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Preoperative Ultrasound Is Not Useful For Identifying Nodal Metastasis In Melanoma Patients Undergoing Sentinel Node Biopsy

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Abstract

Background—Sentinel lymph node biopsy (SLNB) is widely used in melanoma. Identifying nodal involvement preoperatively using high-resolution ultrasound may offer less invasive staging. This study assessed feasibility and staging results of clinically-targeted ultrasound (before lymphoscintigraphy) compared to SLNB.

Methods—From 2005–2009, 325 patients with melanoma underwent ultrasound before SLNB. We reviewed demographics and histopathologic characteristics, then compared ultrasound and SLNB results. Sensitivity, specificity, positive and negative predictive value (PPV, NPV) were determined.

Results—325 patients, 58% male; 42% female, median age 58 years (range 18–86) were included. A total of 471 basins were examined with ultrasound. Only 6 patients (1.8%) avoided SLNB by undergoing ultrasound-guided fine needle aspiration of involved nodes, then therapeutic lymphadenectomy. 65 patients (20.4%) had 69 SLNB positive nodal basins; 17 nodal basins from 15 patients with positive ultrasounds were considered true-positive. 45 SLNB positive basins had negative ultrasounds (false-negative). 7 node-positive basins did not undergo ultrasound because of unpredicted drainage. 253 patients with negative SLNBs had negative ultrasounds in 240 nodal basins (true-negative) but false-positive ultrasounds occurred in 40 basins. Overall, sensitivity of ultrasound was 33.8%, specificity 85.7%, PPV 36.5% and NPV 84.2%. Sensitivity and specificity

improved somewhat with increasing Breslow depth. Sensitivity was highest for the neck, but specificity was highest for the groin.

Conclusions—Routine preoperative ultrasound in clinically node-negative melanoma is impractical due to low sensitivity. Selected patients with thick or ulcerated lesions may benefit. Because of variable lymphatic drainage patterns, preoperative ultrasound without lymphoscintigraphic localization will provide incomplete evaluation in many cases.

Keywords

Melanoma; sentinel node biopsy; ultrasound; staging

INTRODUCTION

Nodal status is an important prognostic indicator in melanoma patients and guides optimal treatment methods.[1, 2] Sentinel lymph node biopsy (SLNB) has been accepted as a preferred method for initial lymph node staging of patients with clinically node-negative melanoma.[3–5] However, it is still invasive, associated with definite morbidity, and usually performed under general anesthesia. Furthermore, only 15 to 30% of clinically node-negative melanoma patients will have a positive SLNB,[2, 6] and a delay before undergoing therapeutic lymphadenectomy is usually experienced by those patients while waiting for the final pathology result. Thus, detecting nodal involvement using a preoperative ultrasound appears to be an attractive option to eliminate the need for SLNB and its potential complications, costs of lymphoscintigraphy, and minimize the delay to therapeutic lymphadenectomy for node-positive patients.

High resolution ultrasound has been shown to be useful in follow-up evaluation of nodal basins postoperatively.[7–12] However, the role of preoperative ultrasound in the initial staging of cutaneous melanoma patients is unclear.[13–18] Studies have suggested that ultrasound-guided fine needle aspiration (FNA) of suspicious lymph nodes may accurately detect nodal metastasis, enabling one-stage lymphadenectomy of affected nodal basins.[16, 17] The purpose of our study was to assess feasibility of preoperative nodal ultrasound without lymphoscintigraphy localization of draining nodal basins as a screening tool in melanoma patients prior to SLNB. The secondary purpose was to compare the sensitivity and specificity of preoperative ultrasound in the detection of nodal metastases when compared to SLNB.

