

# False-Positive Fine Needle Aspiration in the Initial Management of Squamous cell Carcinoma of the Head and Neck

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## Abstract

### Objective

There is considerable variability in the work-up and management of head and neck squamous cell of unknown primary (HNSCCUP). In some cases, a multimodality treatment plan is devised and carried out based on a cytopathologic diagnosis achieved with fine needle aspiration (FNA). While FNA has historically been reported to be reliable, a false-positive result could lead to devastating treatment in a patient without malignancy. Thus, we sought to elucidate the true false-positive rate of FNA and provide a safe algorithm for the workup of HNSCCUP.

### Methods

We performed a retrospective chart review of patients treated by the senior author (Y.D.) between 1998 and 2019 for a neck mass concerning for squamous cell carcinoma (SCC) on fine needle aspiration (FNA) who did not have localized primary disease after imaging and surgical investigations of the upper aerodigestive tract.

### Results

89 patients with HNSCCUP underwent neck dissection, and 75 (84%) were confirmed to have SCC. 14 (16%) patients, however, had no evidence of malignancy on histopathology of the neck contents, and none of these patients developed cancer after one year of follow-up.

### Conclusion

FNA is a reliable tool in the diagnosis of adult neck masses, but it carries a small yet significant false-positive rate for malignancy. In the study herein, we demonstrate that 16% undergoing extensive work-up for presumed HNSCCUP will have benign pathology following neck dissection. Thus, it is important for surgeons to confirm the diagnosis histologically before committing patients to toxic, multimodality cancer therapies.

**Keywords:** head and neck cancer; squamous cell carcinoma; cancer unknown primary

## Introduction

A neck mass presenting in an adult warrants special attention considering the most common etiology is malignancy [1]. Initial evaluation should begin with a thorough history and physical, indirect laryngoscopy, and possible biopsy if a concerning lesion in the upper aerodigestive tract is identified. Unless there is a strong suspicion for lymphoma, fine needle aspiration (FNA) is often performed to obtain a cytopathologic diagnosis. When FNA is concerning for squamous cell carcinoma (SCC), but no primary site is readily identified, then the patient is considered to have

head and neck squamous cell carcinoma of unknown primary (HNSCCUP).

HNSCCUP is uncommon and only accounts for 3-5% of cancers of the head and neck [2-4], but there is no standardized approach to the management of the newly diagnosed patient with HNSCCUP. Considerable heterogeneity exists in the literature regarding optimal identification of the primary and treatment. The National Comprehensive Cancer Network (NCCN) recommends performing either a computed

tomography (CT) scan with contrast, or positron-emission tomography (PET) scan combined with CT to aid in identification of a primary tumor.<sup>5</sup> If the primary tumor remains elusive following appropriate imaging and panendoscopy, some surgeons advocate proceeding with bilateral palatine tonsillectomy with or without lingual tonsillectomy, as 80-90% of unknown primaries are eventually localized to the oropharynx [4,6].

Although these more invasive techniques can improve detection of the primary tumor, they are often performed prior to treatment of the neck. Furthermore, some will proceed with primary radiation to the neck after imaging, exam under anesthesia, directed biopsies, and tonsillectomy are negative, assuming the case is truly HNSCCUP.

FNA is regarded as accurate and reliable when it comes to diagnosis of malignancy in metastatic SCC; it is reported to have a positive predictive value of 96% in a recent meta-analysis [7]. However, a false-positive FNA masquerading as HNSCCUP is possibly more frequent than anticipated by most surgeons and could lead to treatment of patients who don't have cancer with toxic cancer therapies. Herein, we review our experience with false-positive FNAs of neck masses and present a treatment algorithm to prevent radiation and other cancer therapies in patients without malignancy.

