Douglas G. Adler MD, FACG, AGAF, FASGE, Series Editor

Endoscopic Ultrasound Guided Tissue Acquisition from Unusual Targets: A Review of Less Commonly Biopsied Sites

Jason DuBroff

Douglas G. Adler

Since the first described case of endoscopic ultrasound fine needle aspiration (EUS-FNA) nearly 30 years ago, EUS guided tissue acquisition has become a preferable diagnostic method that allows for high resolution imaging of the gastrointestinal tract and nearby structures as well as the means for biopsy in real time. The aim of this review is to assess the diagnostic accuracy and safety profiles of less commonly biopsied sites under EUS guidance, which includes lesions of the head and neck, the lungs, the adrenal glands and the pelvis.

INTRODUCTION

Endoscopic guided ultrasound (EUS) has become an invaluable tool for providing high-resolution imaging of the gastrointestinal tract as well as adjacent structures while providing the ability of real-time tissue acquisition via endoscopic ultrasound fine needle aspiration (EUS-FNA) and endoscopic ultrasound fine needle biopsy (EUS-FNB). Common indications for EUS guided tissue acquisition include: pancreatic lesions, biliary strictures, liver lesions, mediastinal and abdominal lymph node assessment, splenic masses, and subepithelial gastrointestinal tumors.[1] This article aims to review unusual or less common indications for EUS and unusual sites for EUS guided biopsies including head and neck masses, adrenal gland lesions, and lesions of the pelvis with a particular emphasis on diagnostic accuracy and safety profiles associated with tissue acquisition from these sites.

Jason DuBroff, MD, MPH Douglas G. Adler, MD, FACG, AGAF, FASGE University of Utah School of Medicine Gastroenterology and Hepatology, Salt Lake City, UT

Head and Neck Malignancies

The utility and high diagnostic accuracy of EUS in detecting mediastinal masses has been well-described.[2,3] However, there is less research regarding EUS-guided tissue acquisition in patients with lesions of the head and neck. Most research examining EUS-FNA in this region describes how EUS may be used to stage malignancies that originate in the head and neck. For example, one study showed that EUS-FNA may play a role in staging squamous cell carcinoma of the head and neck, and their mediastinal spread. The study included cancers originating in the salivary gland,

Figure 1a. EUS image of an intraparenchyma lung lesion

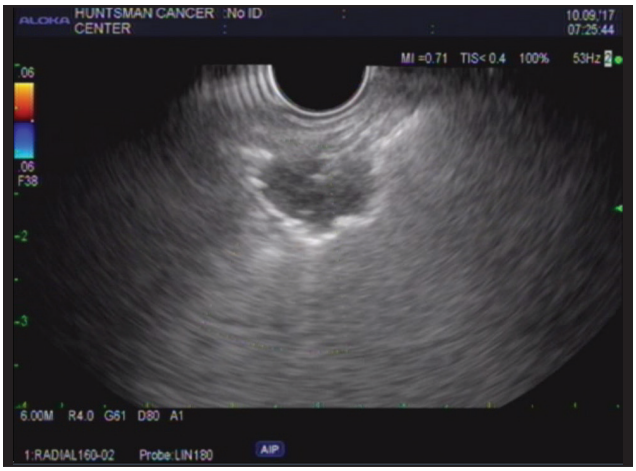

Figure 1b. EUS-guided core biopsy of lesion seen in Figure 1a. Pathology revealed non-small cell lung cancer.

oropharynx, larynx and thyroid. Although the study only included 17 patients, it found that EUS was able to diagnose and stage head and neck malignancies by demonstrating esophageal invasion, lymph node involvement and, on two occasions, provide the initial tissue diagnosis.[4] Similarly, a prospective study conducted in Japan showed that EUS can have greater diagnostic specificity and accuracy than MRI or barium swallow study for assessing the esophopharyngeal involvement of thyroid cancer.[5] Of the 52 patients included in this analysis, EUS had a specificity and accuracy of 82.9% and 82.7%, respectively, for determining invasion into the muscularis propria when compared to MRI (which had corresponding rates of 60% and 65.4%, respectively) or barium swallow study (58.8% and 60%, respectively).[4] However, the authors noted that diagnostic accuracy was decreased for thyroid cancer invasion of the upper lobe.[4]

