ultrasound

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Accurate staging of the draining lymph node basin is essential if patients who present with primary cutaneous melanomas are to be managed in the most appropriate way. Following the introduction of the minimally invasive technique of sentinel node (SN) biopsy in the early 1990s, several large studies have shown that SN biopsy, with careful histopathologic assessment of the SNs that are removed, provides more accurate nodal staging than any other test.[1–4] However, the suggestion has been made that ultrasound (US) examination of regional lymph nodes, with or without fine needle biopsy of suspicious nodes, may provide similarly accurate staging and avoid the need for surgical removal of SNs.[5–11]

The availability of prospectively collected preoperative US data for patients with primary cutaneous melanomas enrolled in a large international randomized multicenter trial, the second Multicenter Selective Lymphadenectomy Trial (MSLT-II), provided the opportunity to examine this matter and determine the accuracy of US in detecting metastatic tumor deposits in the SNs of clinically node-negative patients. Patient accrual to MSLT-II was completed in March 2014, when 1939 patients had been randomized, and the initial report of the trial was published in 2017.[12] In MSLT-II, patients found to be SN-positive, and who agreed to enter the study and fulfilled all eligibility criteria, were randomized to have an immediate completion lymph node dissection (CLND) or to have the residual lymph nodes in that node basin monitored with regular US examinations. If evidence of further nodal metastasis was found during follow-up on US or clinical examination, and histological confirmation was obtained (usually by fine needle biopsy), a ''late'' CLND was performed at that time. At the 20 centers that entered patients into the ''screening phase'' of MSLT-II (in which patients were enrolled before SN biopsy), routine preoperative US examination of the relevant node basin(s) was performed.

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The prospective collection of preoperative US data in MSLT-II provided an ideal opportunity to compare the results of preoperative US with the subsequent detailed histologic assessment of SNs that were surgically removed. The aim of the present study was thus to document and analyze the results of preoperative US assessment of regional node basins in patients enrolled in the screening phase of MSLT-II, and to compare the accuracy of US with the gold standard of histologic SN assessment.

METHODS

The protocol for the screening phase of MSLT-II mandated preoperative US evaluation of the relevant regional lymph node basin for all patients, and a preoperative lymphoscintigram (LSG). In some centers, general US assessment of the entire node basin was performed before the LSG, while in other centers it was performed after the LSG, when the location of SNs was known, allowing focused US examination of them if the result of the LSG was known to the ultrasonographer.[13] Either was permitted by the trial protocol.

Before commencement of patient enrolment in the trial at each center, the relevant personnel received written guidelines, detailed in the trial operations manual, to ensure uniform application of the US protocol. This protocol was also explained and discussed at the initial investigators' meeting in December 2004. The US guidelines stated that an abnormal node was characterized by the detection of either 1 or 2 of the following: (1) length:depth ratio <2; (2) a hypoechoic center; (3) inability to identify a nodal hilar vessel; (4) a focal rounded area of low-level echoes with increased vascularity in that area.

US data for each center were collected prospectively, and were correlated with the findings from subsequent histologic examination of the SN(s) removed from each patient. Patients in whom no SN was identified (n = 12) were excluded. Patients in whom the preoperative US was of a basin other than the SN basin subsequently demonstrated by lymphoscintigraphy were also excluded (n = 5). Of 3437 possible SN basins, 25 had no SN identified and 110 basins assessed by US were non-SN basins, resulting in 3302 eligible basin evaluations (see Fig. 1). Patients with SNs found to be positive only by RT-PCR were considered pathologically negative for this study.

At all centers, the SN histopathology was assessed using standard hematoxylin and eosin (H&E) stained sections, and with immunohistochemistry (including S100, Mart-1, and HMB45), as previously described.[14,15] Central pathology review of all SNs that had been reported by the contributing centers to contain metastatic disease was performed by one of the authors (AJC).