PATIENTS AND METHODS

Patient Selection

After Institutional Review Board approval, the ultrasound database at our institution was queried for nodal ultrasounds performed on cutaneous melanoma patients. 405 melanoma patients had nodal ultrasounds between June 2005 and September 2009. Of these patients, 325 patients met the inclusion criteria, which were the following:

1. Confirmed diagnosis of primary cutaneous melanoma without palpable lymphadenopathy in regional nodal basins.

2. Ultrasound performed prior to scheduled lymphoscintigraphy and SLNB.
3. No clinical evidence of distant metastasis.

Clinical targeting of nodal basins

The nodal ultrasound was ordered according to the primary melanoma site and was at the discretion of the attending surgeon, but was intended to encompass all basins potentially draining the primary site. Patients with extremity melanomas underwent ultrasound of the ipsilateral groin or axilla. Generally, patients with melanoma on the hand or forearm also had an epitrochlear ultrasound, while patients with melanoma on the lower leg, from toe to calf, had a popliteal ultrasound. Head and neck melanomas underwent, at minimum, ipsilateral neck, parotid and supraclavicular ultrasound. For melanomas on the trunk, Sappey's line was used as a rough guide: melanomas at or above the beltline included axillary ultrasound, and those at or below included groin ultrasound. Lesions in close proximity to the midline had bilateral ultrasounds performed.

Nodal ultrasound

The preoperative ultrasound was performed using high resolution linear 9 and 12 MHz transducers either immediately or several days prior to lymphoscintigraphy. No absolute criteria were used for evaluating nodes ultrasonographically, but in general suspicious lymph nodes appeared round in shape, had partial or complete absence of the fatty hilum and/or diffuse or eccentric thickening of the cortex.[10, 14, 19] The loss of central perfusion or presence of peripheral perfusion was not included in the morphologic criteria.[20] The size of the lymph node by itself was not considered an indication of abnormality.[13] For correlation with SLNB results, readings of "benign" or "no nodes visualized" were considered negative, and readings called "abnormal," "suspicious" or "indeterminate recommending a short-term follow up" were scored as positive. In cases of an abnormal ultrasound performed prior to the day of surgery, patients were offered an ultrasound-guided FNA and, if positive, proceeded directly to therapeutic lymphadenectomy without SLNB; patients with a negative FNA underwent SLNB.

Sentinel lymph node biopsy

SLNB was offered to medically fit patients with melanoma depth ≤ 0.76 mm without palpable lymphadenopathy or <0.76 mm with high-risk features such as ulceration, high mitotic rate or a positive deep margin.[21, 22] Lymphoscintigraphy was performed the morning of surgery by injecting radiolabeled colloid (either ^{99m}Tc -sulfur colloid or ^{99m}Tc -tilmanocept[23]) at the primary tumor site. In the operating room, 1 to 2 mL of isosulfan blue dye was injected intradermally. Sentinel lymph nodes were identified based on blue color, radioactivity above background and at least 10% of the hottest node, or palpable abnormality. All sentinel nodes were serially sectioned and evaluated by hematoxylin-eosin and immunohistochemical staining. All lymph nodes with proven tumor deposits, regardless of size, were considered positive.

Ultrasound and sentinel lymph node

By the nature of our study, we were unable to determine whether a pathologically involved node was in fact visualized and abnormal by ultrasound. To provide a best-case estimate of the accuracy of preoperative ultrasound, whenever the ultrasound was considered abnormal and the SLNB was positive, it was considered to be a true-positive (TP). An abnormal ultrasound with a negative SLNB was considered a false-positive (FP), and a normal ultrasound with a positive SLNB was considered a false-negative (FN). Any nodal basin with a normal ultrasound and negative SLNB was considered true-negative (TN). We calculated sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) using these variables. The evaluation of data was performed with the statistical package SPSS 18.0.0 and standard formulas.

RESULTS

Patient and tumor characteristics

325 patients (58% male, 42% female) with median age of 58 years (range 18 – 86) at the time of presentation were included in our study (Table 1). The primary melanoma sites, in decreasing order of frequency, were trunk (39.7%), upper extremity (31.1%), lower extremity (18.8%) and head and neck (10.5%). Median tumor depth was 1.78 mm (range 0.42 – 14.40): 17.2% of patients had a melanoma ≤ 1.00 mm; 41.8% were between 1.01 mm – 2.00 mm; 27.1% were between 2.01 mm – 4.00 mm; and 13.5% were >4.00 mm. The depth was not measurable in one patient due to missing epithelium in the biopsy specimen. The majority (90.8%) of tumors were Clark's level $\leq$ IV and ulceration was seen in 29.8%.