Another retrospective study of 100 cases analyzed the frequency of thyroid gland masses among patients undergoing routine EUS.[6] Twelve cases were identified with abnormal lesions of the thyroid with three patients receiving a new diagnosis of thyroid cancer; two with papillary thyroid cancer and one with poorly differentiated thyroid cancer.[5] Ultimately, the authors concluded that routine EUS examination of the thyroid should be performed to identify potentially unexpected thyroid lesions.

EUS-FNA can also be utilized to directly biopsy the thyroid gland itself. The authors of the aforementioned study noted that of their twelve identified cases, only two cases underwent EUS-FNA. The remaining cases were either referred for transcutaneous ultrasound guided biopsy or followed clinically.[5]

A small number of case reports exist describing direct tissue acquisition from the thyroid gland via EUS-FNA. One representative case report describes a case of 3x4cm mass in the left thyroid lobe that was not amenable to conventional, transcutaneous ultrasound guided biopsy due to a large amount of adjacent blood vessels, per the authors report. The authors noted that technical success was achieved and the patient was diagnosed with Hurtle cell neoplasm of the thyroid.[7] Another case report, published in 2004, described a patient with a 5.7cm x 3.9cm superior mediastinal mass, who was ultimately diagnosed with a benign nodular goiter after undergoing EUS-FNA.[8] In 2014, a case of primary papillary thyroid cancer was diagnosed via EUS-FNA after the authors initially noted a 1.7cm x 1.5cm hypoechoic lesion upon withdrawal of the echoendoscope during an evaluation for mediastinal adenopathy.[9]

EUS-FNA has also been used to diagnose a parathyroid adenoma in a case report detailing a patient who presented with pancreatitis as well as a mass extending from the right inferior aspect of the thyroid gland into the mediastinum. The diagnosis of parathyroid adenoma was confirmed from EUS-FNA biopsy and the patient subsequently underwent surgical resection.[10]

Figure 2a. Right sided adrenal gland mass. Note atypical appearance than a normal adrenal gland.

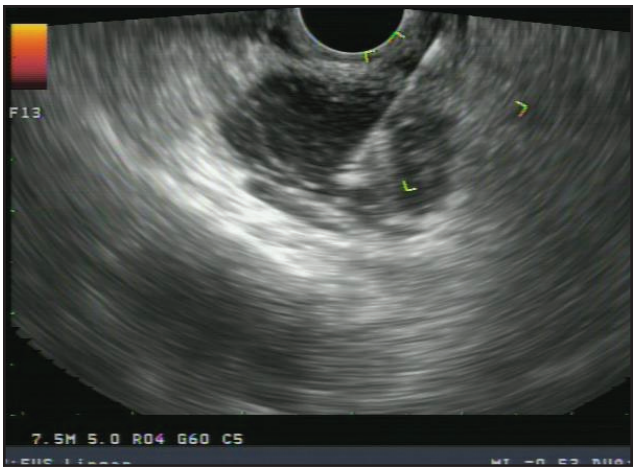

Figure 2b. EUS-guided FNA of right sided adrenal mass through the 2nd duodenum.

Head and Neck Infections

Case reports have also described EUS-FNA as a useful technique for diagnosing abscesses in the head and neck. One such report described a case of a soft tissue mass, approximately 5cm x 3cm, located between C7 and T1. Following EUS-FNA, the patient was diagnosed with a paraspinal abscess and underwent successful treatment with surgical drainage and debridement and long-term parenteral antibiotics.[11] Similarly, parapharyngeal abscesses have also been drained using EUS via a transoral approach in place of the traditional ultrasound guided transcutaneous drainage.[12]

Lung Masses

Traditionally, tissue biopsy from the lung is acquired via bronchoscopy or endobronchial ultrasound (EBUS), usually performed by interventional pulmonologists, interventional radiologists or thoracic surgeons. EUS has been shown to provide tissue diagnosis in cases where bronchoscopy samples were non-diagnostic or where lesions were not within reach of a bronchoscope.[13]

