Fine Needle Aspiration Cytology of Palpable and Nonpalpable Lymph Nodes to Detect Metastatic Melanoma


Background
Fine needle aspiration cytology (FNAC) is usually used to evaluate palpable nodes in patients with melanoma. The goal of our study is to review the sensitivity and specificity of this technique when applied to palpable but also to nonpalpable nodes.

Methods
FNAC was performed during 1984–2007 in 1279 patients with suspicious lesions and/or lymph nodes. Indications for biopsy included increased size and/or palpability of nodes or abnormal ultrasound findings such as increased perfusion or focal lesions within the lymph nodes. The sensitivity, specificity, and positive and negative predictive values of FNACs guided by palpation or ultrasound were calculated for all patients and for subgroups of patients with palpable nodes or nonpalpable but sonomorphologically suspicious nodes.

Results
A total of 2446 FNACs were performed in 1279 melanoma patients, of which 2011 (82.2%) FNACs had clinically or histologically confirmed results. Increased size and/or palpability of nodes was observed in 376 (29.4%) of 1279 patients, and abnormal ultrasound findings occurred for 903 (70.6%), indicating that a biopsy was needed. FNACs guided by palpation had sensitivity, specificity, and positive and negative predictive values similar to that of FNACs guided by ultrasound (sensitivity = 98.4% vs 97.2%, specificity = 100% vs 99.8%, positive predictive value = 100% vs 99.9%, and negative predictive value = 95.2% vs 96.4%, for palpation-guided FNACs vs ultrasound-guided FNACs, respectively). Results did not differ between patients with the palpable nodes and patients with nonpalpable but sonomorphologically suspicious nodes.

Conclusions
Ultrasound-guided FNAC of suspicious lymph nodes and lesions in melanoma patients has a high sensitivity and specificity, and FNAC should not be limited to palpable nodes. FNAC of normal-sized nodes and/or lymph nodes with abnormal ultrasound findings can be used to identify early metastatic disease.

J Natl Cancer Inst 2011;103:1771–1777

The incidence of melanoma is increasing worldwide. Despite a higher detection rate and an increasing trend toward lower Breslow thickness (1) (a measurement of the depth of invasion and a proven prognostic factor in melanoma), the mortality rate has continued to increase during the last decades (2). After the diagnosis of primary melanoma, most metastases will develop within the first 3 years, and about two-thirds of all recurrences are lymph node metastases (3). Most specialists agree that early detection of metastatic disease is an important prognostic factor and fine needle aspiration is often only performed on enlarged and palpable nodes so that cytology and histopathology can be done to confirm metastatic disease.

Our group previously initiated fine needle aspiration cytology (FNAC) primarily only on palpable lymph nodes. After the introduction of ultrasound in the follow-up of melanoma patients, we also started to perform FNAC on nonpalpable lymph nodes with suspicious ultrasound findings. For this study, we investigate the clinical differences, sensitivity, and specificity of palpation-guided FNACs vs ultrasound-guided FNACs on palpable and nonpalpable lymph nodes. Furthermore, we calculated the sensitivity and specificity of ultrasound-guided FNACs in patients who had been treated for primary melanoma vs those who had already experienced a recurrence. The goal of our study is to help determine if ultrasound-guided FNAC is able to detect early melanoma metastases to the lymph nodes at an early stage, that is, to nonpalpable or enlarged nodes.

Patients and Methods
Study Population
All patients included in this study had a history of histologically proven melanoma. Patients were referred for evaluation of lymph nodes and/or melanoma lesions at any time during the course of their disease (pre- or postoperatively and during regularly scheduled follow-up). Our ultrasound section evaluated patients with melanoma during the study period between January 1, 1984, and
Prior knowledge
Fine needle aspiration followed by cytology and histopathology is a method often used for the early detection of metastases in melanoma patients. However, this procedure is typically only performed on enlarged and palpable lymph nodes.

Study design
The clinical differences, sensitivity, and specificity of palpation-guided and ultrasound-guided fine needle aspiration cytology (FNAC) were compared among 2446 patients with a history of histologically confirmed melanoma.

Contribution
The standard policy of performing FNAC only on palpable lymph nodes may miss early metastatic disease in some patients. The overall sensitivity and specificity of palpation-guided and ultrasound-guided FNAC were similar in both patients who were previously treated for a melanoma with no recurrence or in patients who had a previous recurrence.

