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ORIGINAL REPORT

Rotterdam Criteria for Sentinel Node (SN) Tumor Burden and the Accuracy of Ultrasound (US) -Guided Fine-Needle Aspiration Cytology (FNAC): Can US-Guided FNAC Replace SN Staging in Patients With Melanoma?

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ABSTRACT

Purpose
Sentinel node (SN) status is the most important prognostic factor for overall survival (OS) for patients with stage I/II melanoma, and the role of the SN procedure as a staging procedure has long been established. However, a less invasive procedure, such as ultrasound (US) -guided fine-needle aspiration cytology (FNAC), would be preferred. The aim of this study was to evaluate the accuracy of US-guided FNAC and compare the results with histology after SN surgery was performed in all patients.

Patients and Methods
Four hundred consecutive patients who underwent lymphoscintigraphy subsequently underwent a US examination before the SN procedure. When the US examination showed a suspicious or malignant pattern, patients underwent an FNAC. Median Breslow thickness was 1.8 mm; mean follow-up was 42 months (range, 4 to 82 months). We considered the US-guided FNAC positive if either US and/or FNAC were positive. If US was suggestive of abnormality, but FNAC was negative, the US-guided FNAC was considered negative.

Results
US-guided FNAC identified 51 (65%) of 79 SN metastases. Specificity was 99% (317 of 321), with a positive predictive value of 93% and negative predictive value of 92%. SN-positive identification rate by US-guided FNAC increased from 40% in stage pT1a/b disease to 79% in stage pT4a/b disease. US-guided FNAC detected SN tumors more than 1.0 mm in 86% of cases, SN tumors of 0.1 to 1.0 mm in 46% of cases, and SN tumors less than 0.1 mm in 23% of cases. Estimated 5-year OS rates were 92% for patients with negative US-guided FNAC results and 51% for patients with positive results.

Conclusion
US-guided FNAC of SNs is highly accurate. Up to 65% of the patients with SN-positive results in our institution could have been spared an SN procedure.

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INTRODUCTION

Epidemiologists report that not only melanoma incidence, but also melanoma mortality has been increasing over the past decades.[1,2] Breslow thickness and ulceration of the primary tumor are important prognostic factors.[3,4] However, the nodal status of patients with melanoma has been demonstrated to be the overriding factor predicting disease outcome.[3-5] The goal of the sentinel node (SN) staging procedure is to identify patients with nodal metastases as early as possible so they might benefit from the early removal of these metastatic nodes before the disease can spread any further. This is based on the concept of an orderly progression of lymphatic dissemination to the regional draining SN as first station, which occurs in a majority of approximately 90% of all patients with melanoma.[6] The big advantage of the SN procedure over elective lymph node dissection is that only those patients with metastases in their SN will undergo a complete lymph node dissection. In the past, the role of elective lymph node dissection was investigated, but a number of underpowered studies failed to demonstrate a true benefit.[7-10] The Multicenter Selective Lymphadenectomy Trial (MSLT-I) was developed to answer the question of whether SN followed by early complete lymph node dissection would have an

overall survival benefit in patients with intermediate-thickness melanoma.[11] Although the published interim results of the MSLT-I study showed a significant impact on disease-free survival, and a subgroup analysis was suggestive of improved survival for patients with node-positive disease, this did not translate into an overall survival benefit in the intention-to-treat population.[11,12] However, the status of the SN procedure as a staging procedure has been established widely for a number of years. Although the SN procedure is the best predictor of survival so far, it is still an invasive procedure, usually carried out under general anesthesia.

The current state of results entitles us to enter new research fields, such as the role of ultrasound (US) in the staging of patients with stage I/II melanoma. US has been increasingly incorporated and accepted as a follow-up tool for patients with melanoma in Europe and Australia.[13-15] It is also used for follow-up in the MSLT-II trial, currently recruiting patients.[16] A previous study from our institute by Voit et al[17] revealed that US can accurately identify which lymph node is the SN before excision by the surgeon.

The aim of the present study was to evaluate the accuracy of US-guided fine-needle aspiration cytology (FNAC) in the detection of melanoma metastases to the SN, before patients undergo the SN procedure. The gold standard for this study was the final histologic analysis of the SN excised during surgery. Survival analyses for different patient groups have been performed.