The literature contains a relative paucity of studies regarding EUS-guided tissue acquisition from the lung, most likely due to concerns about inadvertently causing a pneumothorax. A study of 32 patients found a high diagnostic accuracy of EUS-FNA for establishing the diagnosis of lung cancer in 31 patients (97%) with *periesophageal* lung lesions.[14] The authors reported no significant adverse events following EUS-FNA.[13] Another study published in 2019, which included 19 patients, found a similar efficacy with diagnostic EUS-FNA in 100% of cases, without reported complications.[15] In seven cases, EUS-FNA had the added advantage of obtaining tissue from distant metastatic sites (adrenal glands, mediastinal lymph nodes and liver metastasis), during the same session.[14]

A review of the literature yielded an additional 15 patients who underwent EUS-FNA for lung lesions and nodules as reported in case reports or as a subset of larger cohorts.[16,17,18] Additionally, two cases of successful endoscopic ultrasound fine needle biopsy (EUS-FNB) of periesophageal, *intraparenchymal*, lung masses have been described, neither of which were associated with adverse events.[19] (Figure 1) This last study suggests that intraparenchymal lesions can be biopsied without causing a pneumothorax, although the rate with which this adverse event arises in this setting remains unknown given the small number of patients treated in this manner to date.

Lastly, one case of pulmonary aspergillosis diagnosed by EUS-FNA has been reported. The authors describe 74-year-old patient with a history

Figure 3a. Small 2.5cm pericolonic abscess seen on EUS

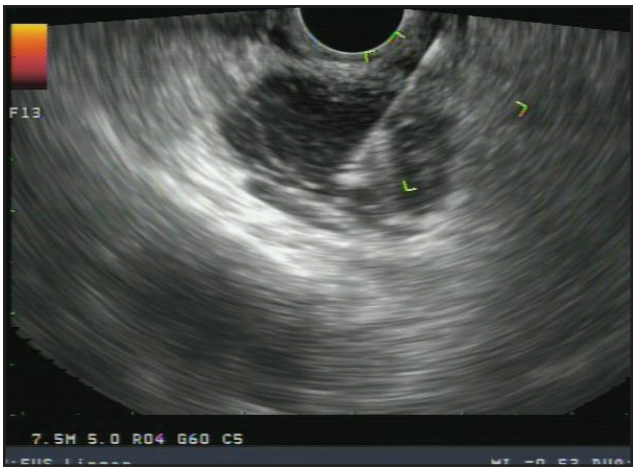

Figure 3b. The lesion in Figure 3a was treated via simple aspiration with an FNA needle as it was felt to be too small for transmural stent placement. The patient also received antibiotics and did well.

of acute myeloid leukemia who presented with febrile neutropenia as well as a 3cm x 2.2cm mass in the right upper lung on CT imaging. After EUS-FNA, microbiology ultimately proved positive for *Aspergillus fumigatus*.[20] No post procedural complications were noted, including pneumothorax, and the patient improved after treatment with antifungals.[19]

Adrenal Glands

As mentioned above, EUS-FNA has been used to diagnose adrenal metastasis in primary lung cancers during the same session.[14] Comparatively more evidence is available to document the utility of EUS-FNA with regards to identifying and sampling adrenal lesions. A recent meta-analysis documented the high diagnostic accuracy for EUS-FNA for detection of adrenal gland lesions. The study included a total of 360 adrenal lesions, of which 137 were sampled and found to be positive for malignancy. Reported sensitivity and specificity of EUS-FNA for detecting metastatic adrenal gland lesions were 95% and 99%, respectively.[21] Of the 25 articles included for meta-analysis, none reported adverse events associated with EUS-FNA for adrenal gland lesions.[20] Similarly, a review article, which included 17 original articles and a total of 416 cases also found a low rate of adverse events with a single reported case of adrenal hemorrhage.[22] Due to anatomical constraints, the majority of tissue acquisition was obtained from the left adrenal gland. However, in 40 cases from the studies mentioned above, the right adrenal was sampled successfully.[20, 21] (Figure 2)

