EUS-guided FNA of the left adrenal gland in patients with thoracic or GI malignancies

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Background: The diagnostic yield and safety of trans-gastric EUS-guided FNA of the left adrenal gland are not well defined.

Methods: All patients with an enlarged left adrenal gland on abdominal imaging and known or suspected malignancy referred to two EUS centers over a 3-year period were included in this study. EUS-guided FNA was performed on an outpatient basis by one of 4 experienced endosonographers.

Results: Thirty-one consecutive patients (21 men, 10 women; mean age 64.8 years) were evaluated. Tissue adequate for interpretation was obtained in all patients; no attempt to obtain tissue was unsuccessful. The median number of needle passes was 4.5 (range 1-8). No immediate complications were encountered. EUS-guided FNA confirmed malignant left adrenal involvement in 42% (13/31) of the patients. Patients with malignant left adrenal masses were more likely to have known cancer at another site (OR 12.0: 95% CI[1.6, 87.9]). Patients with benign masses were more likely to have preservation of the normal sonographic appearance of the adrenal gland (“seagull” configuration) compared with those with malignant masses (OR 9.8: 95% CI[1.9, 51.0]). The accuracy of EUS imaging based on size (≥3 cm) alone was 81%: 95% CI[63, 93]). Of the patients with malignant adrenal masses, 85% (11/13) died or their clinical condition deteriorated during follow-up, while 15% (2/13) were being treated and were stable clinically.

Conclusions: EUS-guided FNA of the left adrenal gland is a minimally invasive, safe, and highly accurate method that confirms or excludes malignant adrenal involvement in patients with thoracic or GI malignancies. (Gastrointest Endosc 2004;59:627-33.)

Metastatic cancer to the adrenal gland carries a grave prognosis and precludes curative surgical resection.1,2 Screening of patients with lung cancer for metastatic disease yields adrenal masses in 3% to 16%.3-5 Because imaging characteristics and size do not accurately differentiate benign from malignant adrenal enlargement, it is well accepted that tissue sampling from an enlarged gland is required before surgical resection of the primary tumor.1,6 Routinely, US- or CT-guided FNA of the adrenal glands is performed.7-9 However, although high success rates are achievable by using the percutaneous approaches,9 both inadequate sampling and complications remain significant problems.1,7,10,11

Comparative studies have found EUS to be superior to transabdominal US for imaging the left adrenal gland.12,13 EUS-guided FNA (EUS-FNA) has emerged as an effective method for sampling perigastric organs, such as the pancreas14,15 and liver and peri-intestinal and celiac lymphadenopathy.16 Since publication of the first case description of EUS-FNA of the left adrenal gland,17 the feasibility, the safety, and the yield of EUS-FNA in evaluating the left adrenal gland in patients with known or suspected thoracic or GI malignancies has not been studied. This study, therefore, evaluated the role of EUS-FNA in the diagnosis of metastatic disease to the left adrenal gland in a cohort of patients with known or suspected thoracic or GI malignancy at two EUS referral centers.

PATIENTS AND METHODS

The study was approved by the respective institution review boards at both participating institutions. All patients with an enlarged adrenal gland on abdominal imaging (CT, magnetic resonance imaging [MRI], and/or
positron emission tomography (PET)) (Fig. 1), with known or suspected malignancy referred to two centers with EUS expertise over a 3-year period (2000-2003) were included. Data were collected prospectively as an ongoing observational study of EUS-FNA at one center (University of Alabama) and by retrospective cohort design at the other (University Hospital Eppendorf). Informed consent was obtained from all patients. EUS-guided FNA was performed on an outpatient basis with the patient under conscious sedation as described previously.16 To identify the left adrenal gland with the curvilinear echoendoscope, the descending aorta was traced to the celiac trunk (usually located about 45 cm from the incisor teeth). At that level, gentle clockwise torque of the echoendoscope rapidly identified the left adrenal gland as a “seagull” shaped structure. The length of the gland was measured from the end of one wing to the other, and the width was measured at the widest mid portion or body of the gland as previously described.17 The shape of the gland was documented as one of the following: round, seagull, or seagull with enlargement of one wing.

