Objective: To assess the value of ultrasonography (US) combined with fine-needle aspiration (FNA) cytology for the investigation of lymph node metastases in patients with head and neck cancer.

Design: Comparison of clinical examination (palpation) and preoperative US-FNA examination results of cervical nodes in a sample of patients with head and neck cancer. The histological features of the neck dissection specimens are used to validate these 2 variables.

Setting: A head and neck oncology service in a tertiary referral hospital.

Patients: A consecutive sample of 56 patients with head and neck squamous cell carcinoma, first seen between April 1, 1996, and July 30, 1998, who had neck dissections performed after the US-FNA examination.

Intervention: Cervical US-FNA preoperatively, followed by elective or therapeutic radical modified or selective neck dissection.

Main Outcome Measures: The histological examination results of subsequent neck dissection specimens are used to determine the sensitivity, specificity, and accuracy of US-FNA for individual nodes. Second, the results of node staging by clinical examination and US-FNA examination are compared.

Results: The sensitivity was 89.2%; specificity, 98.1%; and accuracy, 94.5%. Correct node stages were obtained in 52 (93%) of the patients using US-FNA compared with 34 (61%) using palpation.

Conclusions: Ultrasonography combined with FNA is a highly accurate technique for the investigation of cervical lymph node metastases. A more accurate diagnosis may result in more appropriate treatment, particularly in a setting with limited resources. Retropharyngeal nodes, micrometastases, and lymph nodes smaller than 4 mm are limitations of US-FNA. Ultrasonography combined with FNA is a useful technique for the staging of head and neck cancer.


Invasive squamous cell carcinoma of the upper aerodigestive tract has a strong potential for metastatic spread to the cervical lymph nodes. The neck status is probably the single most important prognosticator in head and neck cancer, as the presence of metastatic disease drastically reduces the patient’s chance of survival.1-3 Clinical examination for the detection of metastases by palpation is unreliable, as occult neck disease can occur in up to 50% of patients, depending on characteristics of the primary tumor.4,12 Factors that have been shown to increase the risk of cervical metastases include the site of the primary tumor, tumor thickness, DNA ploidy, and tumor growth patterns such as infiltrating margins, perineural spread, and angioinvasion.1,10-12 Despite this knowledge, it remains difficult to accurately predict the metastatic behavior of these lesions. Elective neck dissection has, therefore, found many proponents as a diagnostic-therapeutic procedure for cancers, with a risk of occult metastases of 15% to 20% or higher. Examples of such lesions are oral cavity, oropharyngeal, and supraglottic cancers.3-7,9-11 This, however, implies up to 80% of unnecessary operations with its associated morbidity. In addition, in a setting with shrinking resources, it has significant cost-benefit implications.

Reported figures for the accuracy of palpation for detecting metastatic lymph nodes range between 59% and 84%, depending on the site of the primary tumor.14 Imaging has become the next logical step for obtaining a more accurate node stage, with the aim at more appro-
PATIENTS AND METHODS

Between April 1, 1996, and July 30, 1998, 56 patients with head and neck cancer were enrolled into this study. A routine physical examination was followed by an examination under anesthetic, and CT or MRI was used in some cases. Treatment decisions were based on clinical data and this imaging information. All these patients’ necks were then examined ultrasonographically. An ultrasonograph (Sonoline Versa Pro; Siemens Medical Systems, Inc, Issaquah, Wash) was used with a 7.5-MHz linear array transducer, and the entire examination was recorded on videotape.

The examination comprises the following: assessment of soft tissues of the neck, salivary glands, thyroid, and vascular structures. The level and size of the enlarged lymph nodes are documented. Ultrasonographically guided FNA is performed with 21- or 23-gauge needles and a 20-ml syringe mounted in a syringe holder. A local anesthetic is not routinely used. In cases of multiple enlarged lymph nodes, at least 2 nodes are aspirated per side. Additional aspirates are obtained from nodes at unusual sites. The correct position of the needle tip within the lymph node is confirmed on the screen (Figure 1). All aspirations are performed with the assistance of a cytology technician, who immediately processes the smears. The specimens are stained with the Papanicolaou and with the May-Grünwald-Giemsa techniques.

All the patients underwent elective therapeutic or salvage neck dissection. Immediately after the resection, the specimen was spread out and pinned onto a piece of sponge and fixed in 10% formaldehyde solution. The specimen was oriented for the pathologist (M.L.), and the individual lymph nodes were identified and labeled. The histological features of the lymph nodes were then compared with the preoperative US-FNA findings.