Ultrasound guided fine-needle aspiration

In our study, only 10 patients (3.1%) were able to have an ultrasound guided FNA prior to SLNB. Of the 10 patients, six had metastases seen on cytology and underwent a therapeutic lymphadenectomy. All six patients had evidence of nodal metastasis in the lymphadenectomy specimen ranging from 1 to 5 positive lymph nodes. The median tumor depth for these six patients was 7.04 mm (3.9 – 14.0 mm); 5 of 6 had a depth >4 mm, and all had ulceration. The four patients who had negative cytology also had a negative SLNB. However, one of the four who had negative FNA and SLNB presented with a nodal metastasis 6 months after SLNB. Systemic and practical issues precluded most of our patients with an abnormal ultrasound from undergoing ultrasound-guided FNA; almost all went on to same day lymphoscintigraphy and SLNB.

Ultrasound and lymphoscintigraphy

Excluding the six FNA-positive patients, 319 patients underwent lymphoscintigraphy after ultrasound and prior to SLNB. A total of 506 nodal basins were evaluated using either ultrasound or lymphoscintigraphy or both. Ultrasound was performed on 471 nodal basins, while the lymphoscintigraphy identified only 374 draining nodal basins. Only 342 basins had both ultrasound and lymphoscintigraphy evaluation: 99 patients had lymphatic basins evaluated by ultrasound but not localized by lymphoscintigraphy, meaning 31% of patients had a superfluous ultrasound of one or more non-draining basins. Of these 99 patients, 77%

had a primary located on the trunk, 15% on shoulder/ upper extremity and 8% on the scalp/ neck. 24 patients had the popliteal region evaluated with ultrasound, however 22 of these patients were not localized with lymphoscintigraphy. One of the two patients with lymphoscintigraphy localization had a positive popliteal SLNB, and the other had a negative popliteal SLNB. 4 patients had ultrasound of an epitrochlear basin not localized with lymphoscintigraphy.

On the other hand, 29 patients (9.1%) had basins localized by lymphoscintigraphy but not evaluated by ultrasound: 24 (83%) had the primary located on the trunk and 5 (17%) on shoulder/upper extremity. 8 (27.6%) patients had in-transit nodes not predicted clinically but mapped by lymphoscintigraphy, such as latissimus, inframammary and scapular region. Furthermore, 7 of 29 patients (24.1%) had positive SLNBs in nodal basins not examined with ultrasound. One patient had ultrasound of a non-draining nodal basin while the actual draining basin identified by lymphoscintigraphy was not examined with ultrasound; this patient was not included in further analysis for comparison between ultrasound and SLNB.

Ultrasound and sentinel lymph node biopsy

Of 318 patients with SLNBs, 65 patients (20.4%) had 69 basins with at least one histologically positive sentinel lymph node. Four patients had 2 positive SLNBs and, as stated above, 7 node-positive patients (10.8%) did not have preoperative ultrasound of the positive nodal basin. 17 of the 65 node-positive patients (26%) also had an abnormal ultrasound, but only 15 patients had true positive correspondence between the ultrasound and SLNB, as two patients had two nodal basins localized by lymphoscintigraphy and each contained positive nodes but only one site was identified as positive by ultrasound. In the face of a negative SLNB, 40 nodal basins had an abnormal ultrasound. 253 patients had negative SLNB resulting in 305 negative nodal basins, however, only 279 of those nodal basins had both ultrasound and lymphoscintigraphy localization.