PATIENTS AND METHODS

Patients

We report on the analysis of a prospectively defined database of 400 consecutive patients with a primary melanoma (American Joint Committee on Cancer stage I/II) scheduled to undergo an SN procedure at the Department of Dermatology of the Charité, Humboldt University of Berlin, Berlin, Germany. Primary tumors had at least a Breslow thickness of $\geq$ 1 mm, or regardless of Breslow thickness, tumors were Clark stage IV/V, ulcerated, or showed signs of regression.

Patients' primary tumor data were not known in all cases before the US examination of the regional lymph node basin(s). The institutional ethical review board approved the study, and informed consent was obtained from all patients enrolled. Recruitment to this study started in 2001, and we now report the first 400 consecutive patients.

Methods

All patients were scheduled for an SN procedure and were examined by US in B-Mode and Power Doppler after lymphoscintigraphy, because lymphoscintigraphy proved to be helpful before the US examination. In case of a result that was malignant or suggestive of abnormality during the US examination, at least three FNACs of the lesion were performed. Afterwards, the patients proceeded to undergo the SN surgery later the same day or the next day. During the study, there was a shift in the hospital policy, allowing the surgeon to proceed directly to performing a therapeutic lymph node dissection (TLND) in patients for whom FNAC was positive (n = 14).

US

Preoperatively we performed a high-resolution US examination of the lymphatic basin and the lymphatic drainage of the tumor. All US examinations were performed using the high-end device Technos (Esaote, Genova, Italy) equipped with three transducers between 3.5 and 14 MHz (B-mode, 30 pictures per second, color Doppler, Power Mode). The lymph node was measured and was classified as benign, suspicious, or malignant.

Table 1 lists the morphology criteria used for this US classification. To be considered for either US category (suspicious or malignant), at least one of the morphology criteria summarized in Table 1 had to be present. In cases of malignant US examinations, the presence of a balloon-shaped lymph node, with or without peripheral perfusion, had to be observed. Peripheral perfusion is an early sign of involvement, whereas balloon-shaped lymph nodes and the loss of central echoes are late signs that correspond to advanced microscopic involvement. When none of the criteria were present or if a cap structure was present, the node was considered benign.

Table 1. Morphologic Criteria for Suspicion on Ultrasound

Criterion	Malignant	Suggestive of Abnormality	Benign
Balloon-shaped lymph node*	X		
Loss of central echoes†		X	
Peripheral perfusion‡		X	
Hump structure§		X	
Cap structure‖			X
Loss of central perfusion¶		X	
Echo-poor islands#		X	X

*Echo-poor, round, enlarged lymph node, usually without any central echoes.
†Observation that a lymph node has lost central echoes or has still some residual central echoes, but these are wandering toward the rim, giving an asymmetrical central aspect.
‡Perfusion at the rim of a space-occupying lesion in ultrasound depicted by Power Mode.
§Asymmetrical broadening of the parenchyma like a camel hump.
‖Cap-like structure seen as broadening of the parenchyma to the smaller end of an ovally shaped lymph node, as described by Kahle et al.[18]
¶Central perfusion of a space-occupying lesion on ultrasound measured by Power Mode.
#Echo-free areas like islands within an otherwise normal-appearing lymph node with central echoes and echo-poor parenchyma, interrupting the normal architecture of the lymph node.

The region was always examined in comparison with the contralateral side. All examinations were performed by experienced sonographers (C.A.V. and G.S.).

FNAC

FNAC was performed with a hand-held "Binder"-valve, which provides an especially short distance between the button for initiation of aspiration and the region of interest. This makes it possible to aspirate even small targets without losing contact with the lesion in the process. US-guided FNAC uses an alcoholic fluid as a conductor medium, thus minimizing the danger of infection. The fine needle for superficial lymph nodes has a diameter of approximately 0.4 mm (26 G). For deeper lymph nodes (depth $>$ 25 mm) a 22-G lumbar puncture needle is used. The negative pressure for aspiration is performed with a 20-mL syringe by fixing the plunger at the 10-mL position, creating an approximate negative pressure of approximately -300 cmH2O. We performed at least three aspirations under sonographic guidance to receive multiple smears for representative cytodiagnostic evaluation. A smear was considered to be technically efficient if it contained approximately 100 cells. FNAC procedures performed in small targets such as intranodal areas within an SN with a needle diameter of only 0.4 mm often achieve a smaller number of cells and thus tend to give unrepresentative results; these cases were considered negative. To deliver representative results, at least three FNAC procedures must be performed; in those cases in which the cytologist deemed the aspirated material macroscopically insufficient, a possible extra (fourth) FNAC could be performed.