When an adrenal gland mass was identified, EUS-FNA was performed by using one of several linear array echoendoscopes (GF-UC-140P, UC-30P, UC-140; Olympus Optical Co., Tokyo, Japan) by one of 4 endosonographers, each of whom had performed greater than 2000 procedures. Before EUS-FNA, the presence of vessels along the needle path was excluded by color-flow and Doppler US (Fig. 2A). A 22-gauge needle (Echotip; Wilson-Cook Medical Inc., Winston-Salem, N.C.) was used in all cases. When the tip of the needle catheter sheath was visualized endosonographically, the needle then was advanced from the sheath, through the wall of the stomach, and into the target lesion under US guidance (Fig. 2B). Once in the target lesion, the stylet was removed, and the needle was moved back and forth for 15 to 30 seconds and then withdrawn. Suction was not applied during the puncture unless the first pass yielded no cellular material. If additional passes were needed, the stylet was re-inserted, and the above steps were repeated.

Specimens were placed onto glass slides; both air-dried and alcohol-fixed smears were prepared. Air-dried smears were stained with the Diff-Quik method (Baxter, McGraw Park, Ill.) and reviewed to ensure specimen adequacy. The material remaining in the needle then was flushed out and collected in preservative (Cytolyt; Cytyc Co., Boxborough, Mass.) for subsequent preparation of a Thin Prep slide (Cytyc) and a cell block. Alcohol-fixed smears were stained later with Papanicolaou’s stain. For purposes of analysis, the cytopathologist’s report constituted the final diagnosis. The cytologic diagnoses were categorized into the following groups: positive for malignancy; suspicious for malignancy; atypical cells, indeterminate for malignancy; benign; and

Figure 1. Positron emission tomography coronal section showing intensely hyper-metabolic focus in left adrenal gland consistent with metastasis (arrows). EUS-guided FNA confirmed malignant involvement.

Figure 2. A, EUS image of left adrenal gland, showing preservation of one seagull wing (arrows) and destruction of opposite wing by a malignant mass. Color Doppler US excluded vessel interposition in the needle path, allowing FNA to be performed safely. B, EUS image showing trans-gastric FNA of left adrenal gland, which confirmed malignant involvement.
non-diagnostic. The final diagnosis of malignancy was defined by the following criteria: an initial malignant cytology with clinical and/or imaging follow-up that was consistent with the diagnosis of malignancy, such as death from disease or clinical disease progression. Adrenal lesions were considered benign if there was no progression, and the patient remained well.

Follow-up was by review of medical records, by contact with the referring physician, or by contact with the patient. Immediate complications were assessed by the endoscopist at each center and documented in research databases. A common data sheet was used to collect summary information retrospectively at one center (University Hospital Eppendorf). Collected data were entered into a database before statistical analysis.

Statistical analysis

Continuous variables are reported as range, mean, standard deviation, and median. The largest adrenal mass diameter was compared between benign and malignant masses by using the Mann-Whitney-Wilcoxon test because of skewed distribution of the variables and a small sample size. The variable “shape of adrenal gland” was categorized according to the presence or absence of altered shape because of an adrenal mass. The odds ratios (OR) were calculated with their corresponding 95% confidence intervals (CI). The \( p \) values were calculated by using the Fisher exact two-tailed test. A \( p \) value <0.05 was considered statistically significant. Statistical analysis was performed with statistical software (SAS, version 6.12; Cary, N.C.).