Statistical Methods

Data were extracted from the central MSLT-II trial database for all patients screened for trial eligibility from the commencement of the trial on December 20, 2004, to May 6, 2013. A trial protocol amendment on the latter date removed the previous requirement for baseline US examination of nodes (coinciding with termination of the screening phase of MSLT-II). Variables recorded included the treatment center, node basin, US result, histology result, size of tumor deposit/s (where applicable), and Breslow thickness of the patient's primary tumor. The cross-sectional area (CSA) of each tumor deposit was calculated using the formula: CSA = tumor length x tumor width x 0.25 x π. Sensitivity, specificity, and positive and negative predictive values, with corresponding 95% confidence intervals, were calculated. Diagnostic accuracy for overall patients was calculated as the percentage of total tests with true results according to the formula (TP+TN)/(Total Tests), where TP is true-positive and TN is true-negative. IBM SPSS Statistic 19.0, SAS Enterprise Guide 7, and Microsoft Excel 2010 were used for statistical analyses.

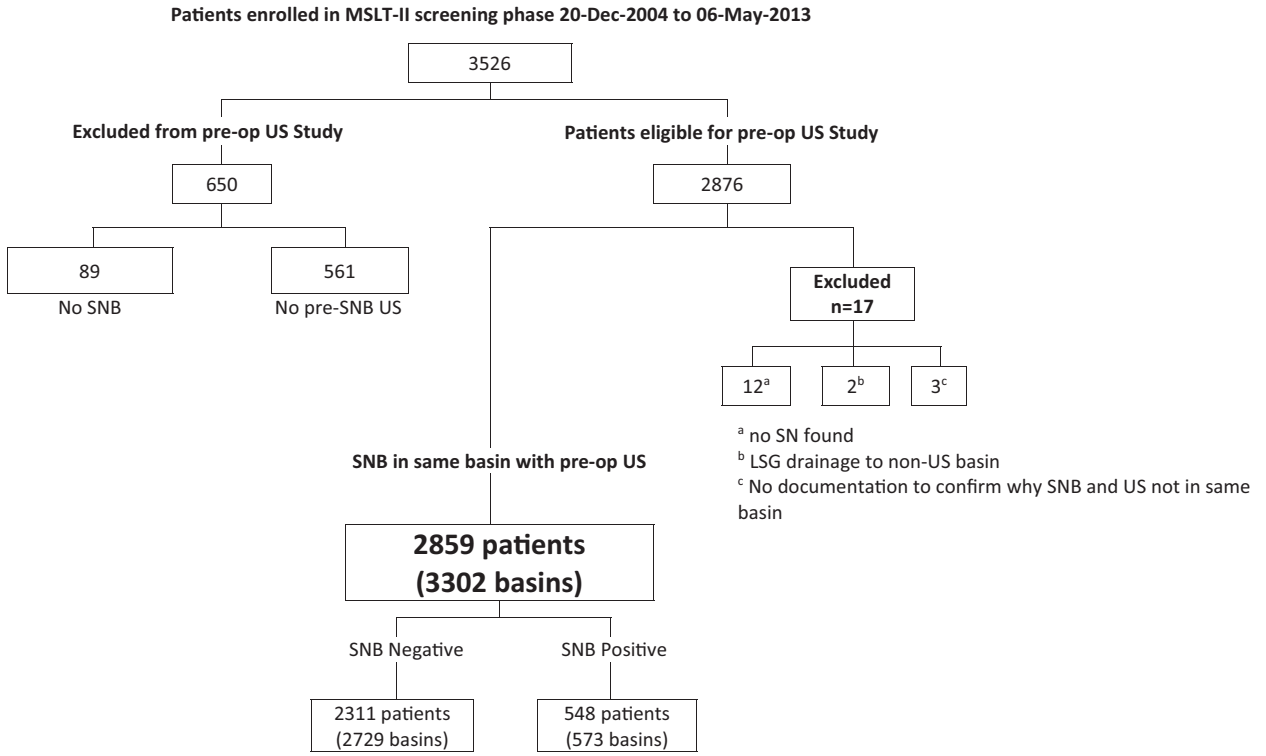

FIGURE 1. CONSORT diagram.

TABLE 1. Sensitivity, Specificity, and Positive and Negative Predictive Values of Ultrasound by Sentinel Lymph Node Basin

		Ultrasound Result					Sensitivity	Specificity	Predictive Value	
Basin	**N**	**%**	**True Positive**	**True Negative**	**False Positive**	**False Negative**	**%**	**%**	**Positive**	**Negative**
Axilla	1721	52.1%	22	1414	25	260	7.8%	98.3%	46.8%	84.5%
Groin	855	25.9%	11	654	7	183	5.7%	98.9%	61.1%	78.1%
Neck	693	21.0%	5	579	23	86	5.5%	96.2%	17.9%	87.1%
Other*	33	1.0%	0	27	0	6	0.0%	100.0%	NA	81.8%
Overall	3302	100.0%	38	2674	55	535	6.6%	98.0%	40.9%	83.3%

*popliteal, n = 17; epitrochlear, n = 15; chest wall, n = 1.

