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# Fine needle aspiration in the diagnosis of metastatic melanoma

Lori K. E. Rodrigues, MD,<sup>a</sup> Stanley P. L. Leong, MD,<sup>b</sup> Britt-Marie Ljung, MD,<sup>c</sup>  
Richard W. Sagebiel, MD,<sup>a</sup> Nancy Burnside, MD,<sup>a</sup> Tsu-lung William Hu, BS,<sup>c</sup> Brenda W. Ng, MD,<sup>c</sup>  
James R. Miller III, PhD,<sup>c</sup> and Mohammed Kashani-Sabet, MD<sup>a</sup> *San Francisco, California*

**Background:** Fine needle aspiration is an accurate technique to diagnose metastatic melanoma. Few reports exist in the literature describing its usefulness in many patients with melanoma confirmed by open biopsy.

**Objective:** The purpose of this study was to determine the utility and predictive value of fine needle aspiration in patients with malignant melanoma who presented with lesions suspected to be metastatic.

**Methods:** We retrospectively reviewed 99 cases of fine needle aspiration and the corresponding histologic findings obtained by open biopsy in 82 patients.

**Results:** Of the 99 cases, 86 were positive for melanoma, 12 were negative, and one was indeterminate. The positive predictive value of fine needle aspiration was 99%. One patient had a false-positive diagnosis.

**Conclusion:** Fine needle aspiration is a rapid, accurate, and minimally invasive procedure that is useful in the diagnosis of metastatic melanoma. Patients with a positive aspirate of palpable regional nodes can proceed directly to surgery, bypassing the need for an open biopsy. (*J Am Acad Dermatol* 2000;42:735-40.)

**M**alignant melanoma is the seventh most common malignancy in the United States.<sup>1</sup> Until the mid 1990s, increases in its incidence and mortality rates have been the largest of any cancer. The current lifetime risk for the development of cutaneous malignant melanoma in the United States is estimated to be 1 in 87, and this is projected to rise to 1 in 75 by the year 2000.<sup>2</sup> However, increases in melanoma mortality are not as steep as those recorded in past decades. Future trends indicate that the mortality rate of melanoma will reach a peak in the early decades of the 21st century, then decline.<sup>3</sup> Despite recent changes in these rates, the poor survival of patients with metastatic disease remains a primary public concern because melanoma is an aggressive tumor with the potential

to metastasize. Regional metastases (ie, satellitosis, in-transit metastases, and regional lymph node involvement) are seen in two thirds of patients with metastatic spread of malignant melanoma.<sup>4</sup> Moreover, patients with metastatic disease may initially present with cutaneous or subcutaneous nodules as a sign of distant metastases. Finally, given the improvement in scanning techniques, patients may be diagnosed with distant metastasis while asymptomatic and when tumor burden is relatively low. Early detection of both primary malignant melanoma and metastatic disease is important for initiation of appropriate treatment.

Fine needle aspiration is a rapid and accurate tool used to diagnose many human cancers,<sup>5-10</sup> including malignant melanoma.<sup>11</sup> In the clinical setting, a diagnosis can be obtained within minutes after the aspirate is collected, thus allowing prompt and proper triage of the patient's care. This article presents our experience with this technique and correlates the result of fine needle aspiration with that obtained by subsequent open biopsy.

## MATERIAL AND METHODS

We retrospectively reviewed the medical records of melanoma patients at the University of California, San Francisco/Mount Zion Medical Center between

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From the Melanoma Center, Cutaneous Oncology Division, Department of Dermatology,<sup>a</sup> and the Departments of Surgery<sup>b</sup> and Pathology,<sup>c</sup> University of California/Mount Zion Medical Center.

