Original Investigation

Accuracy of Ultrasonography-Guided Fine-Needle Aspiration in Detecting Persistent Nodal Disease After Chemoradiotherapy

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IMPORTANCE Few patients with persistent adenopathy following chemoradiotherapy (CRT) for head and neck squamous cell carcinoma harbor viable disease. Improved selectivity for surgical salvage is needed to prevent unnecessary salvage neck dissection.

OBJECTIVE To determine whether ultrasonography-guided fine-needle aspiration (FNA) can be used to identify viable cancer cells in the lymph nodes of patients with persistent radiographic adenopathy following CRT.

DESIGN, SETTING, AND PARTICIPANTS A pilot study included patients undergoing preoperative ultrasonography-guided FNA of lymph nodes considered suspicious on radiography prior to planned neck dissection at a quaternary care facility from February 28, 2011, to March 18, 2013. Data analysis was performed from April 28 to December 24, 2013. Patients treated for head and neck squamous cell carcinoma with CRT who were determined to have persistent neck disease on a 6-week posttreatment computed tomographic scan of the neck and scheduled for salvage neck dissection were considered candidates for this pilot study. All patients enrolled in the study underwent ultrasonography-guided FNA of the suspicious lymph nodes within 2 weeks of the planned neck dissection. The cytopathologist reading the samples was blinded to the patient's identity.

EXPOSURES Fine-needle aspiration with a 23- to 25-gauge needle following CRT.

MAIN OUTCOMES AND MEASURES The accuracy of ultrasonography-guided FNA cytologic results was compared with the standard of surgical pathologic examination of neck dissection specimens.

RESULTS Fourteen patients (11 [79%] men; mean [SD] age, 57.8 [11.2] years) were enrolled in this pilot study; data were collected on 17 lymph nodes. Among these 14 patients with incomplete radiographic clinical response, 17 lymph node aspirations were performed. Ultrasonography-guided FNA identified squamous cell carcinoma in the aspirates of 4 (80%) of the 5 nodes with squamous cell carcinoma identified on pathologic testing and confirmed the absence of disease in the remaining 12 (71%) lymph nodes. The statistical analysis of these results revealed a sensitivity of 80%; specificity, 100%; positive predictive value, 100%; and negative predictive value, 92.3%. The diagnostic accuracy of ultrasonography-guided FNA at detecting residual persistent cancer was 88%.

CONCLUSIONS AND RELEVANCE This pilot study suggests that ultrasonography-guided FNA may be a feasible ancillary diagnostic imaging tool to imaging to assess patients with radiographic persistent disease prior to consideration of salvage neck dissection.

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Head and neck squamous cell carcinoma (HNSCC) affects approximately 500 000 patients worldwide each year, frequently metastasizing to cervical lymph nodes. At initial presentation alone, more than half of the patients affected with HNSCC exhibit clinical evidence of cervical node metastasis.[1-3]

Primary chemoradiotherapy (CRT) is a well-established treatment for locally advanced HNSCC.[4-6] However, not every patient has complete response to this treatment modality, necessitating eventual salvage neck dissection.

Although the rate of persistent disease after primary nonsurgical therapy has been reported[7] to be as high as 40%, identifying patients with residual disease has been fraught with challenge. Persistent clinical and radiographic adenopathy is frequently seen after nonsurgical therapy but does not necessary imply pathologic disease. Furthermore, studies[8-12] have shown that approximately 80% of patients who undergo neck dissection after receiving CRT have no viable tumor detected on permanent pathologic examination. The dilemma, therefore, is how to detect true histopathologic disease without performing a diagnostic neck dissection. Combined positron emission tomographic (PET) and computed tomographic (CT) scans have been proposed to help further select patients with residual disease. However, although obtaining a PET/CT scan 12 weeks after therapy is the most common practice, there is still debate over the timing of the scan, its sensitivity and specificity, and the future management of the treatment for these patients.[13,14]