All 10 patients who underwent ultrasound-guided FNA were included in our analysis for the usefulness of preoperative ultrasound. The 6 patients who underwent one-stage therapeutic lymphadenectomy were counted as TP. Analysis was performed per patient and per basin. If a patient had multiple nodal basins evaluated and had a FN in one basin, the patient was considered to be FN. The sensitivity of preoperative ultrasound, per patient, was 31.8% and the specificity was 86%. The PPV was 36.8% and the NPV was 83.1%. When these values were analyzed per nodal basin, the results were similar (Table 2). In-transit or epitrochlear nodal basins were not included in the analysis since the nodal basins either lack ultrasound evaluation or SLNB result. When the data was analyzed by tumor and anatomic subsets, sensitivity increased with increasing Breslow depth but was still low (45.8%) even for the thick melanomas. The PPV improved with increasing Breslow depth, but the NPV decreased. When comparing by anatomical location of draining nodal basins, the neck had the highest sensitivity at 43.3%, while specificity and PPV were the highest for the groin.

Of 279 nodal basins with negative SLNBs and negative ultrasounds, 8 nodal basins required subsequent completion lymphadenectomy – false negative SLNB. 6 nodal basins produced metastatic lymph nodes, but 2 nodal basins only demonstrated soft tissue metastasis without lymph node involvement. 4 of the 6 basins had a negative ultrasound sound evaluation

preoperatively, and one had indeterminate findings with non-specific lymph nodes recommending a short-term follow up. The other nodal basin showed suspicious nodes on ultrasound, leading to a preoperative ultrasound guided FNA. However, the cytology was negative, and the SLNB was also negative. Unfortunately, the patient presented with nodal metastasis 6 months postoperatively.

DISCUSSION

While the morbidity of SLNB is much lower than for elective lymph node dissection, it is not negligible.[24] Considering that most patients with thin and intermediate-thickness melanomas will have negative SLNBs, pursuit of less invasive and expensive methods seems logical.[25–27] Imaging modalities such as ultrasound,[19] CT, MRI and PET have been considered to be superior to palpation for detection of nodal metastases.[28–30] However, when PET/CT was compared to SLNB for detection of occult lymphatic metastasis, SLNB was better for detecting small tumor deposits.[31]

Compared to other imaging modalities, ultrasound is less invasive, less expensive and better tolerated by patients. Preoperative ultrasound may detect abnormal lymph nodes which could not be localized via lymphoscintigraphy when lymphatic obstruction is present.[32] The false-negative rate for SLNB is not insignificant, with reports ranging from 1.5 to 21% depending on calculation method.[33, 34] Our false negative rate calculated by $[\text{false negative} / (\text{false negative} + \text{true positive})] \times 100\%$ was 10.4%. In addition to 8 nodal recurrences mentioned previously, 1 patient who had a positive SLNB in the observation arm of the MSLT II randomized trial also experienced a recurrence in the nodal basin after 16 months. Ultrasound may detect abnormal lymph nodes by morphological criteria and therefore possibly reduce the false negative SLNB rate.[8, 14, 19] However, ultrasound has its limitations: visualization varies depending on the anatomical location and the operator. Ultrasound is more difficult in the axilla than in the groin or neck, where the nodes are closer to the skin.[13] In our study, the highest sensitivity was seen in the neck (43.2%), then axilla (34.1%) and groin (30%).

Another limitation of ultrasound is the threshold size for detection of tumor deposits. We did not include the tumor deposit size seen in positive lymph nodes in our analysis because no standard method of measuring the tumor deposit was used, but many of our patients had microscopic metastases measuring less than 1 mm. The threshold size of tumor deposit for ultrasound detection has been discussed in multiple studies.[13, 18, 25, 41] Starritt et al. showed that targeted ultrasound (performed after lymphoscintigraphy) of sentinel nodes can detect metastatic melanoma deposits as small as 4.5 mm in diameter.[13] Rossi et al. performed non-targeted preoperative ultrasound in 125 patients with melanoma >1 mm thickness; ultrasound could not detect tumor deposits <2 mm.[18] Van Akkooi et al. reported a lesion as small as 0.5 mm in maximum diameter in a lymph node as small as 6 × 6 mm could be detected by an ultrasound.[6] Voit et al., however, reported that ultrasound-guided FNA could detect sentinel node tumors >1 mm in 76%, 0.1 to 1 mm in 46% and <0.1 mm in 23% of cases.[17] The significance of micrometastases <0.1 mm has been questioned,[42, 43] as whether patients with a positive SLNB need a completion lymphadenectomy. A better understanding of the significance of these very small

micrometastases will help investigators determine the appropriate deposit size the ultrasound must detect.