Implications
Using ultrasound-guided FNAC, metastatic disease can be detected before the metastatic lymph node meets the currently accepted size criteria for palpation-guided FNAC. Studies to determine the effect of detecting metastatic disease in nonpalpable lymph nodes on overall survival of melanoma patients are warranted.

Limitations
The use of ultrasound has inherent limitations because of the learning curve and interobserver variation associated with different examiners. Also, some lymph node regions are easier to examine than others, creating potential bias. Analyses to assess the effect of these potential influences on the study results were not done.

December 30, 2007. However, only patients under the direct clinical care of A. Schoeneng or C. A. Voipt were included in this study (n = 2446). This did not represent a selection bias but allowed easier data acquisition and clinical follow-up. In our study, the initial subgroup of patients had “palpable” findings [observed in 376 (29.4%) of 1279 lymph nodes]. Subsequent patients were always evaluated with ultrasound even in the absence of palpable findings [903 (70.6%) of 1279 lymph nodes]. The Charité University Medicine Berlin Institutional Review Board approved the initial study and subsequent modifications of our clinical approach. Written informed consent was obtained from all study participants.

Ultrasound
All patients were either seen on their regular ultrasound follow-up schedule following a history of melanoma or were referred because of an unusual finding on clinical examination (4). Additional imaging such as computed tomography (CT) or positron emission tomography (PET) did not have a crucial role for the ultrasound exam, as most of these additional cross-sectional exams were performed after the ultrasound evaluation. All patients were examined by both clinical examination and ultrasound according to the recommendations by the German Skin Cancer Society (5). The scheduled intervals between follow-up depended on the tumor stage and were more frequent in stages with higher risk. Patients who had stage I and II primary tumors with a Breslow Index greater than 1 mm or tumor thickness were subject to follow-up every 6 months by ultrasound (in the first 5 years), patients who had stage III tumors were subject to follow-up every 3–6 months, and patients who had stage IV tumors had an individual more frequent follow-up schedule determined by the clinician. An FNAC was only performed when the ultrasound identified suspicious or malignant lymph nodes. Patients were examined by ultrasound in B-Mode and later by power Doppler (6). In B-mode ultrasound, a linear array of transducers simultaneously scans a plane through the body that can be viewed as a two-dimensional image on the screen. The “B” stands for brightness mode, in which the ultrasound shows echoes in a gray scale. Imaging with color Doppler requires a scanner setting able to detect superficial slow flows: the highest Doppler frequencies, relatively low pulse repetition frequency (the lowest not causing aliasing or excessive reduction in the frame rate), the lowest wall filter, and color gain immediately below the noise threshold. In most scanners, the power Doppler mode is more sensitive and able to depict very slow flows compared with the color Doppler mode and is therefore preferred. The ultrasound examination included all major lymph node locations, the in-transit distances, and the region of any palpated or unclear lesion itself. Our criteria for suspicious ultrasound findings in nonpalpable lymph nodes were recently reviewed and include increased peripheral perfusion and lack of central echogenicity (the ability to return the signal in an ultrasound exam). Within the normal “reactively enlarged lymph node,” the central portion is echo rich and corresponds to the hilum region, whereas the peripherally echo-poor portion corresponds to the parenchyma (7). All ultrasound examinations were first done with a simple B-mode device with a 7.5 MHz linear scanner (Sonoline; Siemens, Munich, Germany) from January 1, 1992, until December 30, 2000. For the remainder of the study, the high-end devices Technos and MyLab 70 (Esaote, Genova, Italy) equipped with three transducers between 3.5 and 18 MHz (B-mode, 30 pictures per second, color Doppler, power Mode) were used. The lymph nodes, in-transit lesions, or subcutaneous lesions were measured and classified as benign, suspicious, or malignant. In-transit lesions are distinct and classified as those within the area between the primary tumor and the first lymph node basin, whereas lesions within a circle of 2–3 cm around the primary lesion are considered satellite metastases. The region was always examined in comparison with the contralateral side.