Preliminary data suggest that ultrasonography-guided fine-needle aspiration (FNA) is a highly accurate, safe, and inexpensive method of assessing lymph node metastasis in untreated HNSCC. However, limited data are available to evaluate the efficacy of this technique in the setting of prior CRT.[15]

Our aim was to conduct a pilot study to evaluate the feasibility and diagnostic accuracy of ultrasonography-guided FNA at detecting persistent malignant cells in the lymph nodes of patients with HNSCC after definitive treatment with CRT. We hypothesized that ultrasonography-guided FNA would have similar sensitivity, specificity, and accuracy in patients who received CRT and therefore can more accurately predict which patients will benefit from salvage neck dissection.

Methods

Patients

All patients with locally advanced (categories N1, N2, or N3) HNSCC treated with primary nonsurgical therapy between February 28, 2011, and March 18, 2013, were eligible for this investigation. With the use of American Joint Committee on Cancer[16] oncologic staging, any T, N1 to N3, and M0 categories were included.

The cases of patients were presented to the University of North Carolina Hospitals Multidisciplinary Tumor Board; at that time, imaging was reviewed by a board-certified neuroradiologist, results of pathologic examination were reviewed by a board-certified pathologist, and plan of care was determined by a team of medical oncologists, radiotherapy oncologists, and head and neck surgeons. Patients with persistent cervical adenopathy noted on CT imaging after definitive CRT for whom the multidisciplinary tumor board recommended salvage neck dissection were included in this study. A secure database was maintained and results were recorded by a deidentified numeric system.

All patients provided written informed consent to participate. Financial compensation was not provided. The study was approved by the University of North Carolina Biomedical Institutional Review Board and met the tenets of the Declaration of Helsinki.[17]

Treatment Plan

All patients with node-positive HNSCC received standard-of-care, definitive primary nonsurgical therapy: chemotherapy, radiotherapy, or CRT with curative intent. At the time of this study, our institutional standard of care was to perform a 6-week posttreatment CT scan following CRT and then institute therapy (eg, neck dissection) based on the results of the scan. Every patient received posttreatment imaging in the form of a contrasted CT scan performed 4 to 6 weeks after completing primary CRT. The CT scan was independently interpreted by a neuroradiologist.

Computed tomographic criteria for the diagnosis of residual disease included (1) short-axis (>1.0 cm) or long-axis (>1.5 cm) diameter size, (2) internal heterogeneity of the nodal parenchyma, or (3) significant enhancement. Patients with residual disease noted on imaging were selected to undergo immediate salvage neck dissection in accordance with the National Comprehensive Cancer Network Guidelines.[18]

Ultrasonography-Guided FNA

Ultrasonography-guided FNA was performed by one of us (T.G.H.) within 2 to 4 weeks of the 6-week posttreatment CT scan and within 2 weeks of the planned neck dissection and was targeted at the lymph nodes seen on the posttreatment CT scan. The target lymph node appearance on ultrasonographic imaging was also recorded and included rounded shape, size (>1.0 cm), hyperechogenicity, cystic appearance, hyperechoic punctuations, loss of hilum, and peripheral vascularization.[19] The location of each node was carefully recorded to correlate with the location indicated on the CT scan. Ultrasonography-guided FNA was performed using a 10-mHz linear array probe with 2 passes of a 23- to 25-gauge needle into each lymph node. Each node deemed suspicious on the posttreatment CT was biopsied.

Touch prep and formalin-fixed slides were prepared by one of us (T.G.H.), deidentified by a random numeric system, and then sent by courier to a blinded cytopathologist (M.D.) who independently reviewed these deidentified samples. These results of the cytologic examination were determined before surgery, were kept confidential, and were not included in the patient's medical record.