The results of the nodal aspirates and their cytologic examination are shown in Table 1. The cytologic examination correctly predicted metastatic squamous cell carcinoma in the aspirates from 66 nodes. Two nodes were falsely reported as positive for cancer. A total of 113 nodes were characterized as “negative for cancer.” This consisted of 86 with features of reactive lymphadenopathy and 25 that were “unrepresentative smears.” An additional 2 nodes were missed and, therefore, also considered to have constituted a negative examination result. The diagnosis of reactive lymphadenopathy from the lymph nodes was histologically confirmed in 85 cases, ie, there was 1 false negative. The inclusion of the 25 nondiagnostic smears and the nonaspirated (US-missed) nodes are explained in the “Comment” section. The 2 missed nodes were found to contain cancer at a subsequent histological examination. Of the 25 nondiagnostic smears, 6 were in fact positive for cancer on histological examination. The total false-negative rate was, therefore, 8.

The statistical analysis of these results was done in 2 ways: first, the calculation of sensitivity, specificity, and accuracy (Table 2) based on the results of individual nodes, as seen in Table 1; and second, the comparison of node staging using US-FNA with clinical node staging. These 2 methods were then compared with the pN staging obtained from histological examination and expressed as a percentage of this criterion standard. This information is expressed in Table 3 and Table 4.

Palpation resulted in the correct node stage in 34 (61%) of the 56 patients. Ultrasonography combined with FNA correctly classified the nodes in 52 (93%) of the patients. In one third of the patients (n = 18), US-FNA changed the node stage (Table 4). A higher stage resulted in 11 patients and a lower stage in 7. The 4 incorrect US-FNA–derived node stages were due to false-positive cytologic features in 2, ultrasonographically missed nodes in 1, and a nondiagnostic aspirate from a metastatic node in 1. (There were 2 false-positive and 2 false-negative examination results.)

COMMENT

There was a marked learning curve in interpreting the results at our head and neck US-FNA clinic. The average examination time, as recorded on videotape, decreased from 45 minutes in the beginning to between 10 and 15 minutes toward the end of the study period. In-
creasing confidence and dexterity are reflected in the increasing proportion of diagnostic aspirates (Figure 2). The rate for inadequate samples of between 6% and 10% is well within reported figures of 5% to 20%.18,19 Immediate cytologic evaluation of the smears in the US-FNA clinic could further improve these figures and almost eliminate nondiagnostic aspirates.20 The results reflect the early part of the learning curve as well, so one could expect better results in the future.

This study confirms findings of previous researchers,15-17 who showed US-FNA to be a highly sensitive, specific, and accurate technique for the determination of metastatic neck disease in patients with head and neck cancer (Table 2). Modern high-resolution US enables the examiner to reliably distinguish structures with a diameter of 3 mm or even less, whereas CT and MRI commonly use a slice width of between 3 and 6 mm for the neck.15 Don et al21 found 67% of malignant lymph nodes to be smaller than 10 mm.

The dilemma of all imaging techniques is the necessity for morphologic criteria to distinguish benign from malignant nodal disease (Figure 3 and Table 5). Numerous criteria and their combinations have been proposed to improve the accuracy of the investigation.15,22-24 Application of liberal criteria will increase the pickup rate of the investigation (sensitivity) but reduce its ability to clearly distinguish benign from malignant nodal enlargement (specificity). Strict criteria will exclude certain nodes, leading to loss of sensitivity, but will increase the specificity of the test. During the past decade, color Doppler examination of the lymph nodal vasculature has been shown to be a highly specific technique for distinguishing benign from malignant adenopathy. The distribution of feeding vessels and the pulsatility and resistance indexes of these small vessels are variables that make an accurate diagnosis based on only radiological criteria possible. However, reliable, reproducible results are only obtained with this technique from nodes with a diameter of 8 mm or larger. As the focus of primary diagnostic investigations is shifting toward ever-smaller lymph nodes and micrometastases, color Doppler imaging is not yet an alternative to FNA in nodes with a diameter of less than 8 mm but is useful in the follow-up of patients who undergo primary irradiation for their disease. Although morphologic criteria are still used to guide the examiner, US-FNA relies on the high precision of the cytologic diagnosis to arrive at a conclusion.18 This explains the high specificity of 98% of the method. It has been extensively documented by many of the previous reports that US alone lacks speci-
ficity and, therefore, there no longer exists any merit in comparing US alone with US-FNA.

Limitations of US-FNA may be related to difficulty in ultrasonographic imaging, the aspiration of small nodes, or the inadequacy of the smear obtained. There were 3 nondiagnostic aspirates from metastatic nodes during the first 4 months of the US clinic. All 3 nodes were 6 mm or more in smallest diameter and, hence, easy targets for US-FNA. Increasing experience and technique subsequently led to fewer inadequate aspirates from nodes with a greater diameter of more than 4 mm.