A recent national, multisite study of EUS guided tissue acquisition conducted in Spain found comparable results with regards to diagnostic yield and safety for EUS-FNA of the adrenal glands. The study included a total of 204 cases of tissue acquisition from the adrenal glands obtained in 200 patients. The authors found a diagnostic yield of 91.17%, inclusive of malignant plus benign diagnostic results, with no significant difference between FNA (n=153) or FNB (n=31). Fourteen of the reported cases were obtained from the right adrenal gland. The authors state that no serious adverse events occurred during the study. In two cases, patients were diagnosed with previously undiscovered pheochromocytomas. The patients did not have prior urine studies but did not suffer puncture associated hypertensive events. The authors concluded that urine studies may not be needed, especially in cases with known primary malignancy.[23]

Pelvic Masses

EUS guided biopsy can be used for a number of intrapelvic pathologies including: malignancy, cysts, abscesses and even endometriosis.[24,25,26,27,28] (Figure 3) Several single-center retrospective studies exist in the literature documenting the diagnostic efficacy and safety of EUS guided

tissue acquisition for pelvic masses.[23,24,25] The largest of these studies included a total of 127 patients with pelvic lesions, of which 44 cases had surgical pathology available for comparision.[25] The authors concluded that EUS-FNA of pelvic lesions to have a sensitivity of 89.3%, specificity of 100%, and a diagnostic accuracy of 93.2%.[25] Of the cases included for analysis, 45% were positive for malignancy, 4.7% were considered suspicious/atypical and 50.3% were negative for malignancy.[25] Among malignant cases, adenocarcinoma was identified in 18%, undifferentiated carcinoma in 16%, squamous cell carcinoma in 4%, neuroendocrine tumor in 2%, urothelial carcinoma in 2%, gastrointestinal stromal tumor in 1% and non-Hodgkin lymphoma in 1%.[25] No complications were noted during the study.

One study of 20 patients with pelvic lesions who underwent EUS-FNA found similar sensitivities and specificities (90% and 100%, respectively) when compared to available surgical pathology.[24] No early or late complications were noted during this study.[24] Another study included 29 patients with pelvic masses, of whom 17 had surgical pathology available for comparison, which found EUS-FNA to have a sensitivity of 88% and a specificity of 100%.[23] The authors also included 5 cases where EUS-FNB was also performed, which had a lower sensitivity of 67% and a specificity of 100%.[23] Two patients with cystic lesions developed abscesses after undergoing EUS-FNA, both of which required antibiotic treatment and percutaneous drainage.[23]

DISCUSSION

Since the initial case report of EUS guided FNA of a pancreatic head lesion in 1992,[29] EUS guided tissue acquisition has expanded its utility to a broad range of clinical scenarios. EUS guided tissue acquisition can be used to biopsy virtually any target within close proximity of the gastrointestinal tract including disparate sites all over the mediastinum, abdomen and pelvis. This review has detailed some unusual or less commonly biopsied sites including: thyroid, parathyroid, head and neck masses, lung masses, adrenal glands and pelvic masses. Given the diversity of biopsy sites presented here, successful EUS guided tissue acquisition should involve a detailed understanding of individual patient anatomy and, when appropriate, interdisciplinary discussion with interventional radiology, as well as relevant medical and surgical specialties.[30] As EUS guided FNA and FNB continue to be implemented in novel ways, additional research is needed for to further assess the safety profile and diagnostic accuracy of EUS guided tissue acquisition ■