Salvage Neck Dissection

Based on existing standard institutional head and neck tumor board protocol, a planned neck dissection was scheduled if anything less than a radiographic complete response

Table. Treatment Group Demographics and Results

Patient Sex/ Age, y	Diagnosis	Permanent Histopathologic Results	Ultrasonographically Guided FNA Results	Pathologic/Cytologic Correlation
M/71	T2N2bM0 SCC L BOT after CRT	Negative	Negative	Direct
M/57	T4N3M0 OP SCC after CRT	Negative	Negative	Direct
F/53	T3N2cM0 SGL SCC after CRT	Negative	Negative	Direct
M/57	T3N2cM0 SCC L BOT after CRT	Negative	Negative	Direct
F/60	Stage IV OP SCC after CRT	Positive	Positive	Direct
M/50	T1N2bM0 SCC L tonsil after CRT	Negative	Negative	Direct
M/41	T2N2bM0 SCC OP after CRT	Positive	Positive	Direct
M/50	T2N2bM0 SCC OP after CRT	Negative	Negative	Direct
M/80	TxN3M0 SCC after CRT	Positive	Positive	Direct
F/53	T2N2bM0 SCC OP after CRT	Positive[a]	Negative	FNA missed SCC[a]
M/44	T2N2cM0 SCC R tonsil after CRT	Negative	Negative	Direct
		Negative	Negative	Direct
		Negative	Negative	Direct
M/54	T2N2bM0 SCC L BOT after CRT	Negative	Negative	Direct
M/65	T3N0M0 SCC SGL after CRT	Positive	Positive	Direct
M/74	T4N2cM0 SCC L BOT after CRT	Negative	Negative	Direct
		Negative	Negative	Direct

Abbreviations: BOT, base of tongue; CRT, chemoradiotherapy; FNA, fine-needle aspiration; L, left; OP, oropharynx; R, right; SCC, squamous cell carcinoma; SGL, supraglottic.

[a] Focus of remnant SCC on permanent pathologic testing in the lymph node measured 1 mm.

was noted on the post-CRT CT scan. The decision to perform a neck dissection was made before consideration of enrollment in this study. The type of neck dissection (eg, modified radical, selective, superselective, or nodal pluck) to be performed was selected at the discretion of the surgeon.

The borders of each nodal neck level in the neck dissection specimen were carefully delineated and tagged by the surgeon according to the American Academy of Otolaryngology, Head, and Neck Surgery classification system.[20] The lymph nodes assessed as "concerning" on the CT scan preoperatively were sent separately from the remaining specimen. The specimen was fixed in formalin in the operating room and sent to the pathology laboratory for histologic evaluation.

Cytologic and Pathologic Testing

The neck dissection specimens underwent routine pathologic processing. Hematoxylin-eosin staining of the neck dissection specimens was performed, and histopathologic specimens were interpreted by the pathologists who were blinded to the results of the FNA as part of stand-of-care treatment.

Evaluation and Assessment of Ultrasonography-Guided FNA

To determine the accuracy of ultrasonography-guided FNA in identifying pathologic residual disease in lymph nodes of HNSCC patients 6 to 8 weeks after treatment with definitive CRT, ultrasonography-guided FNA cytologic results were compared with matched neck dissection specimens, and the sensitivity and specificity of the cytologic results were compared with the standard of histopathology.

Statistical Analysis

Cytologic results were coded as no lymphoid cells identified, no malignant cells identified, and squamous cell carcinoma (SCC). Histopathologic findings from subsequent neck dissections were classified as no tumor present, residual SCC present, and necrosis or chronic inflammation consistent with treatment effect present. Cytologic results were compared with the standard of histopathology. Sensitivity, specificity, and negative and positive predictive values were calculated. Data analysis was conducted from April 28 to December 24, 2013. Statistical analysis was performed using SOFA, version 1.4.6 (Paton-Simpson & Associates Ltd).