Other researchers have reported on difficulties with US-FNA from lesions with a diameter of less than 4 to 5 mm. Two aspirates obtained from metastatic nodes with a diameter of 3 and 3.5 mm were nondiagnostic. Factors influencing the size limit for reproducible aspirates are patient compliance, needle size, resolution of the ultrasonographic image, and criteria for cellularity of the biopsy specimen laid down by the cytopathologist. Although nodes with a diameter of 3 mm have been successfully aspirated in our clinic, the lower limit for consistent results was 4 mm.

Two lymph nodes in the retropharyngeal space were not detected by US. Both were found in the neck dissection specimen of patients who had undergone salvage surgery for a tumor of the lateral and posterior hypopharyngeal wall after failure of primary radiotherapy. Gritzmann et al found all cervical lymph nodes amenable to US examination, except for medial retropharyngeal nodes. Further imaging in the form of CT or MRI must hence be considered in patients with tumors that have the tendency for metastatic spread to the retropharyngeal space. Surgical emphysema from a recent tracheotomy led to a nondiagnostic scan in 4 patients. A second examination was successful after a few days.

A reactive cellular aspirate from a node harboring a metastasis was obtained in one case. Morphologic criteria of the 6 × 5 × 5-mm lymph node had raised the sus-

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**Table 4. How US-FNA Influenced Change in Node Classification**

<table>
<thead>
<tr>
<th>Node Classification Higher by US-FNA (n = 11)</th>
<th>Node Classification Lower by US-FNA (n = 7)</th>
<th>US-FNA Failures (n = 4)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PALP</strong></td>
<td><strong>US-FNA or HISTO</strong></td>
<td><strong>PALP</strong></td>
</tr>
<tr>
<td>N0 (4)</td>
<td>N1 (2), N2b (1), and N2c (1)</td>
<td>...</td>
</tr>
<tr>
<td>N1 (3)</td>
<td>N2b (2) and N2c (1)</td>
<td>N1 (3)</td>
</tr>
<tr>
<td>N2a (1)</td>
<td>N2b (1)</td>
<td>N2a (0)</td>
</tr>
<tr>
<td>N2b (3)</td>
<td>N2c (3)</td>
<td>N2b (1)</td>
</tr>
<tr>
<td>N2c (0)</td>
<td>...</td>
<td>N2c (3)</td>
</tr>
</tbody>
</table>

* The number of patients is given in parentheses after the node classification. US indicates ultrasonography; FNA, fine-needle aspiration; PALP, palpation; HISTO, histological examination; and ellipses, data not applicable.

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**Figure 3. Ultrasonographic images of lymph nodes.** Left, These nodes show the characteristics of benign (reactive) nodes, oval shape and echogenic hilum (above "LN"). Right, These are matted, round nodes showing hyperechoic stroma due to edema. The echogenic hilum is absent. LN indicates lymph node; SCM, sternocleidomastoid; and IJV, internal jugular vein. Plus signs indicate the dimensions of the nodes.
picon of malignant infiltration, and histological features showed a metastatic focus of 2 × 3 mm in the fixed specimen. Despite great efforts to obtain a representative sample by making several passes in different planes through the lymph node, the metastasis had been missed in this case. It is known that most micrometastases are found in lymph nodes with a diameter of less than 10 mm.21 This micrometastasis was readily detected by US, but cytologic confirmation could not be obtained. “Micrometastasis” is an ill-defined term. A size of less than 3 mm has been suggested as the criterion, which places at least some micrometastases well within the resolution of modern US; FNA of these lesions, however, becomes a problem.8

Two false-positive results were the consequence of misinterpretation of the smears. In both cases, a less experienced colleague had reported on the biopsy results. After a histopathologic examination failed to detect any malignant disease in the designated nodes, the slides were reviewed by one of us (M.L.), who found evidence of cellular atypia and dysplasia but none of metastatic carcinoma.

Ultrasonography combined with FNA correctly classified the nodes of 52 (93%) of our 56 patients. There are no comparable figures for US-FNA node staging in previous reports we have found since these all report only on sensitivity, specificity, and accuracy. From the reported rates of accuracy of the method, correct node stages would be expected in more than 90% of the patients.15-17 This is in keeping with the results of a study9 on occult metastases, in which disease that was not detectable by any available radiological technique was found in 9% of neck dissection specimens. If the risk of occult metastatic disease can thus be reduced to around 10%, the practice of elective neck dissection in the N0 neck must be questioned, especially when the patient can be followed up and discovered a problem.8

In 27 (48%) of the 56 patients, US-FNA discovered nodes additional to the clinically detectable disease. In 11 (20%) of these patients, this led to a higher node stage. This ability of US-FNA to detect occult disease has been documented by various investigators.15-17,22 In 7 (13%) of the patients, the US-FNA examination, however, resulted in a lower node stage (N0 in 5 and N2c to N1 in 2 patients). This was observed particularly in patients with short, fat necks and after radiotherapy or previous surgery.