RESULTS

Over the study period, 31 patients (21 men, 10 women; median age 65 years; range 48-85 years) underwent EUS-FNA of an enlarged left adrenal gland at the two centers. The majority (24/31; 77.4%) were white (Table 1). In one patient, CT-guided FNA before EUS-FNA was unsuccessful. In another patient, the mass was not amenable to CT-guided sampling, and this patient, therefore, was referred for EUS-FNA. Tissue adequate for interpretation was obtained in all patients; no EUS-FNA was unsuccessful. The median number of needle passes needed for tissue diagnosis was 4.5 (range 1-8). There were no immediate complications resulting from EUS-FNA; no patient experienced abdominal pain, hypertensive crisis, bleeding, or pneumothorax.

EUS-guided FNA confirmed malignant involvement of the left adrenal gland in 42% (13/31) of the patients. No cytologic specimen was interpreted as atypical or suspicious. Ten patients (32%) did not have cancer at any other site when EUS-FNA was performed of the enlarged adrenal mass (Table 2). In all but one patient with malignant adrenal involvement, the malignancy was metastatic. The most common primary site was lung, followed by pancreas (Table 2). Patients with malignant adrenal gland involvement were more likely to have a known cancer at another site (OR 12.0: 95% CI[1.6, 87.9], \( p = 0.02 \)). In addition, men were at higher risk to have a primary malignancy at another site (OR 3.2: 95% CI[0.7, 15.7], \( p = 0.22 \)).

The normal seagull configuration of the left adrenal gland was not preserved in 41% (12/29) of the patients. Patients with benign masses were more likely to have preservation of the normal shape (seagull configuration) than those with malignant
masses (OR 9.8; 95% CI [1.9, 51.0], \( p = 0.01 \)). Malignant adrenal masses tended to lose their original configuration and become mass-like in appearance. Malignant adrenal masses were significantly larger in diameter compared with benign masses (\( p = 0.01 \)).

Eighty-two percent (9/11) of masses with a diameter of 3 cm or greater were malignant, whereas 20% (4/20) of those less than 3 cm in diameter were malignant (OR 18.0; 95% CI [3.2, 101.1], \( p = 0.002 \)). Only two of the adrenal masses 3 cm or greater in diameter were benign. The accuracy of EUS imaging based on size alone, therefore, was 81% (95% CI [63, 93]). By using size as the only criterion, the EUS findings in 4 patients would have been falsely negative, and the findings in two would have been falsely positive. Stated differently, the mass in 19% (6/31) of the patients would have been misclassified, based on EUS appearance alone.

Thirty-nine percent (7/18) of patients with benign adrenal masses underwent surgery for the primary tumor, whereas none of the patients with a malignant adrenal mass underwent an operation. Of those patients who died, 57% (8/14) had malignant adrenal masses. Of the 18 patients with benign masses, 50% had a primary malignancy at another site. Median follow-up for patients with benign masses was 369 days (one patient was lost to follow-up and was excluded). The median follow-up for patients with malignant masses was 244 days. When the deceased patients were excluded (benign, 6; malignant, 8) from the analysis, the follow-up period was 455 days for those with benign masses and 225 days for those with malignant adrenal masses.

The clinical condition of patients at last follow-up is shown in Table 3. The condition of 11 patients (61%) with benign masses remained “unchanged.” Five of the 6 (83%) deceased patients (with benign adrenal mass) had cancer at another site. The cause of death was unknown for only one patient with a benign adrenal gland aspirate. Eighty-five percent of patients (11/13) with malignant adrenal masses died or their condition “worsened” during follow-up, while two patients (15%) remained in stable clinical condition and were undergoing treatment.

### DISCUSSION

The detection of distant metastasis in patients with lung cancer has a major impact on prognosis and management. Studies have shown that in patients with non-small-cell lung cancer, an isolated adrenal mass is more likely to be an adenoma, and, thus, tissue diagnosis is required before a decision against potential curative resection is made. In addition, it cannot be assumed that an isolated adrenal mass in a patient with non-small-cell bronchogenic carcinoma represents metastasis, because 2% to 9% of the general population harbor benign adrenal adenomas. In one study of 330 patients with non-small-cell lung cancer, an isolated adrenal mass was found in 32 patients (10%). Of the 25 patients with proven isolated adrenal lesions, 8 (32%) had metastases, and 17 (68%) had adenomas. Therefore, an enlarged adrenal gland on an imaging study is not synonymous with metastasis.