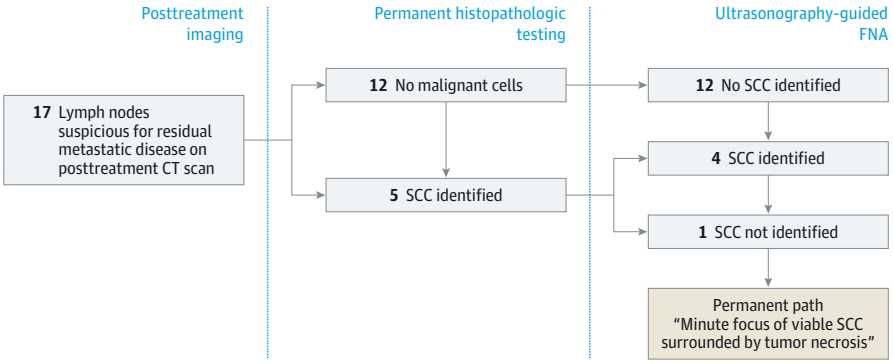
Results

The study population was a cohort of 14 adults (aged ≥18 years) with SCC of the nasopharynx, oropharynx, larynx, oral cavity, or hypopharynx treated with CRT with curative intent. The stage at presentation, results of nodal aspirates, and histologic examination results are summarized in the **Table**.

Fourteen consecutive patients with HNSCC with incomplete radiographic clinical response on their post-CRT CT scan were enrolled in the study in a prospective manner. The study population consisted of 11 men (79%) and 3 women (21%), with a mean (SD) age of 57.8 (11.2) years (range, 41-80 years). Location of the primary tumor was the oropharynx in 12 patients (86%) and supraglottic larynx in 2 patients (14%). Clinical nodal stage at presentation was category N0 in 1 patient, N2a in 2 patients, N2b in 6 patients, N2c in 4 patients, and N3 in 1 patient. The patient who initially presented with category T3N0 prior to CRT had a suspicious node at the completion of CRT identified on the 6-week posttreatment CT scan, which in retrospect was also present on pretreatment films (1.2 cm, level 2 of the ipsilateral neck) but was not indicated as positive at that time. After treatment, this lymph node showed concerning necrosis warranting removal.

Among the 14 patients with incomplete radiographic clinical response, 17 lymph node aspirations were performed. Each lymph node suspicious for residual disease based on CT cri-

Figure. Comparison of Permanent Histopathologic and Ultrasonography-Guided Fine-Needle Aspiration (FNA) Cytologic Testing



CT indicates computed tomography; SCC, squamous cell carcinoma.

teria was biopsied twice, and all (100%) of the sampled lymph nodes were deemed satisfactory for cytologic diagnosis. All of the posttreatment lymph nodes sampled on ultrasonography-guided FNA were rounded, showed a heterogeneous internal appearance, and had no distinct hilum. In retrospect, the malignant lymph nodes were not distinct in appearance from the benign treated lymph nodes. On histologic analysis of the neck dissection samples, no malignant cells were found in 12 (71%) of the 17 nodes (**Figure**). Squamous cell carcinoma was, however, identified on permanent pathologic examination in 5 lymph node specimens. Ultrasonography-guided FNA did not detect the presence of any malignant cells in the 12 aspirates that had negative results on pathologic examination. Ultrasonography-guided FNA correctly indicated SCC in the aspirates of 4 (80%) of these 5 SCC-positive nodes but was unable to detect a minute focus of viable squamous cells in 1 of the nodes. There were no nondiagnostic samples in this study. The statistical analysis of these results revealed sensitivity, 80%; specificity, 100%; positive predictive value, 100%; and negative predictive value, 92.3%. The diagnostic accuracy of ultrasonography-guided FNA at detecting residual persistent malignant cells was 88%.