## Method

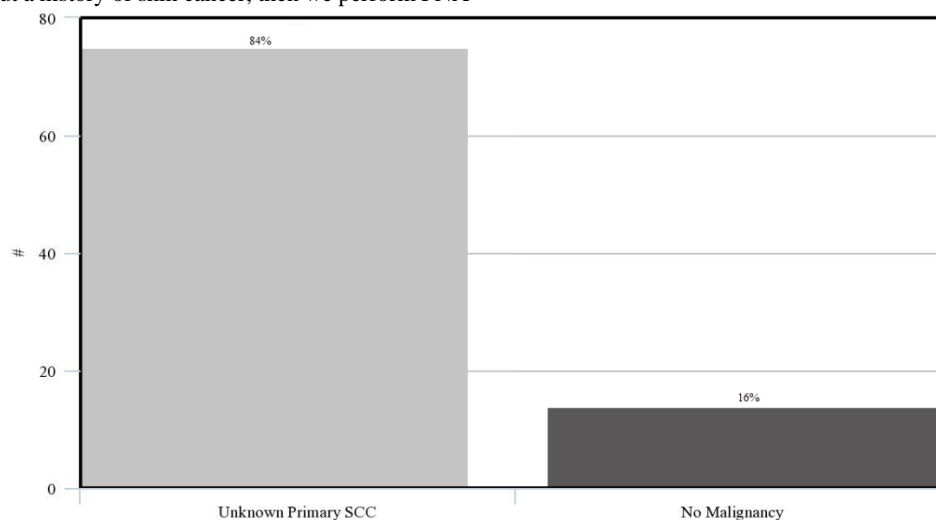
We performed a retrospective review of patients treated by the senior author (YD) between 1998 and 2019 for a neck mass, with initial FNA demonstrating SCC but no evidence of primary or distant disease on exam with laryngoscopy, positron-emission tomography (PET), or panendoscopy with tonsillectomy. We excluded patients who were lost to follow-up before one year. Approval for our study was granted by the John Peter Smith Hospital institutional review board, Fort Worth, TX. Statistical analysis was completed in Graph Pad Prism, version 8 (San Diego, CA).

It has been standard in our practice to approach adult neck masses concerning for carcinoma as follows: when there is an obvious primary site, it undergoes biopsy followed by FNA of the neck mass, and a treatment plan is then developed based on those results. In the case of a neck mass without an obvious primary lesion on physical exam or flexible laryngoscopy and without a history of skin cancer, then we perform FNA

of the neck mass. If FNA is concerning for SCC, imaging is performed to evaluate for a primary site of disease and any distant metastases. Commonly, imaging will include a computed tomography (CT) scan of the neck and chest or a positron emission tomography (PET) scan of the entire body. Following, the patient is scheduled for operative panendoscopy with biopsy of any primary site suspicious on imaging or directed biopsies and tonsillectomy, if no primary site is found and confirmed. If a primary is still not identified, then we proceed with a neck dissection for both therapeutic and diagnostic reasons. If the initial neck mass is in level 2, 3, or 4, then the initial neck dissection includes levels 2-5. If the initial mass is in level 1, then a supraomohyoid (levels 1-3) neck dissection is performed. Our treatment algorithm is depicted in Figure 1. If pathologic evaluation of the neck contents confirms SCC, we consider performing lingual tonsillectomy to continue the search for the primary site. Then, we proceed with multimodality cancer therapy including radiotherapy (RT) and chemotherapy as appropriate. If, however, the neck contents do not demonstrate malignancy on histologic examination, then we follow patients for at least one year both clinically and with serial imaging of the neck to include repeat CT scans or magnetic resonance imaging (MRI).

## Results

We identified 89 patients in the study period who met inclusion criteria for our study; all had a neck mass with concern for SCC on FNA, but no evidence of primary or distantly-metastatic disease on PET (if performed), and no primary disease pathologically identified after panendoscopy with tonsillectomy and directed biopsies. Neck dissection was performed in all patients, and SCC was confirmed in 75 (84%) patients, all of whom subsequently underwent further therapy. Fourteen patients (16%) did not have invasive SCC on final pathologic examination after neck dissection and underwent no further treatment (Figure 2). Of these, 12 (86%) had a cystic neck mass on presentation, while 2 (14%) had a solid mass. None of these fourteen patients had evidence of disease based on serial imaging and clinical exam at one-year follow-up. Given these results, the positive predictive value of FNA in our patient population is 84.27%.