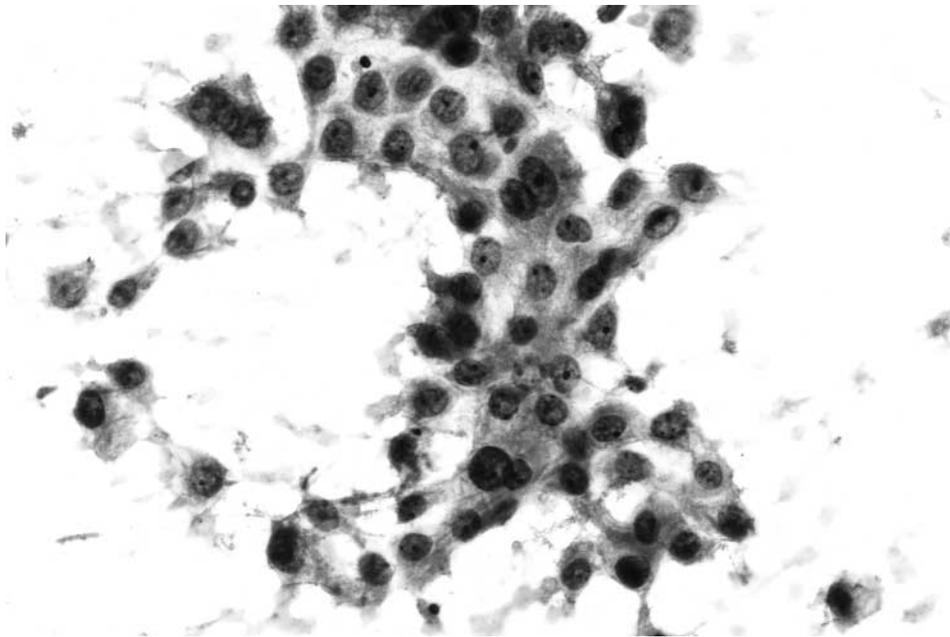
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Reprint requests: Mohammed Kashani-Sabet, MD, UCSF Melanoma Center, 2356 Sutter St, 4th Floor, San Francisco, CA 94115. E-mail: kashanisabet@orca.ucsf.edu.

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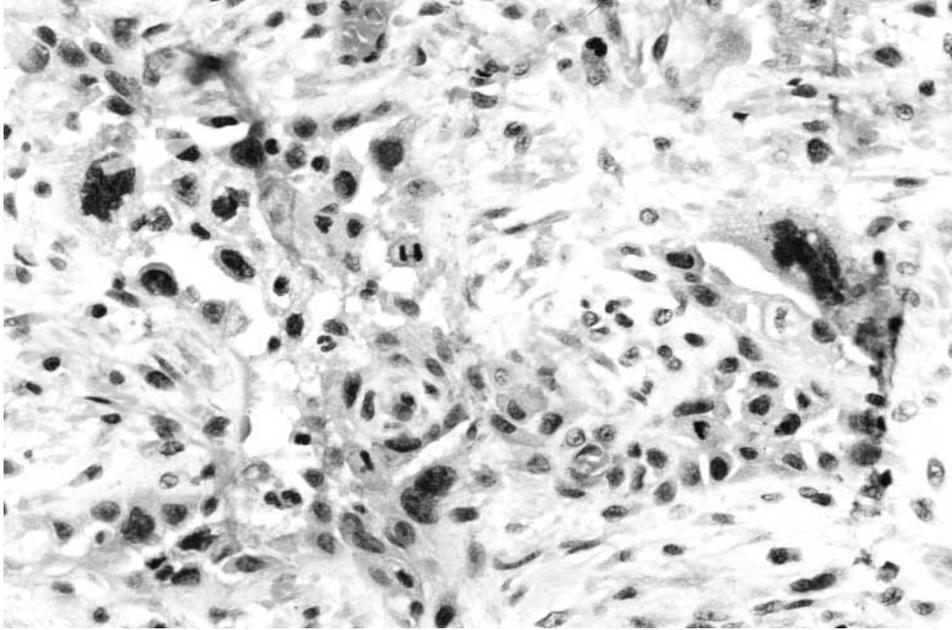
**Fig 1.** Fine needle aspiration smear typical of melanoma. Hematoxylin-eosin–stained section reveals discohesive population of pleomorphic cells with irregular nuclear contours, coarse chromatin and prominent nucleoli. (Original magnification  $\times 400$ .)