Pathologic Review

SNs were identified by the triple technique, which consists of the preoperative lymphoscintigraphy with the use of radioactive nanocolloid, intraoperative use of patent blue dye, and the intraoperative use of a hand-held gamma probe. The SNs were histologically worked up by the European Organisation for Research and Treatment of Cancer Melanoma Group protocol for pathologic examination.[19] This requires trans-hilar bivalving of the nodes and step sections from both faces of the lymph node. Staining was performed with hematoxylin and eosin (H&E), S-100, and Melan-A. The SN metastases

were microanatomically analyzed for location according to Dewar et al[20] and for SN tumor burden by the Rotterdam Criteria, with maximum diameter of the largest lesion categorized as less than 0.1 mm, 0.1 to 1.0 mm, or more than 1.0 mm.[21,22] Because of a change in hospital policy during the course of this study, after preliminary results, some patients with a positive FNAC proceeded immediately to undergo a TLND (n = 14); these nodes were examined by routine bivalving and H&E staining, not by an advanced SN protocol.

Statistics

To assess diagnostic value of US-guided FNAC, sensitivity, specificity, and positive and negative predictive values were calculated using the Pearson's square test. The combination of US-guided FNAC was only counted as a positive test result if either the US and/or FNAC were positive. If US was suggestive of abnormality, but FNAC was negative, it was considered a negative result. Disease-free and overall survival were calculated from time of US until recurrence of the disease or death, respectively. Patients without such an event at their last follow-up were censored at that time. Univariate analyses of end points was performed using the Kaplan-Meier method and the log-rank test. *P* values of less than .05 were considered as significant. The statistical analyses were performed with STATA version 8.2 (STATA, College Station, TX).

RESULTS

Baseline characteristics of all 400 patients are listed in Table 2. Mean and median Breslow thickness was 1.5 mm and 1.8 mm, respectively. Mean age at the time of US was 58 years. Mean and median follow-up durations of all patients were both 42 months (range, 4 to 82 months).

Table 2. Characteristics of All Patients and Their Primary Tumors

Characteristic	No. of Patients	%
Sex		
Male	219	55
Female	181	45
Histology		
SSM	275	69
NM	81	20
LMM	17	4
ALM	17	4
Unknown	10	3
Breslow depth		
T1, ≤ 1.00 mm	121	30
T2, 1.01 to 2.00 mm	126	32
T3, 2.01 to 4.00 mm	85	21
T4, > 4.00 mm	68	17
Clark level		
II	9	2
III	152	38
IV	215	54
V	21	5
Unknown	3	1
Ulceration		
Present	130	33
Absent	252	63
Unknown	18	4
Location		
Extremity	185	46
Trunk	171	43
Head and neck	44	11

Abbreviations: SSM, superficial spreading melanoma; NM, nodular melanoma; LMM, lentigo maligna melanoma; ALM, acral lentiginous melanoma.

A total of 79 patients (20%) had metastases in their SN on histology. For the different American Joint Committee on Cancer categories of Breslow thickness, this was 4%, 9%, 29%, and 56%, respectively. US was considered malignant in 45 patients (11%), suggestive of abnormality in 112 patients (28%), and benign in 243 patients (61%). FNAC was performed in a total of 134 patients (34%). Unfortunately, in four patients there was not sufficient time to perform an FNAC, and FNAC yielded an unrepresentative result in 19 patients as a result of inadequate smears (< 100 cells). All 23 patients have been analyzed as FNAC negative.

Of the 400 patients, 331 patients (83%) had a single draining basin, 61 patients (15%) had two draining basins, and eight patients (2%) had three draining basins, all of which were examined. Four patients with multiple draining basins had one positive FNAC; none had multiple positive FNACs from different basins. These four patients subsequently underwent a surgical SN procedure of all draining basins. One of these four patients had two positive SN basins; the others had only one positive SN basin.

Table 3 lists the values of US-guided FNAC; it shows an overview of the sensitivity, specificity, and positive and negative predictive value of the combination of US-guided FNAC in total and also per T stage. Table 3 also lists the results for the three most important US morphology criteria.

There was one case were the FNAC was false positive, because histologic examination of the SN was negative. However, this patient soon developed a regional nodal recurrence in the same nodal basin where the FNAC was performed, so most likely this node was the US-identified node and the SN retrieved by surgery was not the nodal metastasis found with FNAC.