RESULTS

SNs were identified and removed from 3302 node basins in 2859 eligible patients. Histologically positive SNs were identified in 573 node basins (17.4%) in 548 patients (19.2%). Eighty-seven patients (3.0%) had a positive (abnormal) US result in at least 1 node basin. US was true-positive for histologically positive SNs in 38 node basins (1.2%). The sensitivity of US in the detection of positive SNs in all lymph node basins was 6.6% (95% CI: 4.6–8.7), and the specificity 98.0% (95% CI: 97.5–98.5). Data for individual lymph node basins are summarized in Table 1. The sensitivity of US was 7.8% for axillary basins, 5.7% for inguinal basins, and 5.5% for cervical basins. US did not yield a true-positive result in any of the 33 ectopic basins (popliteal, epitrochlear, chest wall) that were evaluated.

TABLE 2. Effectiveness of Ultrasound for Overall Patients (n = 2859)

Measurement	**%**	**95% CI (%)**	
Sensitivity	7.1%	5.0%	9.3%
Specificity	97.9%	97.3%	98.5%
Positive Predictive Value	44.8%	34.4%	55.3%
Negative Predictive Value	81.6%	80.2%	83.1%
Diagnostic accuracy	80.5%	79.1%	82.0%

TABLE 3. Effectiveness of Ultrasound for Overall Basins (n = 3302).

Measurement	**%**	**95% CI (%)**	
Sensitivity	6.6%	4.6%	8.7%
Specificity	98.0%	97.5%	98.5%
Positive Predictive Value	40.9%	30.9%	50.8%
Negative Predictive Value	83.3%	82.0%	84.6%
Diagnostic accuracy	82.1%	80.8%	83.4%

The sensitivity, specificity, positive and negative predictive values, and diagnostic accuracy for the detection of nodal tumor by US when analyzed both per patient and per basin are reported in Tables 2 and 3. By patient, the diagnostic accuracy of US, calculated as the percentage of total tests with true results, was 80.5% (Table 2). Per basin, the diagnostic accuracy was 82.1% (Table 3).

The median and mean Breslow thicknesses of the primary melanomas were 1.65 and 2.24 mm, respectively. Sensitivity, specificity, and positive and negative predictive values for US were calculated for each Breslow thickness subgroup (0 to 1.0, 1.01 to 2, 2.01 to 4, and >4 mm) (Table 4). US sensitivity for melanomas ≤2 mm in thickness was 2.2%. For melanomas >2 mm in thickness, sensitivity was 10.6%.

Dimensions of the largest tumor deposits were histologically measured for 354 lymph node basins, which contained 424 positive SNs; these are reported in Table 5. The median CSA of the tumor deposits in the SNs was 0.13 mm^2, but values ranged from 0.0001 to 143.2 mm^2. Tumor deposits in patients with true-positive US results (n = 19) were significantly larger than those in patients with false-negative US results (n = 335) (median CSA 6.84 vs 0.117 mm^2, Mann-Whitney *U* test, $P < 0.001$).

There was a significant difference in the median CSA of tumor deposits that were not detected by US (false-negative) when

TABLE 5. Cross-Sectional Area of Metastases in Positive SLNs and Ultrasound Results (Overall)

Tumor burden measurements obtained for positive SLNs	354
Median CSA for all positive SLNs (mm^2)	0.13
Range of CSA for all positive SLNs (mm^2)	0.0001–143.169
True-Positive US Results	19
Median CSA for true-positive US (mm^2)	6.84
Range of CSA for all true-positive US (mm^2)	0.010–126.771
False-Negative	335
Median CSA for false-negative US (mm^2)	0.12
Range of CSA for all false-negative US (mm^2)	0.0001–143.169

TABLE 4. Sensitivity, Specificity, and Positive and Negative Predictive Values of Ultrasound by Breslow Thickness (mm) (by Patient).