Fine Needle Aspiration Cytology
FNAC was performed, as previously described (8), with a handheld Binder-valve, which provides an especially short distance between the button for initiation of aspiration and the region of interest (Supplementary Figure 1, A, available online). This facilitates easier aspiration of very small targets without any loss of contact with the lesion and is aided by the use of a spacer (Supplementary Figure 1, B, available online) that creates and maintains pressure until the binder valve is pressed (Supplementary Figure 2, available online). Ultrasound-guided FNAC uses an alcoholic fluid (Octenisept Spray; Schülke & Mayr GmbH, Norderstedt, Germany) as a conductor medium, thus minimizing the danger of infection. The aspiration material was collected using a 25- to 27-gauge fine needle except...
when intra-abdominal lesions were present. All needles were manufactured by Becton Dickinson (Dublin, Ireland). A 22 gauge fine needle (Supplementary Figure 1, C, available online) was used for aspiration (22 gauge Chiba needle; Peter Pflugbeil GmbH Medizinische Instrumente, Zorneding, Germany) of cells from lymph nodes at a depth greater than 70 mm. For deeper lymph nodes at a depth of 25–69 mm, a 25 gauge lumbar needle was used (Supplementary Figure 1, D, available online), whereas a short 27 gauge fine needle was used for subcutaneous lesions (<25 mm) (Supplementary Figure 1, E, available online). The negative pressure for aspiration is created with a 30-mL syringe by fixing the plunger at the 20-mL position, thereby creating an approximate negative pressure of approximately −300 cm H₂O. The aspiration material was cautiously expelled onto glass slides for cytology. Multiple FNACs of the lesion were performed only when a suspicious finding occurred during the ultrasound examination. Most patients had three aspirations to assure sufficient material for cytdiagnostic evaluation.

A smear was considered to be technically efficient if it contained approximately 100 cells or more on two different glass slides. Some FNAC procedures were performed on small targets such as small intranodal or tiny subcapsular areas within a node with a needle having a diameter of 0.4 mm. Such FNAC procedures on small targets usually capture only a smaller number of cells (<100 cells) and thus tend to give unrepresentative results.

Staining for Cytology
Glass slides containing aspirates were air dried and put into absolute methanol for 10 minutes (FA Merck, Darmstadt, Germany) and incubated in a May–Gruenwald Eosin Methylenblue Solution (three parts May–Gruenwald and one part buffer) (FA Merck) for 7 minutes at room temperature. The glass slides were next stained with Giemsa Azur Eosin Methylenblue solution (one part Giemsa and four parts buffer) (FA Merck) for 20 minutes at room temperature. Afterward they were washed in buffer (containing 290 mL of 0.2 mol potassium hydrogen phosphate and 125 mL of 0.2 mol sodium hydrogen in 10L aqua demineralisata, at pH 6.8) at room temperature for 1 minute and a second time for 7 minutes. All aspirates were examined by a trained cytologist (A. Schoengen). Patients with a positive (malignant) cytology were scheduled for surgery, whereas those with negative cytology were managed with a close follow-up evaluation and a repeat ultrasound.

Melanoma normally presents with well-preserved dissociated cells with a wide basophile cytoplasm and granular chromatin in different subtypes that include the epithelial cell type, the spindle cell-like type, or the mixed cell type with or without pigment, and often with inclusions or as giant cells. After staining, samples were viewed under a compound microscope (Carl Zeiss MicroImaging GmbH, Jena, Germany) at ×400 magnification. The histopathologic finding after the surgical resection of a lesion was considered to be the gold standard for this study (Supplementary Figure 3, available online). Benign cytological results were confirmed by a clinical and ultrasound follow-up.

Statistical Analysis
To assess the value of any diagnostic procedure, sensitivity, specificity, and positive and negative predictive values (PPV and NPV, respectively) were calculated with 95% confidence intervals. Data were stratified by clinical scenario for analysis: FNACs performed on patients during follow-up after treatment with no recurrence (scenario 1) or after a recurrence (scenario 2). The statistical analyses were performed with SAS 9.1.3 (SAS Institute, Cary, NC). The sensitivity was determined on a lesion-to-lesion basis.