For all patients, the technique demonstrated a 65% sensitivity rate, a 99% specificity rate, a 93% positive predictive value, and a 92% negative predictive value. Of the 79 SN-positive patients, 28 patients (35%) had false-negative results on US-guided FNAC. For the entire population, this translated into 7% and 8% of all patients who were incorrectly identified as having SN-positive and SN-negative results, respectively.

Because 14 patients underwent a TLND after positive FNAC, without a previous SN procedure, only 65 (of the 79) positive SNs could be microanatomically analyzed for SN metastasis location and tumor burden. Thirteen patients (20%) had metastases less than 0.1 mm, 37% had 0.1 to 1.0 mm SN tumor burden, and 43% had an SN tumor burden more than 1.0 mm (Table 4). All 14 patients with a positive FNAC, followed by a TLND, demonstrated at least one positive lymph node on routine bivalving and H&E staining.

Survival

The Kaplan-Meier–estimated 5-year overall survival rate was 92% for patients with US-guided FNAC–negative results, as compared with 51% for those with US-guided FNAC–positive results, respectively (Fig 1A). Figure 1B shows the Kaplan-Meier estimated 5-year overall survival rate for the groups: 93% for patients with negative results on US-guided FNAC and histology (true-negative patients), 53% for patients with positive results on US-guided FNAC and histology (true-positive patients), and 71% for patients with negative US-guided FNAC results but positive histology results (false-negative patients). The distant metastasis–free survival rate was calculated for the same three patient groups. The Kaplan-Meier estimated 5-year distant metastasis–free survival rate was 92% for patients

Table 3. Sensitivity, Specificity, PPV, and NPV of the Combination US-Guided FNAC for All Patients per T Stage and According to Separate US Morphology Criteria

US Morphology and T Stage	Sensitivity			Specificity			PPV			NPV		
	No.	Total No.	%	No.	Total No.	%	No.	Total No.	%	No.	Total No.	%
Balloon-shaped lymph node			30			100			96			85
Loss of central echoes			60			92			65			90
Peripheral perfusion			77			82			52			93
T stage												
1	2	5	40	116	116	100	2	2	100	116	119	97
2	6	11	55	113	115	98	6	8	75	113	118	96
3	13	25	52	59	60	98	13	14	93	59	71	83
4	30	38	79	29	30	97	30	31	97	29	37	78
All patients	51	79	65	317	321	99	51	55	93	317	345	92

Abbreviations: PPV, positive predictive value; NPV, negative predictive value; US, ultrasound; FNAC, fine-needle aspiration cytology.

with negative results on US-guided FNAC and histology, 35% for patients with positive results on US-guided FNAC and histology, and 82% for patients with negative results on US-guided FNAC but positive results on histology (Fig 2).

The Kaplan-Meier estimated 5-year overall survival rates according to the Rotterdam Criteria for SN tumor burden were 93% for SN-negative patients, 92% for patients with metastases less than 0.1 mm, 46% for patients with metastases 0.1 to 1.0 mm, and 51% for patients with metastases more than 1.0 mm (Fig 1C).

DISCUSSION

The present study demonstrates, in the largest US-guided FNAC melanoma patient cohort ever to be reported, that US in combination with FNAC is a highly accurate presurgical SN staging procedure for patients with stage I/II melanoma. In our hands, this technique has an overall sensitivity of 65%, which is the highest rate ever reported. Rossi et al[23] reported a rate of 39% (12 of 31), Starritt et al[24] reported a rate of 21% (seven of 33), and van Rijk et al[25] reported a rate of 34% (12 of 37). A possible clarification for this large difference in sensitivity compared with previous studies could be the introduction and recognition of peripheral perfusion as a sign of early involvement.

Another possible reason for the increase in sensitivity in our study is the easy access to quick cytology reports and the more frequent use of FNAC. Other centers do not have access to an overnight FNAC report and will therefore not perform an FNAC. At our center, patients undergo subsequently a lymphoscintigraphy, a US exam with or without FNAC, and an SN procedure the next day. The definitive FNAC report is available for the surgeon before the scheduled operation.

In other centers, such as the Sydney Melanoma Unit, FNAC is only performed in those cases in which a large disruption of the US image has already been observed. Most patients with stage I/II melanoma scheduled to undergo an SN procedure will not yet have such advanced SN disease, and therefore the yield and sensitivity is lower than that reported in the present study. In contrast, at our center, FNAC is performed quite often, when there is a small, early disruption of the US image. However, because of the single-institution nature of the present study, we stress that the results of this study need to validated in a multicenter prospective study.