			Ultrasound Result				Sensitivity	Specificity	Predictive Value	
Breslow Thickness, (mm)	**N**	**%**	**True Positive**	**True Negative**	**False Positive**	**False Negative**	**%**	**%**	**Positive**	**Negative**
≤ 1	486	17.0%	0	448	8	30	0.0%	98.2%	0.0%	93.7%
1.01–2.0	1256	43.9%	5	1038	23	190	2.6%	97.8%	17.9%	84.5%
2.01–4.0	792	27.7%	21	569	11	191	9.9%	98.1%	65.6%	74.9%
>4	294	10.3%	13	180	5	96	11.9%	97.3%	72.2%	65.2%
Unknown	31	1.1%	0	28	1	2	0.0%	96.6%	0.0%	93.3%
Overall	2859	100.0%	39	2263	48	509	7.1%	97.9%	44.8%	81.6%

TABLE 6. Cross-Sectional Area of Metastases in Positive SLNs and Ultrasound Results (by Lymph Node Basin)

	All Positive SLNs		Ultrasound False-Negative		Ultrasound True-Positive	
SN Basin	N	Median CSA, mm^2	N	Median CSA, (mm^2)	N	Median CSA, (mm^2)
Axilla	179	0.19	166	0.17	13	6.84
Groin	122	0.06	118	0.06	4	2.94
Neck	51	0.13	49	0.13	2	88.7
Other	2	0.50	2	0.50	0	NA
All	354	0.13	335	0.12	19	6.84

comparing the axillary (n = 166, CSA = 0.17 mm^2) and groin (N = 118, CSA = 0.06 mm^2) lymph node basins (Mann-Whitney *U* test, *P* = 0.007). No significant difference was observed when comparing median CSA of tumors in different lymph node basins for true-positive US results (Table 6).

US was performed before lymphoscintigraphy in 1303 basins (39.5%), and following lymphoscintigraphy in 1999 basins (60.5%) (Table 7). Sensitivity was 3.8% when performed following lymphoscintigraphy and 10.7% when performed without a preceding LSG. US sensitivity varied substantially across trial centers, with a range of 0% to 50%. The observed sensitivity did not appear to be related to trial center case volume (see Supplementary Table 1, http://links.lww.com/SLA/B670).

DISCUSSION

In this large study based on US data obtained prospectively at 20 specialist melanoma treatment centers around the world in the course of a carefully monitored, randomized clinical trial, the sensitivity per basin of preoperative US assessment of SNs was low (6.6%). The highest sensitivity result from an individual center was 50%. However, 7 of the 9 ''high volume'' centers (contributing 50 or more patients) recorded sensitivity rates of less than 6.6%. Not only was there a high false-negative rate for preoperative US, but there were also a number of false-positive US tests. Indeed, the number of false-positive results (55/3302) exceeded the number of true-positive results (38/3302). Although still low, the sensitivity of US was considerably greater for thicker primary tumors (11.9% for tumors >4 mm, 0% for tumors <1 mm).

The results of the study indicate clearly that preoperative US examination is not a reliable alternative to SN biopsy to assess regional lymph node status in patients who present with a primary cutaneous melanoma and who have no clinical evidence of regional node metastasis.

On the basis of the preliminary results of this US study, the MSLT-II trial protocol was amended in May 2010 so that baseline US examination of the regional node basin was no longer mandatory for patients entering the trial. Nevertheless, it may be of some value for patients with thick melanomas (>4 mm) in whom the sensitivity for detection of a positive SN by preoperative US, although still quite low (11.9%), was significantly higher than in patients with thin and intermediate thickness melanomas, with an approximately 1 in 8 chance of detecting a nodal metastasis.

In most other studies reported to date, the results of preoperative US examination of SNs have been similarly dismal[16] (See Table 8). However, there have also been reports published in high-impact journals by Voit et al[6,9] from Berlin, claiming very high sensitivity rates for the procedure (exceeding 80%). These authors have attributed their success to early recognition of an increase in vascular signature, and the high Doppler sensitivity of the US machine used by Voit et al[6,9] may explain some of the differences between their results and those reported by others. Using the same diagnostic US criteria, others have to date been unable to produce sensitivity results approaching those reported by Voit et al.[6,9] A prospective multicenter trial would be required to examine the technique in an objective fashion, but as far as we are aware no such trial has yet commenced.