EUS is highly accurate and is superior to percutaneous transabdominal US for detection with respect to the left adrenal gland. In 3 studies, the combined accuracy for detection by EUS was 97%. For detection of adrenal masses, percutaneous US has an overall accuracy of 70% to 90%. Marchal et al. demonstrated that the left adrenal is more difficult to visualize with US, being detected in only 71% of the patients, even with additional views in the right lateral decubitus or erect positions. The right adrenal, however, was detected by US in 92% of the patients. Although, the right adrenal usually is difficult to visualize from the duodenum at EUS; it was detected in about 30% of cases in one study. In addition, when detected by EUS, the right adrenal gland usually is located deep or adjacent to the inferior vena cava, thereby making EUS-FNA difficult.

Imaging characteristics and size alone are unreliable for differentiation of benign and malignant

<table>
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<th>Clinical status</th>
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Table 3. Clinical status of patients at last follow-up
adrenal diseases. For example, CT appearance alone, in many cases, is insufficient to distinguish benign from malignant lesions. Porte et al. studied the role of CT, MRI, and CT-guided tissue sampling in the evaluation of enlarged adrenal glands in patients with lung cancer. Of patients with non-small-cell cancer, 7.2% (32/443) had an enlarged adrenal gland; in 18, this was because of metastases and, in 14, a benign adenoma. Based on CT classification by Hounsfield units (HU > 10), the results were falsely positive in 21% of patients, i.e., these patients had benign adenomas that were classified as metastasis. In addition, 11% of metastases were misdiagnosed as adenomas (i.e., a false-negative result). Although MRI had a sensitivity of 100%, 50% of the adenomas were misdiagnosed as metastases. Overall, diagnostic certainty of metastasis could not be obtained in 78% of the cases. Therefore, despite extensive morphologic evaluation with unenhanced CT and conventional MRI, imaging-guided tissue sampling is necessary for most patients with operable non-small-cell lung cancer and an adrenal mass. CT-guided sampling was 100% sensitive and specific in this cohort of patients. Burt et al. demonstrated that MRI cannot replace tissue sampling techniques for determining the nature of an enlarged adrenal gland; the false-positive rate in their study was 67%.

The assessment of adrenal gland size is of interest because adrenal masses 3 cm or greater in diameter are malignant in 90% to 95% of cases, whereas, those less than 3 cm in diameter are benign in 78% to 87% of cases. However, size alone is insufficient as a criterion for discriminating adenoma from nonadenoma. In the present study, size alone, as determined by EUS, inaccurately classified 19% of the patients when a 3-cm cutoff value was used. PET scans also have been used to differentiate benign and malignant adrenal masses in patients with lung cancer. Erasmus et al. found that 80% of patients with lung cancer and increased 18F-fluorodeoxyglucose (FDG) activity in an adrenal mass on PET had metastatic disease. Furthermore, all adrenal lesions that exhibited normal FDG activity were benign. Notably, in two patients, a false-positive result was obtained.

The results of the present study suggest that EUS-FNA of the left adrenal gland is safe and provides a tissue diagnosis in all cases. EUS-guided FNA documented malignant involvement of the left adrenal in 42% of the patients, and, thereby, adrenalectomy was avoided. In contrast, the rate of non-diagnostic aspirates when using an imaging-guided percutaneous approach in other studies ranges from 9.2% to 50%. Our findings suggest that EUS-FNA has a distinct advantage in obtaining tissue from the left adrenal, perhaps because the echoendoscope and needle are easy to control when using the transgastric approach.