The clinical implications of US-FNA changing the node stage in these patients can be seen in Tables 3 and 4. Of the patients with a higher stage, the 4 with an N0 classification would have had to undergo neck dissections, whereas by clinical assessment alone they might not have. In addition, one of these patients with an N0 classification, and 4 others, were upstaged to an N2c classification, so they would have had to undergo bilateral neck dissections. Seven patients were assigned a lower node stage by US-FNA and, of these, 5 were correctly assigned an N0 classification, so these patients underwent “unnecessary” neck dissections. In summary then, 13 patients would potentially have had their management altered by having their node staging more accurately classified.

Ultrasonography combined with FNA helped to identify a prominent carotid sinus in 2 patients, a laryngeal gocele in 1, a submandibular salivary gland in 1, and the origin of the mass as an extension of the primary tumor in 2 (1 case each of direct extension of a hypopharyngeal carcinoma and a laryngeal tumor into the soft tissues of the neck). Previous reports15-17,19,20 on US-FNA have highlighted the detection of occult disease and paid less attention to its ability to correctly distinguish other pathological features from cervical metastasis.

Since the early days of aspiration biopsy, implantation of tumor cells along the needle tract has been of concern. There is experimental evidence of tumor cells spreading to the puncture site, needle tract, and possibly even into blood and lymph secondary to the aspiration biopsy. Clinical implications in the form of local or distant metastasis, however, have not been reported.18

Pain is the most common complication of FNA. Infiltration of local anesthetic allowed for unhindered aspirations in 3 of our patients, who could not tolerate the procedure otherwise. Inadvertent penetration of large vessels with a fine needle has been documented by previous investigators,18 without any negative effects to the patient. Possible complications of FNA biopsy include hematoma formation, hemorrhages, nerve damage, and infection. Vasovagal reaction, fainting, and even seizures have been observed on rare occasions.18 However, because of the thinness of the needle, FNA is usually well tolerated by the patient and free of major adverse effects or complications. During FNA, the common carotid artery was inadvertently penetrated in 3 patients. In each case, the error was noted, the needle withdrawn, and manual pressure applied to the neck for 10 minutes. A small ultrasonographically detectable hematoma developed in one of these patients. The patient underwent a second examination after 24 hours, which failed to show progression of the hematoma. No other problems or sequelae resulted from these punctures of the carotid artery. Other structures inadvertently penetrated were the
internal jugular vein, the larynx, the pharynx, and neck musculature. No complications or untoward effects resulted in any of these cases. Most patients reported mild discomfort; more severe pain was experienced by 3 (5%) of the patients and required the use of a local anesthetic.

The inclusion of the 25 nonrepresentative smears and the 2 unaspirated nodes as negative results needs explanation. We were keen to consider the intervention of US-FNA as a unit. The procedure depends on the technique, the US machine, the accuracy of the aspiration, and the staining and examination of the smear. When no tumor is found, this has been considered a negative result, since the method failed to show cancer. Inclusion of these has, of course, reduced the overall accuracy, as shown in Table 1. However, this was considered preferable to their exclusion from the calculations and resultant falsely good results.

The 8 false-negative results included 5 nondiagnostic aspirates from metastatic nodes and the 2 lymph node metastases that were not detected by US. One aspirate from a lymph node with ultrasonographic features of metastatic disease showed typical cytologic characteristics of a reactive node. The histological features of this node showed a metastatic carcinoma.

Ultrasonographic examination of the neck with cytopathologic support from FNA is of great value to our practice. It is quick, safe, and cost-effective and requires no intravenous contrast or ionizing irradiation. Comprehensive US-FNA investigation of the patient with a head and neck tumor before and after treatment results in more appropriate therapy and hence improved patient care.

CONCLUSIONS

Ultrasonography combined with FNA is a highly accurate investigation for cervical metastasis in patients with head and neck cancer. Experience and skill of the ultrasonographer and cytopathologist are prerequisites for good results. Awareness of the limitations of US-FNA is important for patient management decisions. Additional information gained from the US examination and FNA cytologic features is of value for diagnosis and follow-up. We have found US-FNA to be a useful aid in assessing the spread of disease in patients with head and neck cancer.

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