Discussion

At the inception of primary CRT for HNSCC, all patients received planned posttreatment neck dissections regardless of their clinical response to therapy. These neck dissections served both a diagnostic and therapeutic role. Much has changed in the treatment algorithm since the early 2000s. Combination CRT, better imaging protocols, and a shift in the epidemiology of HNSCC to include human papillomavirus have affected current treatment protocols dramatically.[21]

With improved diagnostic measures, such as PET and CT, and given the low incidence of residual neck disease identified on planned posttreatment neck dissection, treatment paradigms have shifted in the attempts to avoid oncologically unnecessary neck dissections, which carry an additional morbidity without benefit. The management of locally advanced HNSCC has evolved from routine neck dissections to a more methodical assessment of tumor response, with salvage surgery reserved for patients with clinical or radiographic evidence of residual disease.

Despite the vast improvement in diagnostic capabilities and the epidemiologic shift in the disease, the question remains: can we identify at-risk patients earlier and more accurately so as to expedite their oncologic care and prevent the remaining population from receiving unnecessary therapy?

At present, several diagnostic modalities are used to assess lymph node response to primary nonsurgical treatment and, therefore, the need for a posttreatment neck dissection. Computed tomography is a commonly used diagnostic modality to evaluate postradiotherapy residual neck disease. When assessed with strict radiographic criteria (lymph nodes >1.5 cm, focal lucency, and extracapsular extension), CT has a high sensitivity but a low specificity (97% and 37%, respectively).[22] As a result, patients with less than a complete response noted on CT require a neck dissection, which serves both diagnostic and potentially therapeutic purposes. However, there is strong clinical evidence that most patients who undergo salvage neck dissections ultimately have a normal neck dissection specimen and, therefore, a pathologic complete response.[8-12] Thus, many of these patients incur the morbidity but not the benefit of a salvage neck dissection.

PET/CT scans have garnered popularity for the assessment of tumor response to nonsurgical treatment and, subsequently, to guide recommendations for adjuvant neck dissections. The increased metabolic activity of tumor cells leads to an increased uptake of fludeoxyglucose F 18 compared with normal tissue. However, inflammatory cells present in freshly radiated tissue also have an avid uptake of fludeoxyglucose F 18, leading to false positivity on PET/CT scans for up to 3 months after radiotherapy.[23] Delaying a PET/CT scan until after the inflammation subsides potentially places the patient outside the optimal operative window, as dense postradiotherapy fibrosis begins to affect the tissues, leading to a more technically difficult salvage surgery. In addition, the false-positive rate on a 12-week posttreatment PET/CT scan is lower than that of a 6-week posttreatment PET/CT.

Salvage neck dissection in patients whose nonsurgical treatment has failed is associated with high morbidity and a

lower probability of cure. A meta-analysis by Goodwin[24] that used studies published between 1980 and 1998 showed an overall 5-year survival rate of only 39% in patients treated with salvage neck dissection after definitive radiotherapy as their primary treatment modality. Agra et al[25] confirmed the poor prognosis of salvage neck dissection in a study of 96 patients whose cancer recurred after radiotherapy, demonstrating a 5-year survival rate of only 25.3%. With this "wait and watch" approach, the tumor has often already become affixed to vital structures in the neck by the time the regional failure is diagnosed, making most of these recurrent tumors unresectable after definitive CRT. Similarly, at our institution, we have observed a 2-year survival rate of 27% after salvage surgery following CRT failure. The ideal test to select patients who would benefit from posttreatment neck dissection would be highly sensitive to conclusively detect occult disease, would be specific enough to avoid unnecessary neck dissection in patients without disease, and would yield dependable results in a time-sensitive manner.

In prior studies,[19,26-29] ultrasonography-guided FNA has been well documented as an accurate and cost-effective method for assessing patients for lymph node metastasis in HNSCC. Knappe et al[19] assessed 56 patients with ultrasonography-guided FNA prior to neck dissection and found the procedure to have sensitivity, specificity, and accuracy values of 89.2%, 98.1%, and 94.5%, respectively. Furthermore, van den Brekel et al[28] determined that ultrasonography-guided-aspiration cytologic examination was significantly more accurate than clinical palpation, CT, or magnetic resonance imaging at staging lymph node disease.