Importantly, in the present study, the frequency of node positivity varies from 4% to 9% in pT1 and pT2 stages (ie, node positivity is an uncommon event). In stages pT3 and pT4, node positivity occurs with a higher frequency of 29% to 56%, respectively. The sensitivity increased significantly from 40% in pT1 to 80% in pT4. This is analogous to the situation in breast cancer, were US-guided FNAC detects a large proportion of the nodal metastases preoperatively, especially in patients with higher T stages, thereby reducing the number of SN operations.[26-28] The survival rates of 92% for patients with US-guided FNAC–negative results versus 51% for patients with US-guided FNAC–positive results in our study are identical to the survival rates from numerous large studies in the literature.[3-5,11,29]

Arguments against the preoperative use of US-guided FNAC in patients with melanoma are that, although US-guided FNAC can

Table 4. Distribution of US-Guided FNAC Positivity According to SN Tumor Burden

US-Guided FNAC Result	SN Tumor Burden								
	SN Negative (n = 321)		< 0.1 mm (n = 13)		0.1 to 1.0 mm (n = 24)		> 1.0 mm (n = 28)		
	No.	%	No.	%	No.	%	No.	%	Total
Negative	317	99	10	77	13	54	4	14	345
Positive	4	1	3	23	11	46	24	86	55
Total	321		13		24		28		400

NOTE. Fourteen patients underwent direct complete lymph node dissection, for a total of 79 patients with node-positive disease.
Abbreviations: US, ultrasound; FNAC, fine-needle aspiration cytology; SN, sentinel node.