References

1. Cazacu IM, Luzuriaga Chavez AA, Saftoiu A, Vilmann P, Bhutani MS. A quarter century of EUS-FNA: Progress, milestones, and future directions. Endosc Ultrasound. 2018 May-Jun;7(3):141-160.
2. Devereaux BM, Leblanc JK, Yousif E, Kesler K, Brooks J, Mathur P, Sandler A, Chappo J, Lehman GA, Sherman S, Gress F, Ciaccia D. Clinical utility of EUS-guided fine-needle aspiration of mediastinal masses in the absence of known pulmonary malignancy. Gastrointest Endosc. 2002 Sep;56(3):397-401.
3. Eloubeidi MA, Khan AS, Luz LP, Linder A, Moreira DM, Crowe DR, Eltoum IA. Combined use of EUS-guided FNA and immunocytochemical stains discloses metastatic and unusual diseases in the evaluation of mediastinal lymphadenopathy of unknown etiology. Ann Thorac Med. 2012 Apr;7(2):84-91.
4. Wildi SM, Fickling WE, Day TA, Cunningham CD 3rd, Schmulewitz N, Varadarajulu S, Roberts SS, Ferguson B, Hoffman BJ, Hawes RH, Wallace MB. Endoscopic ultrasonography in the diagnosis and staging of neoplasms of the head and neck. Endoscopy. 2004 Jul;36(7):624-30.
5. Koike E, Yamashita H, Noguchi S, Ohshima A, Yamashita H, Watanabe S, Uchino S, Arita T, Kuroki S, Tanaka M. Endoscopic ultrasonography in patients with thyroid cancer: its usefulness and limitations for evaluating esophagopharyngeal invasion. Endoscopy. 2002 Jun;34(6):457-60.
6. Alkhatib AA, Mahayni AA, Chawki GR, Yoder L, Elkhatib FA, Al-Haddad M. Endoscopic evaluation of thyroid gland among patients with nonthyroid cancers. Endosc Ultrasound. 2016 Sep-Oct;5(5):328-334.
7. Sawhney MS, Nelson DB, Debol S. Gastrointest Endosc. The ever-expanding spectrum of GI endoscopy: EUS-guided FNA of thyroid cancer. 2007 Feb;65(2):319-20; discussion 320. Epub 2006 Nov 1.
8. Dewitt J, Youssef W, Leblanc J, McHenry L, McGreevy K, Chappo J, Cramer H, Sherman S. EUS-guided FNA of a thyroid mass. Gastrointest Endosc. 2004 Feb;59(2):307-10.
9. Jalil AA, Elkhatib FA, Mahayni AA, Alkhatib AA. Primary papillary thyroid carcinoma diagnosed using endoscopic ultrasound with fine needle aspiration. Clin Endosc. 2014 Jul;47(4):350-2.
10. Balekuduru AB, Rao PS, Subbaraj SB. Endoscopic Ultrasound-guided Transesophageal Biopsy of Parathyroid Adenoma. J Dig Endosc. 2017;8:187-9.
11. Clary K, Varadarajulu S, Canon C, Jhala N, Jhala DN. Diagnosis of paraspinal abscess by EUS-guided FNA. Gastrointest Endosc. 2007 Apr;65(4):729-31.
12. Balekuduru AB, Dutta AK, Subbaraj SB. Endoscopic ultrasound-guided transoral drainage of parapharyngeal abscess. Digestive Endosc. 2016; 28: 755-759.