Table 3 compares the sensitivity, specificity, PPV and NPV of preoperative ultrasound in previous studies and our own. Our study and those done by Rossi, Hocevar, van Rijk and Sibon were performed without lymphoscintigraphy targeting of the draining nodal basin, whereas the studies by Voit and Sanki were performed after lymphoscintigraphy. [15, 16, 18, 41–43] It is difficult to compare these studies directly since targeting draining nodal basins may affect sensitivity and specificity. Furthermore, the patient and tumor characteristics also vary and can influence the results. Table 3 demonstrates a wide variability in the results of preoperative ultrasound.

The reported value of ultrasound-guided FNA also varies widely. The recent study by Voit et al. stated that in their institution up to 65% of patients with positive sentinel lymph nodes could avoid SLNB with a lymphoscintigraphy-targeted ultrasound-guided FNA of suspicious nodes using their criteria.[17] But in the study by Hocevar et al., only 3 out of 57 patients (5.2%) avoided SLNB and proceeded directly to one-stage surgery by ultrasound-guided FNA. Rossi et al.[18] and van Rijk et al.[15] reported the number of patients who avoided SLNB by undergoing ultrasound-guided FNA to be 10% and 2%, respectively.

Recently, Thompson et al. also reported their assessment of preoperative ultrasound efficacy for reliable staging in large multicenter trial based on MSLT-II. In their study, positive sentinel nodes were characterized by either histopathologic or molecular evaluation. The sensitivity of US for detecting positive sentinel node in all lymph node fields was 8% (95% CI 6%–10.5%) and the specificity of 97.3% (95% CI 96.7% –97.9%). The sentinel node with true positive ultrasound result had a median cross-sectional area of 6.11 mm², which is significantly greater than the median CSA of 0.16 mm² in sentinel nodes with false negative ultrasound results (p<0.001).[44]

The potential cost-effectiveness of ultrasound-guided needle aspiration in melanoma has been researched by Van Akkooi et al.[27] The cost analysis was made under the assumption that presurgical ultrasound-guided FNA cytology has a sensitivity of 65% compared with SLNB based on the targeted US study by Voit et al.[17] For 100 patients with stage I/II melanoma, ultrasound guided FNA (€56,115.2) offers a potential saving up to €69,367.80 (or \$101,242.3) compared with SLNB (€125,483) as a staging procedure at their institution.

In our institution, use of axillary ultrasound for patients with T2 breast cancer has been investigated. Ultrasound sensitivity was much higher at 86.2%, which is likely due to inclusion of patients with palpable lymphadenopathy as well as less variation in lymphatic drainage pattern for breast cancer. Avoiding SLNB and proceeding to one-stage lymphadenectomy for breast cancer patients carried a savings of over \$4000 (not including physician fees).[45] However, this result will unlikely translate directly to melanoma patients.