Results
Patient Characteristics
The mean age at the time of ultrasound-guided FNAC was 57 years (range = 9–94 years). The mean follow-up was 35 months (range = 6–276 months) (Table 1). Of 1279 patients, we had a complete record of the Clark level and Breslow tumor thickness for 741 patients. The Clark level is a measure of invasion of malignant melanoma through the skin layers to the subcutaneous layer, ranging from level II–V with Clark I being in situ melanoma, and has been established as prognostic factor for melanoma. In our study, 30 patients presented with a Clark II level, 208 with a Clark III level, 460 with a Clark IV level, and 43 with a Clark V level. The mean Breslow tumor thickness, an actual measurement of the depth of invasion and a prognostic factor in melanoma, was 3.11 mm (range = 0.11–44 mm). The mean Breslow thickness was relatively high given that higher risk melanomas start from a Breslow thickness greater than 1 mm. This is also when the patients are offered a sentinel node biopsy. This does not take into consideration how many patients actually had progressive disease because Breslow tumor thickness is a classification of the primary tumor per se.

Sensitivity and Specificity of Ultrasound-Guided FNAC
A total of 2446 FNACs were performed in 1279 patients between January 1, 1984, and December 30, 2007. A correct interpretation of FNAC was confirmed by positive histopathology for malignant
FNACs or follow-up ultrasound, and/or repeated FNAC. An initial negative result from the fine needle aspiration was evaluated by multiple follow-up ultrasound examinations and if necessary also by FNAC procedures. Of 2446 FNACs, results were confirmed for 2011 (82.2%) procedures, including 1213 (60.3%) by histopathology and 798 (39.7%) by clinical follow-up (Table 1). No complications such as bleeding or distribution of tumor cells along the fine needle tract or morbidity as a result of the procedure were reported. These results indicate that the dataset is relatively complete and mature because outcomes were known for more than 80% of the procedures, and a relatively long follow-up was done. In addition, the lack of complications indicates that FNAC is a minimally invasive procedure.

Among 1041 patients, 1385 (68.9%) of the 2011 confirmed FNACs were guided by ultrasound (Table 1). Also, of all of the FNACs performed (n = 1279), 376 (29.4%) were performed on palpable nodes, whereas 903 (70.6%) were performed on suspicious lesions/lymph nodes that were neither palpable nor enlarged. We therefore had FNACs from both palpable and nonpalpable lymph nodes and suspicious lesions for which to test the sensitivity and specificity of ultrasound-guided FNACs. Because we had added ultrasound for regular follow-up and better visualization of the fine needle, the numbers of ultrasound-guided FNACs increased rapidly.

The sensitivity of palpation-guided FNACs vs ultrasound-guided FNACs differed only slightly (98.4% vs 97.2%). The specificity of palpation-guided FNACs (100%) was also similar to that of ultrasound-guided FNACs (99.8%). Also, PPV and NPV for palpation-guided FNACs vs ultrasound-guided FNACs were similar (PPV = 100% vs 99.9% and NPV = 95.2% vs 96.4%). Further evaluation of these minimal differences and their statistical significance was not performed. These findings indicate that ultrasound-guided FNAC is as specific and sensitive as palpation-guided FNAC, although the lesions are often smaller and in a deeper location (ie, detected by ultrasound only).

In 14 suspected palpable lesions, a melanoma metastasis was clinically assumed, but a second malignancy (including lymphoma and papillary thyroid cancer) or a benign etiology (including salivary gland adenoma) was demonstrated by cytology (Supplementary Figure 3, available online) and confirmed by histopathology. Ultrasound guidance also allowed us to report the sizes of the areas of interest (eg, focal region of interest within a normal-sized node). Four hundred and twenty-one (20.9%) FNACs were performed in lesions smaller than 10 mm. Of these, 216 lesions smaller than 6 mm and 149 lesions smaller than 5 mm were successfully punctured, with sensitivities of 96.3% and 96.9%, respectively. In the 5-mm lesions, a specificity of 98.1%, a PPV of 98.9%, and an NPV of 94.4% were observed. These results indicate that ultrasound-guided FNAC was highly sensitive and specific, with a high PPV and NPV, even for small lesions.