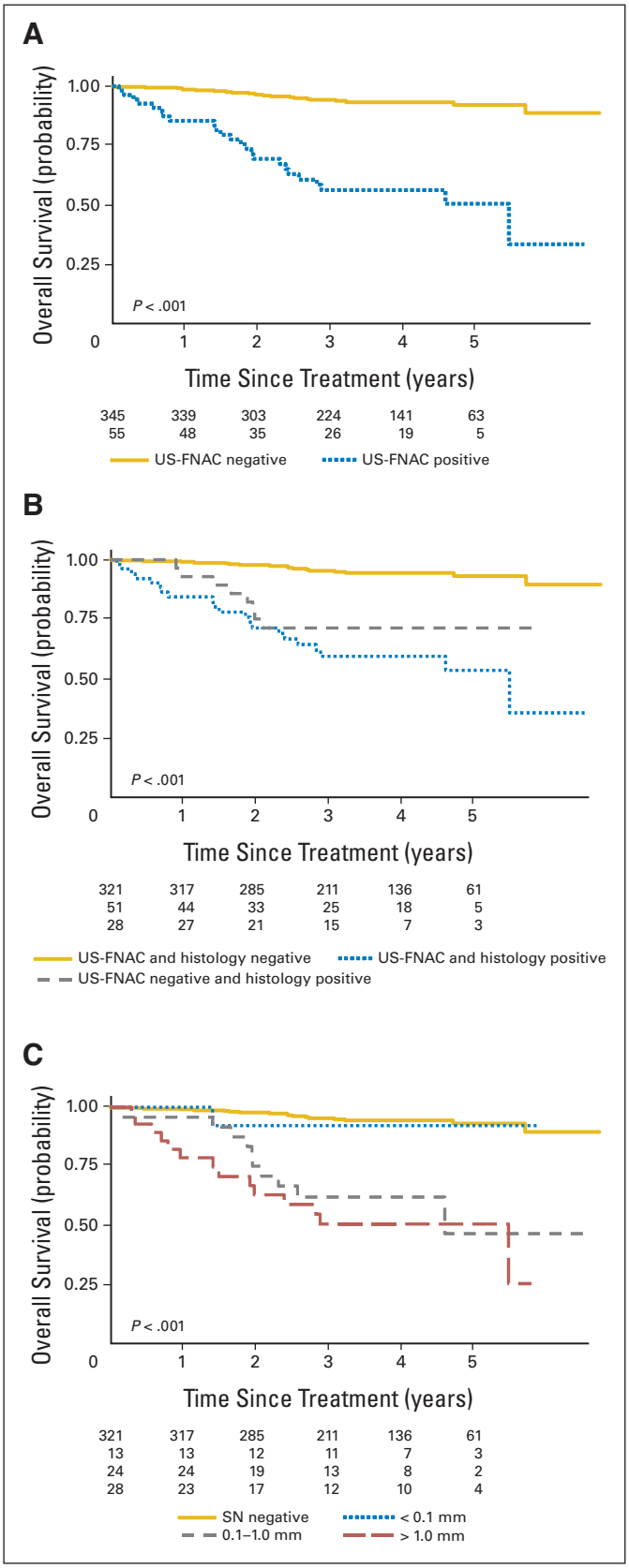

Fig 1. Kaplan-Meier–estimated 5-year overall survival of all 400 patients (A) according to ultrasound-guided fine-needle aspiration cytology (US-FNAC) status, (B) according to US-FNAC and histology status, and (C) according to the amount of sentinel node (SN) tumor burden.

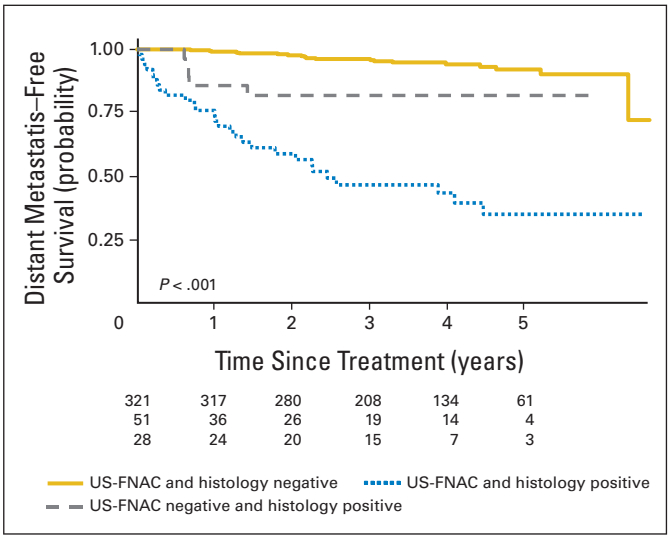

Fig 2. Kaplan-Meier–estimated 5-year distant metastasis–free survival according to ultrasound-guided fine-needle aspiration cytology (US-FNAC) and histology status.

detect approximately two thirds of SN metastases preoperatively, it will still miss one third, and therefore, US-guided FNAC would not be able to replace SN staging in patients with melanoma. However, the questions we want to address are: which metastases is US-guided FNAC missing, and what are the consequences?

The present study has demonstrated that there is a close correlation between the sensitivity of US-guided FNAC detection of SN metastases and the size of SN metastases. Whereas only a few SNs with metastases less than 0.1 mm were detected by US results that are suggestive of abnormality (n = 3; none were positive on FNAC), up to 86% of metastases more than 1.0 mm were detected by US-guided FNAC. A number of studies have demonstrated that minimal, most often subcapsular, SN tumor burden has an excellent prognosis that does not differ from that of patients with SN-negative disease,[20-22,30,31] although these results were not confirmed by some other studies on this subject.[32,33]

The 7% false-negative rate of US-guided FNAC of the total population is in the same range as that reported for the SN procedure, which ranges between 7% and 25%, and thus this argument cannot be used against US-guided FNAC.[4,11,34] Moreover, US-guided FNAC can be repeated in an outpatient follow-up setting.[14,35-37] Therefore, even if a patient does not have a US-guided FNAC detectable SN metastasis at first, it could possibly be detected at a very early phase during follow-up. As such, this could be considered as an acceptable alternative to current SN staging. The ongoing MSLT-II trial is also addressing the value of US-guided FNAC as tool in detecting early relapses and might give more insight into the role for US-guided FNAC.[16]

US-guided FNAC has the obvious benefit of reducing the number of surgical SN procedures and thereby the costs of the surgery, most often performed under general anesthesia, and its associated short- and long-term morbidity. Morbidity rates of 4.6% to 13.4% have been reported; in most cases, this entails wound infections, hematomas/seromas, and, in some cases, lymphedema, even for patients with SN-negative disease.[11,38-40] We argue that US-guided FNAC can

avoid these costs in most, if not all, of the 80% (SN-negative) of all patients with stage I/II melanoma.

With a positive predictive value of 93% and a negative predictive value of 92%, the US-guided FNAC identified 65% of patients with SN-positive disease preoperatively in our single-institution experience. We hope that this report will initiate further multicenter studies to determine the reproducibility of these excellent results in daily practice in multiple institutions. Such prospective studies could also evaluate the learning curve in institutions not familiar with this technique.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

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