In fact, in our series, whether the abnormal lymph node seen on ultrasound is indeed the same node identified as a sentinel node is unclear. We had 40 abnormal ultrasounds in patients with negative SLNB whereas 45 patients with positive nodal basins showed

negative ultrasound. This raises questions about whether all the 17 basins with positive sentinel nodes and abnormal ultrasounds really represented “true positive” findings. Our study suggests that ultrasound is neither sensitive nor specific enough to detect melanoma sentinel node metastases without lymphoscintigraphy targeting. It is well known that the drainage patterns of primary melanomas are not well predicted by conventional rules like “Sappey’s lines.”[46, 47] Lymphoscintigraphy allows identification of draining nodal basins, assuming no lymphatic obstruction is present, and could potentially increase the accuracy – but also very dramatically the cost – of ultrasound for detecting nodal metastases. [13, 34]

CONCLUSIONS

Without preoperative lymphoscintigraphy, clinically targeted ultrasound may image non-draining nodal basins unnecessarily and miss draining basins that may harbor metastasis. Even correctly targeted basins are not reliably staged by preoperative ultrasound, although selective use in patients at high risk of having a relatively large nodal metastasis (e.g., those with thick, ulcerated primary tumors) may occasionally allow SLNB to be avoided. Ultrasound should continue to play a role in patients who chose not to have or are medically unfit for SLNB with the understanding of its low sensitivity. While targeted ultrasound after lymphoscintigraphic localization may improve sensitivity and specificity, the cost effectiveness and accuracy of ultrasound-guided FNA in small tumor deposits remain to be determined.

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Table 1

Patient and Tumor Characteristics

		Patients (n)	(%)
Gender	Male	189	58.2
	Female	136	41.8
Median age (yrs)	58 (18 – 86)		
Median BMI	29.1 (18.1 – 70.2)		
Primary site	Head & neck	34	10.5
	Trunk	129	39.7
	Upper extremity	101	31.1
	Lower extremity	61	18.8
Breslow (mm) Median = 1.78 (range 0.42 – 14.4)	1.00	56	17.2
	1.01 – 2.00	136	41.8
	2.01 – 4.00	88	27.1
	> 4.00	44	13.5
	Unknown	1	0.3
Clark's level	III	24	7.4
	IV	275	84.6
	V	20	6.2
	Unknown	6	1.8
Ulceration	Absent	212	65.3
	Present	97	29.8
	Unknown	16	4.9
Regression	Absent	284	87.4
	Present	26	8.0
	Unknown	15	4.6
Growth phase	Radial	20	6.2
	Vertical	283	87.1
	Unknown	22	6.7
Angio-lymphatic invasion	Absent	290	89.3
	Present	15	4.6
	Unknown	20	6.2
Mitotic rate	0	9	2.8
	>1	303	93.2
	Unknown	23	7.1

Table 2

Sensitivity, Specificity, Positive and Negative Predictive Value of Ultrasound

		N	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Overall	Patients	324	31.8	86	36.8	83.1
	Nodal basin	348	33.8	85.7	36.5	84.2
Breslow depth *	1 mm	60	0	89.6	0	96.2
	1.01 – 2 mm	146	14.3	85.6	14.3	85.6
	2.01 – 4 mm	93	42.8	81.9	40.9	83.1
	> 4 mm	48	45.8	87.5	78.5	61.8
Location of basins **	Neck	44	43.2	56.8	15.8	88
	Axilla	230	34.1	88.3	38.9	86.1
	Groin	72	30	96.1	75	78.1

* 1 case with missing depth

** 2 Popliteal nodal basins not included

*** Epitrochlear nodal basins and in-transit sites were not included in analysis since no corresponding ultrasound and SLNB were performed.

Abbreviations: PPV – positive predictive value; NPV – negative predictive value

Table 3

Reported Studies of Preoperative Ultrasound and Sentinel Node Biopsy

Study	N	Year	Sensitivity	Specificity	PPV	NPV
Rossi [18]	125	2003	39	100	100	85
Hocevar [48]	57	2004	71	84	59	90
Van Rijk [15]	107	2006	34	87	59.1	70.5
Voit [16] *	127	2006	79	72	100	85
Sibon [49]	131	2007	20.6	89.8	41.2	76.5
Sanki [50] *	716	2009	23.3	97.3	59.6	88.3
Present study	324	2011	33.8	85.7	36.5	84.2

Abbreviations: PPV – positive predictive value; NPV- negative predictive value

* Targeted US study with lymphoscintigraphy