### Analysis of FNACs by Clinical Scenario

Our results were further analyzed by dividing them according to two scenarios, which are important in clinical practice—FNACs performed during follow-up after treatment with no recurrence or FNACs performed after a recurrence. Another important scenario refers to FNACs performed in sentinel nodes; however, we previously analyzed data under this scenario (9) and limited our analysis in this study. We found that 385 of 499 confirmed FNACs were performed during follow-up after treatment of a primary melanoma with no recurrence (Table 2). This means that any malignant outcome constituted the first recurrence. A sensitivity of 99.4%, a specificity of 99.6%, a PPV of 99.4%, and an NPV 99.6% were observed for these FNACs. Of the 385 confirmed FNACs, 311 were lymph nodes, of which 128 were confirmed melanoma metastases. Of these 385 FNACs, 46 were subcutaneous masses and included 23 melanoma metastases and 28 lesions that were neither lymph nodes nor subcutaneous masses but located at different anatomical locations including the salivary glands (n = 6), thyroid gland (n = 5), and breast lymph nodes (n = 2) (data not shown). These results indicate that FNAC may be used with sufficient sensitivity and specificity in a relatively safe manner in all organs in which a lesion can be detected or reached by the fine needle.

The second scenario refers to FNACs performed after a recurrence (lymph node or any), when doctors and patients are already more alert (because the first recurrence had taken place), and the

<table>
<thead>
<tr>
<th>FNAC results</th>
<th>Scenario 1 (no relapse) n = 385</th>
<th>Scenario 2 (after recurrence) n = 704</th>
<th>All procedures† n = 2011</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. malignant</td>
<td>151</td>
<td>442</td>
<td>1159</td>
</tr>
<tr>
<td>No. uncertain malignant</td>
<td>9</td>
<td>32</td>
<td>62</td>
</tr>
<tr>
<td>No. benign</td>
<td>0</td>
<td>137</td>
<td>0</td>
</tr>
<tr>
<td>No. uncertain benign</td>
<td>0</td>
<td>5</td>
<td>16</td>
</tr>
<tr>
<td>No. nondiagnostic (no cell material)</td>
<td>1</td>
<td>8</td>
<td>15</td>
</tr>
<tr>
<td>Sensitivity, % (95% CI)</td>
<td>99.4 (96.6 to 100)</td>
<td>97.3 (95.5 to 98.6)</td>
<td>97.9 (96.5 to 98.3)</td>
</tr>
<tr>
<td>Specificity, % (95% CI)</td>
<td>99.6 (97.5 to 100)</td>
<td>100 (99.3 to 100)</td>
<td>99.9 (99.5 to 100)</td>
</tr>
<tr>
<td>PPV, % (95% CI)</td>
<td>99.4 (96.6 to 100)</td>
<td>100 (99.2 to 100)</td>
<td>99.9 (99.5 to 100)</td>
</tr>
<tr>
<td>NPV, % (95% CI)</td>
<td>99.6 (97.5 to 100)</td>
<td>94.4 (90.5 to 97.0)</td>
<td>96.1 (94.5 to 97.3)</td>
</tr>
</tbody>
</table>

* Data from FNACs performed on patients during follow-up after treatment with no recurrence (scenario 1) or after a recurrence (scenario 2) were analyzed. These scenarios are important in clinical practice. Another important scenario refers to FNACs performed in sentinel nodes; however, we previously analyzed data under this scenario (9) and limited our analysis in this study. CI = confidence interval; FNAC = fine needle aspiration cytology; PPV = positive predictive value; NPV = negative predictive value.

† Includes all patients with confirmed results.
probability of developing further metastases (and in parallel, presumably, the detection rate) is higher than in patients with no recurrence to date. Of the total FNACs, 704 confirmed FNACs fall under the second scenario (Table 2). The sensitivity and specificity of FNAC in this scenario was 97.3% and 100%, respectively, with a PPV of 100% and an NPV of 94.4%. Because no difference in outcome was observed between patients who have already had a recurrence and those without any recurrence to date, ultrasound for detection and ultrasound-guided FNAC for verification are sufficiently sensitive and specific, meaning the clinician may not need to know the patient’s history.