13. Fickling W, Wallace MB. Gastrointest Endosc. EUS in lung cancer. 2002 Oct;56(4 Suppl):S18-21.
14. Annema JT, Veseliç M, Rabe KF. EUS-guided FNA of centrally located lung tumours following a non-diagnostic bronchoscopy. Lung Cancer. 2005 Jun;48(3):357-61; discussion 363-4. Epub 2005 Jan 21.
15. Chira RI, Chira A, Ichim VA, Nagy GA, Florea A, Crisan D, Popovici B. Endoscopic ultrasound-guided aspiration (EUS-FNA) of paraesophageal lung tmors – diagnostic yield and added value. Med Ultrason. 2019 Nov 24;21(4):377-381.
16. Dincer HE, Gliksberg EP, Andrade RS. Endoscopic ultrasound and/or endobronchial ultrasound-guided needle biopsy of central intraparenchymal lung lesions not adjacent to airways or esophagus. Endosc Ultrasound. 2015 Jan-Mar;4(1):40-3.
17. Bugalho A, Ferreira D, Eberhardt R, Dias SS, Videira PA, Herth FJ, Carreiro L. Diagnostic value of endobronchial and endoscopic ultrasound-guided fine needle aspiration for accessible lung cancer lesions after non-diagnostic conventional techniques: a prospective study. BMC Cancer. 2013 Mar 19;13:130.
18. Lin LF, Huang PT, Tsai MH, Chen TM, Ho KS. Role of endoscopic ultrasound-guided fine-needle aspiration in lung and mediastinal lesions. J Chin Med Assoc. 2010 Oct;73(10):523-9.
19. Adler DG, Gabr M, Taylor LJ, Witt B, Pleskow D. Initial report of transesophageal EUS-guided intraparenchymal lung mass core biopsy: Findings and outcome in two cases. Endosc Ultrasound. 2018 Nov-Dec;7(6):413-417.
20. Rodrigues-Pinto E, Lopes S, Principe F, Costa J, Macedo G. Pulmonary aspergillosis diagnosed by endoscopic ultrasound fine-needle aspiration. Endosc Ultrasound. 2016 Jan-Feb;5(1):58-60.
21. Patel S, Jinjuvadia R, Devara A, Naylor PH, Anees M, Jinjuvadia K, Al-Haddad M. Performance characteristics of EUS-FNA biopsy for adrenal lesions: a meta-analysis. Endosc Ultrasound. 2019 May-Jun;8(3):180-187.
22. Rashmee Patil, Mel A. Ona, Charilaos Papafragkakis, Sushil Duddempudi, Sury Anand, Laith H. Jamil Endoscopic ultrasound-guided fine-needle aspiration in the diagnosis of adrenal lesions. Ann Gastroenterol. 2016 Jul-Sep; 29(3): 307–311. Published online 2016 May 20.
23. Martin-Cardona A, Fernandez-Esparrach G, Subtil JC, Iglesias-Garcia J, Garcia-Guix M, Barturen Barroso A, Gimeno-Garcia AZ, Esteban JM, Pardo Balteiro A, Velasco-Guardado A, Vazquez-Sequeiros E, Loras C, Martinez-Moreno B, Castellot A, Huertas C, Martinez-Lapiedra M, Sanchez-Yague A, Teran A, Morales-Alvarado VJ, Betes M, de la Iglesia D, Sánchez-Montes C, Lozano MD, Lariño-Noia J, Gines A, Tebe C, Gornals JB. EUS-guided tissue acquisition in the study of the adrenal glands: results of a nationwide multicenter study. PLoS One. 2019 Jun 6;14(6):e0216658.
24. Mohamadnejad M, Al-Haddad MA, Sherman S, McHenry L, Leblanc JK, DeWitt J. Utility of EUS-guided biopsy of extramural pelvic masses. Gastrointest Endosc. 2012 Jan;75(1):146-51.
25. Rzouq F, Brown J, Fan F, Oropeza-Vail M, Sidorenko E, Gilroy R, Esfandyari T, Bonino J, Olyaee M. The utility of lower endoscopic ultrasound-guided fine needle aspiration for the diagnosis of benign and malignant pelvic diseases. J Clin Gastroenterol. 2014 Feb;48(2):127-30.
26. Hassan GM, Paquin SC, Albadine R, Gariépy G, Soucy G, Nguyen BN, Sahai AV. Endoscopic-guided FNA of pelvic lesions: a large single-center experience. Cancer Cytopathol. 2016 Nov;124(11):836-841.
27. Adler DG, Lanke G. Clinical Update on the Role of EUS in Pelvic Abscess. Practical Gastroenterology. 2020 Mar.
28. Pishvaian AC, Ahlawat SK, Garvin D, Haddad NG. Role of EUS and EUS-guided FNA in the diagnosis of symptomatic rectosigmoid endometriosis. Gastrointest Endosc. 2006 Feb;63(2):331-5.
29. Vilmann P, Jacobsen GK, Henriksen FW et al. Endoscopic ultrasonography with guided fine needle aspiration biopsy in pancreatic disease. Gastrointest Endosc. 1992;38:172-3.
30. Fujii LL, Levy MJ.Basic techniques in endoscopic ultrasound-guided fine needle aspiration for solid lesions: adverse events and avoiding them. Endosc Ultrasound. 2014 Jan;3(1):35-45.