A major finding of the current study is that EUS-FNA of the left adrenal is safe by comparison with published data for percutaneous approaches. This is most likely related to the fact that no organ except the stomach is traversed to access the left adrenal gland. Several studies of EUS-FNA of various other organs have demonstrated that traversing the wall of the stomach with a 22-gauge needle is safe. In contrast, the complication rate for the percutaneous approach can be substantial. Reported complications when adrenal biopsy specimens are obtained percutaneously include hemorrhage, pneumothorax, pancreatitis, adrenal abscesses, bacteremia, and needle-tract metastases. In a study of complications associated with 1000 CT-guided biopsies, the adrenal gland was the most common site of complications (4 of 11 complications). In another study of 277 consecutive adrenal biopsies performed over a 10-year period, 8 biopsies (2.9%) resulted in major complications (5 from the left adrenal and 3 from the right). All 8 complications were hematomas, one of which required adrenalectomy. No patient died as a result of a complication. Interestingly, 21 of the 27 false-negative results pertained to specimens from the left adrenal gland. This is probably because the percutaneous approach to the left adrenal is technically more difficult than for the right adrenal gland.

An extensive review of published reports that included 666 percutaneous adrenal biopsies found that the complication rate ranged from 0% to 12%, the rate overall being 5.3%. Pneumothorax, when using the posterior approach, usually is a result of the needle traversing the pleura in the posterior costophrenic sulcus, particularly in prone patients. Hemorrhage occurs despite normal coagulation profiles in these patients. Larger- compared with smaller-diameter needles are thought to be more likely to induce hemorrhage. Complications associated with percutaneous CT-guided biopsies include pneumothorax (3%-9% of cases). In addition, two cases of needle-track metastases were reported. Another feared complication of the percutaneous approach is acute pancreatitis. In the study of Kane et al., two (6%) of 33 patients who underwent percutaneous FNA of the left adrenal gland developed acute pancreatitis. When using the anterior approach, the tail of the pancreas was traversed in 97% of cases. The two patients in whom acute pancreatitis developed were hospitalized for 11 and 13 days after their procedures. Kane et al. recommended that the posterior approach be used to sample the left adrenal gland.
A major limitation of the current study is the lack of a reference standard for confirmation and for comparison of adrenal gland status vs. EUS-FNA results. However, a malignant cytology is well accepted as a basis for patient management. Moreover, it would be unethical to subject patients with metastatic disease to surgery for the sole purpose of confirming adrenal gland status. More importantly, in patients with cancer, a histopathologic analysis of an adequate tissue sample obtained by CT-guided percutaneous biopsy of the adrenal glands that is benign is reliable and predicts a benign course on long-term follow-up. A negative or benign result for a CT-guided percutaneous adrenal biopsy can be regarded as a true negative in patients with cancer, with no necessity to repeat the biopsy.

EUS-guided FNA offers the following advantages: needle insertion is performed under real-time US guidance, and it can be performed during the same session as staging EUS if a lesion is detected. Furthermore, with the transgastric approach, other organs that usually are traversed with a percutaneous puncture (liver, pancreas, spleen, and pleura) are easily avoided. Hence, the complication rate of EUS-FNA is lower by comparison with published data for percutaneous approaches.

The pretest probability for metastasis to the left adrenal gland was high in our study population because of a high primary cancer prevalence and a possible referral bias. It is possible that with increased use of EUS for various indications, endosonographers will increasingly encounter incidental adrenal gland enlargement for which EUS-FNA is not necessarily warranted. The decision for EUS-FNA of the left adrenal should be individualized and based on potential clinical impact and indication, inasmuch as adrenal adenomas are relatively common in the general population and in patients with cancer. In centers with EUS expertise, EUS-FNA provides a minimally invasive alternative to adrenalectomy or percutaneous imaging-guided sampling of the left adrenal gland. It appears to be a safer approach and has an excellent diagnostic yield.

REFERENCES