Although US is noninvasive, it is not without cost, and to obtain the high-resolution images required to detect very low volume metastatic disease high-frequency probes (over 14 MHz) and sophisticated machines are required. In some centers, a physician performs the US examination, while in others it is performed by technical personnel. In either case, the ultrasonographer must be thoroughly familiar with the normal internal structure of regional lymph nodes draining the skin. The anatomy of lymph nodes varies from basin to basin, so that nodes in the groin, axilla, and neck can appear quite different on US in the same patient. There is a steep learning curve, even for those with previous US experience.

The first evidence of metastatic disease in a SN is usually detected in the subcapsular sinus, at the point of entry of the afferent lymphatic that drains the primary melanoma. As long as the CSA of the metastasis is >2 mm^2, reasonable accuracy is possible, especially if the metastasis is a small round focus. Often, however, early nodal melanoma metastases in the subcapsular sinus are elongated tumor cell aggregates that may be several millimeters long but only 1 or 2 microns thick. Such metastases with a low CSA are not detectable on a structural basis using current US technology. The presence of such metastases, however, can cause an increase in the vascular signal in that part of the subcapsular sinus. These changes can be detected using the color Doppler features of current US machines, as mentioned above, but a metastasis is not the only pathology that can cause a focal increase in blood flow in the subcapsular sinus of a lymph node. If a node has received infected debris from a biopsy site, for example, the same changes in vascularity may be seen.

TABLE 7. Sensitivity, Specificity, and Positive and Negative Predictive Values of Ultrasound by Timing of LSG (by Basin)

			Ultrasound Result				Sensitivity	Specificity	Predictive Value	
LSG Timing	N	%	True Positive	True Negative	False Positive	False Negative	%	%	Positive	Negative
Pre-US	1999	60.5%	13	1642	18	326	3.8%	98.9%	41.9%	83.4%
Post-US	1303	39.5%	25	1032	37	209	10.7%	96.5%	40.3%	83.2%
Overall	3302	100.0%	38	2674	55	535	6.6%	98.0%	40.9%	83.3%

TABLE 8. Results of Previous Studies of Pre-Operative Ultrasound Examination of Regional Lymph Nodes with Nodal Metastasis Confirmed by Sentinel Lymph Node Biopsy in Patients with Primary Cutaneous Melanoma

Author	Year	N	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Rossi et al*,† [18]	2003	125	39	100	100	85
Hocevar et al† [28]	2004	57	71	84	59	90
Testori et al[5]	2005	88	94.1	89.8	64	98.7
van Rijk et al† [29]	2006	107	34	87	59.1	70.5
Voit et al[6]	2006	127	79	72	100	85
Sibon et al† [19]	2007	131	20.6	89.8	41.2	76.5
Sanki et al[13]	2009	716	23.3	97.3	59.6	88.3
Voit et al[8]	2009	400	65	99	93	92
Kunte et al[17]	2009	25	33.3	100	100	87.9
De Giorgi et al[30] ††	2010	15	100	61.5	54.5	100
Voit et al** [9]	2010	400	82	80	52	94
Hinz et al[31]	2011	81	22.2	100	100	95.8
Chai et al**,† [32]	2012	325	33.8	85.7	36.5	84.2
Marone et al† [33]	2012	623	15	100	100	87
Stoffels et al**,† [34]	2012	221	13.6	96.9	97.2	12.6
Hinz et al† [35]	2013	20	11.8	100	100	73.7
Voit et al* [36]	2014	1000	51	99	99	89
Ulrich et al* [37]	2015	800	56	99	92	89
Voit et al***	2016	1000	10.8	97.6	50	80.2
Ternov et al[38]	2018	91	30	81	24	83
Present study	2019	2859	7.1	97.9	44.8	81.6

*Assessed the combined use of ultrasound and fine needle aspiration biopsy.
**FNAB if US was suspicious.
†Non-focused ultrasound studies performed.
††Contrast-enhanced ultrasound performed.
***This study was of the same 1000 patients as in the Voit 2014 study, but used only the US feature of an echo-free island to record a positive US result.

In a previously reported retrospective study of 716 patients treated at Melanoma Institute Australia, the sensitivity of preoperative US to detect SLN metastasis at the time of preoperative LS was found to be 24.3%. The highest sensitivity was in the neck (45.8%), with lower sensitivity for the axilla (21.1%) and the lowest sensitivity of all for the groin (15.6%).[13] When the SLN metastasis had a CSA of 1.00 mm^2, the sensitivity was 43%, 3 mm^2 70%, and 5 mm^2 90%. The overall sensitivity was low, as >60% of patients with SLN metastases had microscopic foci of disease. In the present study, overall sensitivity was even lower, with the highest sensitivity in the axilla (7.8%), followed by the groin (5.7%) and the neck (5.5%), see Table 1. The CSA of the metastases in the false-negative US group was also very small, and it is thus not surprising that these microscopic lesions were not detected using US.