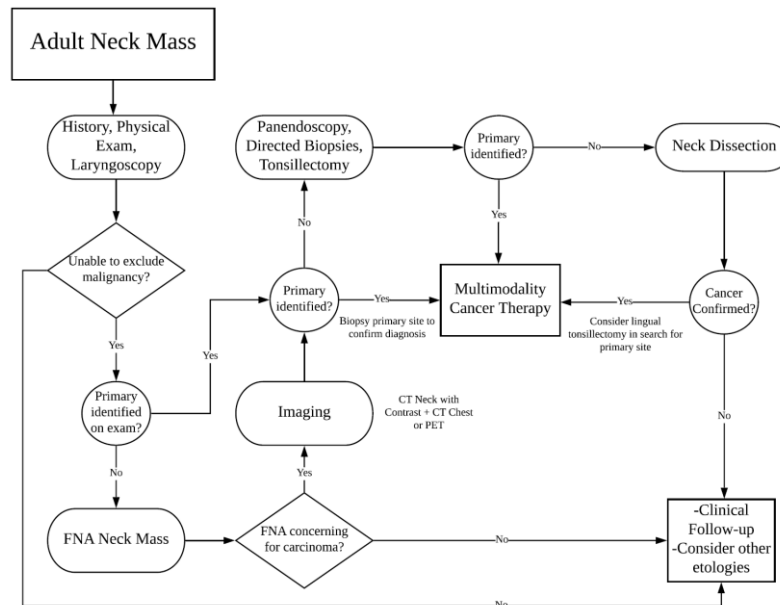


**Figure 1:** Cases of FNA+ neck masses with confirmed malignancy in the neck (unknown primary status) and with a reversal of the diagnosis after neck dissection. 16% of cases initially diagnosed with SCC in the neck based on FNA were found to have no malignancy after neck dissection. FNA: fine needle aspiration. SCC: squamous cell carcinoma.

## Discussion

Our study demonstrates that FNA diagnosis of adult neck masses, while often reliable and correct, can nonetheless be falsely suggestive of carcinoma in an important subset of patients. Thus, we advocate obtaining tissue for histologic confirmation of disease before proceeding with RT or chemotherapy. As in all aspects of medicine, each treatment

step should be pursued after weight the risks and benefits to the patient. It would be devastating to expose a patient unnecessarily to toxic cancer treatments should he or she not have cancer. It would also be unfortunate to expose a patient to anesthesia and the risks of surgery, if non-invasive methods can better guide diagnosis. It is with these considerations in mind that we've adhered to our algorithm presented in Figure 1.



**Figure 2:** Algorithm for workup of an adult neck mass. Importantly, non-surgical interventions for cancer (radiotherapy, chemotherapy) should be delayed until the diagnosis of squamous cell carcinoma (SCC) initially suggested by fine needle aspiration (FNA) has been confirmed histologically. CT: computed tomography. PET: positron-emission tomography.

The initial evaluation of an adult neck mass is widely-accepted to include a comprehensive history and physical exam and, if neoplasm is considered, FNA. We advocate imaging of the neck and distant sites before proceeding to invasive procedures and surgery. Importantly, if PET is pursued, it should precede examination under anesthesia with directed biopsies to avoid a falsely-positive image.

In cases in which a histologic diagnosis cannot be confirmed from the primary site of disease, as in the case of HNSCCUP, excisional biopsy of the neck mass is tempting, but it should be avoided. Excisional biopsy is associated with increased rates of regional recurrence and distant metastasis, possibly due to tumor spillage [8]. Thus, a comprehensive, oncologically-sound neck dissection is necessary to perform when a primary site cannot be identified. Such a neck dissection can be both diagnostic and therapeutic; in early stage HNSCCUP, single modality treatment of the neck, such as surgical excision or RT alone, is acceptable.<sup>4</sup> Further, patients who do go on to require RT to neck contents may be able to receive a lower dose after resection of disease, thus sparing them the toxicities of high-dose treatment.

Next, we also advocate for neck dissection before lingual tonsillectomy, as we feel the recovery from palatine tonsillectomy and lingual tonsillectomy, as would be performed in a comprehensive attempt to identify a primary site of malignancy, is particularly morbid, and would also be devastating in a patient later found to not have cancer in the neck.

## Conclusion

FNA is a reliable tool in the diagnosis of adult neck masses, but it carries a small yet significant false-positive rate for malignancy. In the study herein, we demonstrate that 16% undergoing extensive work-up for presumed HNSCCUP will have benign pathology following neck dissection. Thus, it is important for surgeons to confirm the diagnosis histologically before committing patients to toxic, multimodality cancer therapies.

## Disclosures

The authors have no disclosures. The work herein does not necessarily represent the views of the United States Army or Department of Defense.

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