November 1992 and December 1998 who underwent fine needle aspiration of lesions suspected of being metastatic. We included only those patients who had surgical excision after the fine needle aspiration. During this period, 99 fine needle aspirations and open biopsies were performed on 82 patients. All fine needle aspirations were performed by experienced operators who had received formal training in cytopathology and perform at least 100 fine needle aspirations per year. In 80 patients fine needle aspirations were performed on palpable lymph nodes or subcutaneous nodules. In two patients, computed tomographic (CT) scans (Accuson 128 XP, Mountain View, Calif) of the chest revealed pulmonary nodules that were suspect for metastasis. In these two patients, fine needle aspirations of the pulmonary nodules were performed under CT guidance. All 82 patients underwent open biopsy of the mass in which fine needle aspiration had been performed. Reports of the cytologic diagnosis made by fine needle aspiration and histologic diagnosis made after surgery were reviewed. Slides were re-examined if there was discordance between the cytologic and histologic reading. The results were classified into positive-cellular with features of diagnostic malignancy, negative-cellular without features of malignancy, or indeterminate (too few cells or the features did not allow for a definitive diagnosis of melanoma). We

compared the cytologic diagnosis to the histologic diagnosis to determine the predictive value of fine needle aspiration in the evaluation of patients with metastatic melanoma. The positive predictive value (PPV) was calculated by means of Fisher's exact test.

All patients had a history of malignant melanoma and were being followed up at the University of California San Francisco Melanoma Center with routine clinical examinations. Ages of the patients ranged from 17 to 84 years, with a median age of 55 years. There were 44 male and 38 female patients. Fine needle aspiration was performed on 31 axillary lymph nodes, 28 nodules in the head and neck region, 14 inguinal lymph nodes, 7 nodules on the trunk, 13 on the lower extremity, 4 on the upper extremity, and 2 on the lungs.

In virtually all cases, the mass was aspirated with a 23-gauge needle and the specimen spread on a slide, stained with toluidine blue, and examined by a cytopathologist within minutes after collection. All palpable masses were sampled by specifically trained cytopathologists. The two deep-seated lesions were sampled by radiologists assisted by cytopathologists. Permanent smears were stained with May-Grunewald Giemsa or fixed in alcohol and stained according to Papanicolaou to confirm the immediate reading. In a small subset of cases, cell block preparations were made. The surgically



**Fig 2.** Poorly differentiated squamous cell carcinoma. Hematoxylin-eosin–stained section reveals a tumor with morphologic features consistent with both melanoma and squamous cell carcinoma. A classification of squamous cell carcinoma could be made only after the use of immunohistochemical stains on histologic sections. (Original magnification  $\times 200$ .)

resected nodules were examined using hematoxylin and eosin stains. Immunocytochemistry with S-100 protein, HMB-45, and cytokeratin was used in a subset of cytologic and histologic specimens in which a definitive diagnosis of malignant melanoma was difficult to establish.

## RESULTS

Ninety-nine fine needle aspirations were performed on 82 patients. In 86 specimens, the result was positive for metastatic malignant melanoma (Fig 1), in 12 specimens negative, and in 1 specimen indeterminate. Of the 86 positive aspirates, 85 were confirmed as positive by open biopsy, and one was negative. All 12 negative aspirates were histologically negative. In this study, the PPV of fine needle aspirations in the diagnosis of metastatic melanoma was 99%. One aspirate yielded a false-positive diagnosis of metastatic melanoma (1%; Fig 2). In this case metastatic, poorly differentiated squamous cell carcinoma was misclassified as metastatic melanoma. The cytologic and histopathologic slides and the medical records of this patient were collected for review and are discussed later in this article. There were no false-negative results in this study (Table I).

Finally, one of the aspirates performed was indeterminate because too few cells were obtained to make a definitive diagnosis. This case was excluded in the statistical calculation.

**Table I.** Summary of 98 cases comparing results of fine needle aspiration and open biopsy

	Open biopsy positive	Open biopsy negative
FNA positive	True positive (85)	False positive (1)
FNA negative	False negative (0)	True negative (12)

The number of true and false positive and negative cases are shown in parentheses. *FNA*, Fine needle aspiration.

## DISCUSSION

Malignant melanoma is a potentially aggressive tumor with the ability to metastasize widely. The overall frequency of regional involvement of the disease is extremely high in patients with metastatic disease. The ability to metastasize and the resulting high mortality rates from this cancer underscore the importance of early detection of both primary and metastatic disease. As in most cancers, early detection and proper treatment may prolong disease-free survival and mortality rates in a select group of patients.