The above scenarios did not apply to several FNACs. These included patients who underwent ultrasound-guided FNACs of visceral organs or CT-guided biopsies and were in our database because code words like “FNAC” and “melanoma lesion” were present in their record. They include 36 liver masses (26 of these masses were metastatic melanoma), 24 retroperitoneal lymph nodes (20 were confirmed as metastatic melanoma), five intra-abdominal lymph nodes (three of these nodes were confirmed as metastatic melanoma), 10 adrenal glands (nine were confirmed as metastatic melanoma), six lung (five were confirmed as metastatic melanoma), three kidneys (but no metastatic lesions), and five intra-abdominal masses (of which three were metastatic melanoma) (data not shown).

The combined results of all 2011 FNACs showed a sensitivity of 97.5%, specificity of 99.9%, a PPV of 99.9%, and an NPV of 96.1%. Of all 2011 confirmed FNACs, as many as 31 were false-negative results (Table 2). However, misinterpretation was not a cause of false-negative results, and 16 (51.6%) were attributed to technical issues such as a failed puncture of the lymph node or necrosis. In 15 (48.4%) of 31 FNACs, there was no evaluable material after FNAC, but repeat FNAC confirmed a malignant melanoma.

**Discussion**

In our study, the overall sensitivity and specificity of FNAC was high in palpable enlarged nodes as well as normal-sized nodes. Our results indicate that our initial approach, to perform FNAC only in patients with palpable nodes, may have missed early metastatic disease in some patients. Furthermore, the overall sensitivity and specificity was also similar to the results in two clinically relevant scenarios—evaluation after treatment of a primary melanoma with no recurrence (scenario 1) or performed after a recurrence (scenario 2). Our revised approach detected metastatic nodes before disease could be detected clinically or on the basis of size criteria.

Evaluation for lymph node metastases/lesions in patients with melanoma usually focuses on enlarged lymph nodes identified by palpation, CT (on which enlarged lymph nodes are defined as those with a long axis of 1.5–2 cm or larger), or PET (on which suspicious lesions are identified by an area of significant fluorine-18 2-fluoro-2-deoxy-D-glucose [FDG] uptake with a size >1.5 cm). Ultrasound for staging and surveillance of melanoma patients has been proven to be highly effective for the detection of metastases in several retrospective studies (10–12) and one prospective study (4). Interest in fine needle aspiration of melanoma metastases/lymph nodes has been growing, and several dedicated studies including those by Perry et al. (13), Murali et al. (14), and Doubrovsky et al. (15) have discussed this approach and predominantly refer to enlarged or palpable nodes. Our approach to evaluating lymph nodes/lesions in patients with melanoma changed after we introduced ultrasound into the follow-up (4,16). Initially, we performed FNAC exclusively on palpable and enlarged nodes, in an approach similar to that outlined by Murali et al. (14). We subsequently extended our FNAC evaluations to include other lymph nodes/suspicious lesions identified by ultrasound criteria (7) to test the value of the ultrasound criteria for detection and the sensitivity of FNAC for the application in only ultrasound-detected and ultrasound-guided lesions in melanoma patients.

A recent study by Morton (18) concluded that sentinel node biopsy in a subgroup of patients with intermediate thickness primary melanoma identified patients whose survival might be prolonged by lymphadenectomy. The sentinel nodes were identified with scintigraphy and sentinel node biopsy essentially consisted of surgical removal of the node. The diagnostic approach in this report is actually similar to our approach, except that we always performed sentinel node FNAC before biopsy/surgery. This approach allowed us to substantially reduce the number of our diagnostic lymph node dissections (19).

A recent commentary by Balch et al. (20) stated that ultrasound has a low sensitivity because the majority of patients present with only micrometastasis which cannot produce changes in the node that can be detected with the current technology (21). They conclude that, “a negative ultrasound evaluation is not a reliable substitute for biopsy.” Although this statement is technically correct, we respectfully observe that it does not take into account the complementary roles of ultrasound and FNAC. We often perform FNAC to determine whether the evaluated node is truly involved, and we would not stop monitoring after a negative ultrasound-guided fine needle aspiration. Furthermore, because a node with suspicious features on ultrasound but negative FNAC would always receive close follow-up and repeat FNAC, it is very unlikely that the development of early metastatic disease would be missed. In this very diverse disease, it might be appropriate to identify and evaluate lymph nodes/suspicious lesions with only scintigraphy, palpation, and biopsy. However, this approach has limitations, in our opinion, and we advocate the use of ultrasound, which is of course examiner dependent. The use of ultrasound not only makes identification and monitoring of nodes easier, it also provides the option of performing targeted ultrasound of either normal-sized or enlarged lymph nodes/lesions. Furthermore, a recent meta-analysis by Xing et al. (22) demonstrated that ultrasound is not an outdated staging tool when compared with other newer imaging techniques like CT or PET. Ultrasound proved to be an efficient and useful imaging method for staging and surveillance of lymph node metastases in melanoma.