However, despite the high accuracy of ultrasonography-guided FNA in detecting nodal disease, its ability to identify persistent disease in the neck after CRT has not been conclusively studied.[30,31] Our pilot study aimed to assess the usefulness of ultrasonography-guided FNA in the neck after CRT. Ultrasonography-guided FNA of cervical lymph nodes was performed in 14 patients with HNSCC with persistent adenopathy demonstrated on CT scanning of the neck with contrast immediately before their neck dissection. The accuracy of ultrasonography-guided FNA was assessed by correlating the cytologic examination results determined using needle biopsy with the permanent pathologic findings from the neck dissection specimens. Ultrasonography-guided FNA yielded a sensitivity of 80%, specificity of 100%, positive predictive value of 100%, and negative predictive value of 92.3%, with a diagnostic accuracy of detecting residual persistent carcinoma of 88%.

In our study, the one false-negative ultrasonography-guided FNA specimen was seen in a patient with only 1 mm of viable cancer within a background of necrosis on final pathologic examination 8 weeks after CRT. The FNA results did not show the disease, which points out that one of the limitations of this technique is the potential sampling error of micrometastasis. In addition, ultrasonography-guided FNA is operator dependent and does not assess the primary site, chest, mediastinum, or retropharyngeal zones. Although ultrasonography is a superior imaging tool for assessing thyroid and neck disease, we are not suggesting that it should or can replace CT or PET/CT scans. Furthermore, although ultrasonography provides excellent nodal detail and allows for detection of intranodal micrometastasis in the untreated neck, the same positive predictive value is not seen immediately after treatment. The classic criteria of round shape, heterogeneous core, lack of a hilum, and calcifications were seen in the persistent adenopathy in this study regardless of the presence of viable malignant cells. Radiation-induced nodal necrosis likely clouds the efficacy of ultrasonography as a purely diagnostic tool in this setting, and its guidance of the FNA is where its value lies. Rather, we propose that ultrasonography-guided FNA be considered in the diagnostic algorithm as a means of improving selection of patients for salvage neck surgery when disease is suggested following a 6-week CT or 12-week PET/CT scan.

Ultrasonography costs much less than neck dissection or PET/CT, and the addition of FNA adds a vital pathologic assessment of the tissue. With the potential diagnostic yield and low-cost impact, our pilot study suggests that ultrasonography-guided FNA may add value to the management of care for patients with persistent neck disease following CRT for HNSCC.

Based on our results, we believe that ultrasonography-guided FNA may have a role in the diagnostic algorithm in patients with locally advanced HNSCC with persistent disease following CRT observed on a posttreatment CT or PET/CT scan before or after a 12-week posttreatment PET/CT.[32] Conducting ultrasonography-guided FNA in these patients may allow surgeons to accurately detect the presence or absence of viable tumor cells in a time- and cost-efficient manner, thereby avoiding unnecessary neck dissections or delays in disease recognition. We also believe that ultrasonography-guided FNA is particularly useful for patients with a clinical partial response, since waiting on a 12-week posttreatment PET/CT scan may not be feasible or may delay necessary salvage surgery.

Finally, additional limitations of our study include the lack of a PET/CT arm and the low power. Our low numbers do not permit an accurate assessment of efficacy. However, we believe that this pilot study suggests the potential low-risk and low-cost benefit of adding ultrasonography-guided FNA to the diagnostic algorithm in this patient population and therefore warrants more formal investigation in a large multicenter trial.

Conclusions

Ultrasonography-guided FNA may provide a cost-effective method for assessing patients with possible persistent neck disease following CRT during the optimal surgical window. Further studies are warranted to better quantify the efficacy of this diagnostic modality.

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Study concept and design: Hackman.

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Drafting of the manuscript: Fleischman, Difurio, Hackman.
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