Fine needle aspiration is a technique that has been used in the diagnosis of many human cancers, including malignant melanoma.<sup>11,12</sup> It is a cost-effective, highly reliable technique that is well tolerated by patients when performed by properly trained

operators.<sup>13-15</sup> The sensitivity and specificity of this technique in the diagnosis of metastatic melanoma have been reported to be between 86% and 100% and between 96% and 100%, respectively.<sup>12,16</sup> In one study that compared the impact of operator training on the accuracy of fine needle aspiration, only 2% of cancers were missed by experienced operators, as compared with 25% for less experienced operators (Ljung et al, manuscript submitted for publication). The less experienced operators had no formal training in cytopathology, performed a median of two fine needle aspirations per year, and consisted of gynecologists, surgeons, family practitioners, and radiologists. The quality of the specimens collected by the experienced operators was significantly higher and resulted in fewer nondiagnostic and inconclusive specimens.

The risk of tumor seeding along the needle tract is a rare complication of this procedure and appears to be directly related to the diameter of the needle.<sup>17,18</sup> There have been two reports suggesting tumor dissemination along the needle tract after fine needle aspiration biopsies.<sup>18,19</sup> Despite cutaneous spread of tumor cells along the needle tract, the spread did not affect the natural progression of disease in the cases reported. Engzell et al<sup>20</sup> investigated the possibility of distant dissemination of tumor cells after fine needle aspiration in rabbits and found this to be an uncommon occurrence. Although tumor cells may spread along the needle tract, the spread was judged to lack clinical implications. A retrospective study compared the local recurrence rate in several cancer patients, including those with melanoma, who underwent open biopsy or fine needle aspiration of a lymph node in either the cervical, axillary, or inguinal region. This study found that local recurrence was almost twice as common (41%-44% vs 20%-22%) in patients who had undergone open biopsy before resection when compared with patients who either did not have tissue sampling before resection or had a fine needle aspiration. Therefore fine needle aspiration in patients with melanoma who present with an enlarged lymph node that is suspect for metastatic disease is preferred because of its lower rate of local recurrence when compared with open biopsy.<sup>21</sup>

Fine needle aspiration has been used extensively in the clinical screening of metastatic melanoma. Several groups have documented the utility of fine needle aspiration in the diagnosis of both primary cutaneous melanoma and metastatic melanoma.<sup>11,12,16</sup> To our knowledge, our study has the largest number of fine needle aspirations that were followed with open biopsy. Perry, Seigler, and Johnston<sup>16</sup> compared 298 cases of fine needle aspiration with histopathology (74

cases) and clinical behavior (224 cases) in patients with a history of melanoma. The group demonstrated a high degree of accuracy for this technique, with a PPV of 98% and false-positive and false-negative rates of 8% and 2%, respectively. Inadequate aspirations accounted for the majority of false-negative cases, which may be related to operator training. Misinterpretation was not found to be a contributing factor in this study. Basler et al<sup>22</sup> reviewed 56 fine needle aspirations performed on palpable nodules in lymph node basins in melanoma patients. The diagnostic accuracy was determined by comparing cytologic findings to open biopsy (35 cases) and to clinical follow-up (21 cases). When a definitive diagnosis was obtained, there was a 100% sensitivity and specificity with fine needle aspiration. Hafström et al<sup>12</sup> demonstrated a PPV of 100% in 64 fine needle aspirations in patients with melanoma who presented with a suspicion of recurrent melanoma. There were no false-positive diagnoses and the frequency of false-negative diagnosis was 5%.

Our study supports the utility of this technique in the evaluation of melanoma patients with metastatic disease and confirms its high degree of accuracy. We report a statistically high PPV (99%) of fine needle aspiration and only one case of a false-positive reading.

In the case with a false-positive cytologic finding, the patient had a history of both squamous cell carcinoma and malignant melanoma. The aspirate was collected from a subcutaneous nodule away from the primary tumors. All cytologic and histologic slides, including those from the original cancers, were carefully reviewed. The lesion in question was morphologically different from either of the two primary tumors. The interpretation of the cytology was difficult because of the unusually diverse morphology of the tumor, which was not typical of either squamous cell carcinoma or melanoma (Fig 2). However, the history of squamous cell carcinoma was not known by the cytopathologist at the time of microscopic examination and the cytologic appearance was highly anaplastic and consistent with melanoma. Therefore the cytologic diagnosis of metastatic melanoma was made. Immunoperoxidase stains of the open biopsy were done and the results were positive for HMB-45 and cytokeratin and negative for S-100 protein. Therefore, in this case, the final diagnosis of squamous cell carcinoma was made primarily on the basis of results of the immunoperoxidase stains.