FNAC is only a component of the dedicated patient evaluation. Sensitivity of FNAC is obviously limited by the sensitivity of ultrasound because all lesions are first detected by ultrasound. There are two major advantages for the combination of ultrasound and FNAC: Ultrasound-guided FNAC helps to improve specificity and sensitivity in difficult situations in which ultrasound alone gives unclear results. Ultrasound-guided FNAC also provides a verification of unclear ultrasound findings in anatomical regions...
that are prone to give unclear results such as cervical lymph nodes. We consider our approach to be minimally invasive, and our results as well as the responses received from patients and referring physicians support this observation.

Our study has several limitations. First, it is very difficult to measure clinical expertise, and a different examiner might have had a different impression of palpable nodes or suspicious ultrasound features. We acknowledge that there is not just a learning curve but also some interobserver variation, which was not measured in our study. Second, the size of normal lymph nodes in all the different anatomical locations varies substantially. Although we always documented the size of lymph nodes, we did not incorporate analysis of these detailed data in our study design. Additionally, different lymph node regions are easier to evaluate compared with others (17), for example, the groin, head and neck, and axillary locations, in order of easiest to most difficult. A third limitation of our study is that we ultimately relied heavily on ultrasound. A small number of patients might have had FNAC on the basis of ultrasound criteria although their nodes would have been deemed palpable, enlarged, or slightly enlarged by other means of examination.

A number of biopsies were performed in patients for whom there was low suspicion for malignant disease (n = 355). Similar to the work-up of thyroid nodules or breast lesions, a certain number of negative biopsies is required to maintain a high sensitivity. Our primary goal was to detect as many “early cancers” as possible, and we therefore biopsied nodes with questionable or subtle findings. We do not consider negative biopsies as “unnecessary” but as an important aspect of the evaluation of a patient.

Alternatively, fewer FNACs could be performed to negate those procedures that might be called unnecessary, but this will ultimately increase the number of missed nodes, as a proportion of patients with metastatic disease may be left undiagnosed until later in their disease. It is our opinion that a certain rate of negative (benign) FNACs is acceptable given the potential risks associated with diagnosing metastasis at a later stage in the progression of the cancer. Nevertheless, a more complicated study design with incorporation of these details may not have changed the overall findings of our results.

In summary, ultrasound-guided FNAC allows the accurate evaluation of palpable and nonpalpable lymph nodes. Our data suggest that the evaluation of lymph nodes in melanoma should not be limited to size criteria, such as palpability. Future studies to investigate if evaluation of nonpalpable lymph nodes contributes to overall and relapse-free survival of melanoma patients are warranted. Our group is currently collecting data in a prospective study to evaluate if and how such early detection of metastatic disease contributes to overall and relapse-free survival of melanoma patients.

References


Funding
None

Notes
We wish to thank Irma Loch for technical advice and Petra Siegel and Christo Le Roux for organizational support. The authors are grateful to Aaron Justin Correia for his assistance in the preparation of this article. A. Schoengen and J. Rademaker shared senior authorship.
Affiliations of authors: Department of Dermatology, Charité University Medicine Berlin, Berlin, Germany (CAV, GS-H, WS); Department of Surgical Oncology, Erasmus University Medical Center—Daniel den Hoed Cancer Center, Rotterdam, the Netherlands (ACJvA); Cancer Institute Gustave Roussy, Villejuif/Pari-Sud, France (AMME); Department of Biometry and Medical Documentation, University of Ulm, Ulm, Germany (MK); Department of Dermatology/Skin Cancer Center Harz, Medical Center Quedlinburg, Germany (JU); Department of Internal Medicine, Haematology and Medical Oncology, Armed Forces Hospital, Ulm, Germany (AS); Department of Radiology, Memorial Sloan-Kettering Cancer Center, New York, NY (JR).