The ability of US to detect a focus of metastatic melanoma in a SN depends primarily on the size of the tumor deposit. Most previous studies have indicated that reliable detection of metastatic disease using US is only possible when tumor deposits are >4 to 5 mm in maximum diameter.[17–20] In the present study of patients enrolled in a large, multicenter trial, the great majority of those who were found to be SN-positive had tumor deposits that were well below this 4 to 5 mm threshold, and only 9.0% of positive lymph node basins for which tumor burden was assessed had a metastatic tumor deposit that was histologically determined to be >5 mm in diameter, not markedly different from the 6.6% sensitivity rate for US detection that was recorded.

The maximum diameter of a nodal melanoma metastasis is not an appropriate metric to assess US accuracy, because many nodal tumor deposits are not spherical or even ovoid in shape, but rather are thin, elongated collections of tumor cells. For this reason, the CSA of each nodal metastasis was calculated in the present study, in an attempt to better define the ability of US to detect nodal melanoma metastases. A perfectly spherical tumor deposit 3 mm in diameter, at the lower limit of what has been shown to be detectable by US,[17,18] will have a CSA of 7 mm^2, whereas a tumor deposit that is cylindrical in shape, 3 mm in length but only 0.5 mm in diameter, will have a CSA of only 1.5 mm^2, and will be very unlikely to be detectable by US. In the present study, 93.8% of the SN tumor deposits had a CSA of <7 mm^2, again consistent with the low sensitivity rate for US detection that was observed. Focused preoperative US examination of SNs, made possible by lymphoscintigraphy before the US, did not improve the sensitivity of SN nodal metastasis detection.

The high false-negative rate for US detection of melanoma nodal metastases in this study is clearly not only a major problem but also problematic are the false-positive results, which were in fact as frequent as true-positive results (55/3302). This highlights the importance of fine-needle biopsy to histologically confirm a positive US result before accepting it as reliable staging information.

At the time MSLT-II commenced in 2004, the standard treatment recommendation for melanoma patients found to be SN-positive was a CLND, but whether this additional procedure was necessary when the positive SN or SNs had been removed was the question that MSLT-II sought to answer. Initial results of MSLT-II, published in 2017, suggest that immediate CLND confers no survival benefit (relative to observation and delayed CLND), at least in the short to medium term. Early results of the much smaller DeCOG trial[21] also suggest that CLND may not be necessary, although longer follow-up of the patients in both trials will be required to confirm this.[12,21] Even though CLND is no longer considered appropriate in most circumstances, staging based on knowledge of SN status determined by SN biopsy remains important. Not only is prognosis determined with greater accuracy if SN status is known, but treatment with adjuvant systemic therapy of patients who are identified as SN-positive appears likely to become routine in the near future.

Although preoperative US is clearly not a suitable substitute for SN biopsy due to its poor sensitivity, it may nevertheless be of value for ongoing surveillance of melanoma patients after their initial

definitive treatment. It is well-documented that US is both more sensitive and more specific than physical examination in detecting regional lymph node metastases[22–24] and there is evidence that it improves early detection of nodal metastases.[25,26] Compared with other imaging modalities such as CT or PET-CT, US is superior for detecting lymph node metastases during follow-up surveillance of melanoma patients,[27] and the diagnostic value of US in nodal surveillance does not appear to be affected by prior surgery in the node basin.[22] For all these reasons, US was included in the follow-up protocol of all patients in the observation arm of MSLT-II. As routine immediate CLND is no longer regarded as the standard of care for patients found to be SN-positive, US surveillance of the regional node basin in patients who have had a positive SN removed seems logical, but it is not known whether earlier detection of further lymph node metastases ultimately improves patient outcomes. Randomized clinical trial evidence will be required to definitively answer this question. However, long-term follow-up data for SN-positive patients randomized to the observation arm of MSLT-II, who had regular US examination of the relevant node basin, will provide some insights into the value of US follow-up for SN-positive patients (report for publication in preparation).

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