Although fine needle aspiration can provide an accurate diagnosis of malignancy, this technique can be limited in that only the lesion being aspirated is evaluated for the presence of tumor cells. Patients

with negative findings from fine needle aspiration are not necessarily free of cancer elsewhere. In our study one case illustrated this concept. One patient presented with inguinal adenopathy and underwent fine needle aspiration, which was negative for malignant cells. Given the suspect nature of the palpable mass, the patient underwent an inguinal lymph node dissection, and a total of 6 lymph nodes were resected. The largest node measuring 2.3 cm in diameter (and the one most likely aspirated) was reactive in nature and contained no malignant cells. However, a smaller node measuring 0.7 cm in diameter was shown to contain micrometastatic melanoma as confirmed by immunoperoxidase stains, which were positive for S-100 protein and HMB-45 and negative for cytokeratin. The smaller lymph node, which was probably not aspirated, contained micrometastatic disease. Therefore clinical judgment is required to determine whether further studies are indicated in the event of a positive or negative result.

Both benign and malignant cytologic diagnoses may provide useful information. The findings of malignant cells should initiate a work-up to rule out the possibility of other metastatic disease. The staging work-up we routinely perform in the event of metastatic disease includes a magnetic resonance imaging scan of the brain, as well as CT scans of the chest, abdomen, pelvis, and other areas as indicated. Depending on these results, we can formulate a treatment plan that may include surgical or medical management of the patient. Patients with regional nodal disease who have a positive fine needle aspiration can proceed directly to a lymph node dissection, bypassing the need for an open biopsy. In cases with a positive fine needle aspiration, melanoma cells can be saved at the time of lymph node dissection for the preparation of vaccine for immunotherapy. Proper collection of tumor cells and storage in growth media is essential to the growth of tumor cells in culture. Both freezing and storage in formalin will destroy the cells. Thus patients with positive cytologic findings can be scheduled for surgery with sufficient preparation time to ensure appropriate collection and storage of viable tumor cells.

The differential diagnosis of clinically detectable lesions is diverse. Obtaining a tissue diagnosis of a lesion is important to identify malignant tumors. Subcutaneous nodules may represent metastatic foci or benign lesions such as lipomas, cysts, fibromas, or neuromas. Distinguishing metastatic lymphadenopathy from a reactive lymph node or fatty tissue infiltration of a lymph node is also important because a patient with metastasis to the lymph node will require a lymph node dissection and may be eligible to undergo systemic adjuvant therapy such as inter-

feron alfa or melanoma vaccines. Solitary lung masses may represent a primary lung cancer, benign conditions, or metastatic tumors including melanoma. Thus fine needle aspiration, in combination with other modalities and close clinical follow-up, may help elucidate which of the multitude of diagnostic possibilities is most likely.

In summary, fine needle aspiration is a highly accurate, cost-effective technique that is well tolerated by patients. It has been used frequently in the clinical evaluation of patients with a history of malignant melanoma. Rapid tissue diagnosis permits prompt and appropriate triage of patient care. Practitioners, such as dermatologists and primary care physicians, who are often the first to encounter a melanoma patient with clinically or radiographically suspect lesion(s), should consider fine needle aspiration by an experienced operator.

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#### **NATIONAL REGISTRY FOR ICHTHYOSIS AND RELATED DISORDERS**

The National Institutes for Health, through the National Institute for Arthritis, Musculoskeletal and Skin Diseases, has sponsored a National Registry for Ichthyosis and Related Disorders. The goals of the Registry are to promote the search for basic defects, improve methods of diagnosis, and develop effective methods of treatment and/or prevention of these disorders. Diagnosis of affected persons will be made on the basis of specific listed clinical and histologic criteria and will be confirmed by determination of steroid sulfatase activity where indicated. Investigators and practitioners treating patients afflicted with these disorders or desiring access to the Registry database are encouraged to write or call for information and enrollment forms to:

The National Registry for Ichthyosis and Related Disorders  
University of Washington Dermatology  
Box 356524  
Seattle, WA 98195-65524  
Telephone: 1-800-595-1265  
Fax: 206-616-4302  
E-mail: [ichreg@u.washington.edu](mailto:ichreg@u.washington.edu)  
Website: <http://weber.u.washington.edu/~geoff/ichthyosis.registry>