Endoscopic Ultrasound–Guided Fine-Needle Aspiration

A Cytopathologist's Perspective

Nirag C. Jhala, MD, MIAC,[1] Darshana N. Jhala, MD,[1*] David C. Chhieng, MD,[1] Mohamad A. Eloubeidi, MD, MHS,[2] and Isam A. Eltoum, MD, MBA[1]*

Key Words: Endosonography; Fine-needle aspiration; Cytology; Pancreas; Lymph node; Spleen; Gastrointestinal tract; Liver; Bile ducts; Gallbladder; Adrenal gland

DOI: 10.1309/MFRFJ0XYJLN8NVDP

Abstract

Endoscopic ultrasound (EUS) is used to detect and delineate the extent of lesions in the gastrointestinal tract, periluminal lymph nodes, pancreas and hepatobiliary tree, left kidney, spleen, and adrenal glands. EUS-guided fine-needle aspiration (FNA) has added a new dimension to the capabilities of EUS because it permits characterization of the lesion, thereby enabling triage of patients for more efficient and effective management. This review focuses on the advantages and limitations of EUS-FNA, including a discussion of potential pitfalls in the diagnosis of commonly aspirated deep-seated lesions, such as those of the pancreas and lymph nodes. It also addresses the practical considerations associated with establishing an effective service and the importance of an integrated approach in which the cytopathologist undertakes a key role, interacting extensively with the endoscopist and the patient management team. EUS-FNA is a sensitive modality that enables specific and accurate diagnosis of deep-seated lesions. Samples can be obtained effectively from small lesions (<25 mm), irrespective of the organ site. On-site assessment permits a highly accurate preliminary diagnosis of malignancy for samples obtained by EUS-FNA and provides an opportunity to increase the diagnostic yield of samples.

The attachment of ultrasound probes to endoscopes in the early 1980s permitted improved visualization of the gastrointestinal wall and abdominal organs.[1,2] The resolution of the images of lesions of the gastrointestinal wall and the organs in its vicinity was enhanced owing to the proximity of the ultrasound transducer to the lesion and the use of a high-frequency ultrasound probe. Endoscopic ultrasound (EUS) has been used to visualize, identify, and characterize the extent of lesions not only of the luminal gastrointestinal tract but also of the gastrointestinal tract wall, the periluminal lymph nodes (intrathoracic and intra-abdominal), the pancreas, the liver (mostly the left side), the left kidney, the spleen, and the adrenal glands.[1,3-8] The addition of Doppler imaging has further enhanced the usefulness of EUS in the characterization of vascular structures and hemodynamics.[9-12] However, EUS alone cannot be used to differentiate benign from malignant lesions.

In recent years, advances in technology have permitted the performance of fine-needle aspiration (FNA) biopsy under EUS guidance.[13,14] A curvilinear echoendoscope operating at 5 and 7.5 MHz permits continuous, real-time imaging and guidance for the sampling of lesions using 19- or 25-gauge needles. The ability to obtain cytologic material under direct visualization adds a new dimension to the diagnostic usefulness of this technique because it offers an opportunity for prompt and accurate diagnosis. The effective use of this technology depends, however, on effective collaboration between the cytopathologist and endoscopist and the willingness of the cytopathologist to have an integral role in patient management. Since this technique is being used increasingly in the United States and other parts of the world, the EUS-guided FNA biopsy (EUS-FNA) technique soon will become

the standard of practice for determining the diagnosis and staging of intra-abdominal and intrathoracic malignant neoplasms for proper management of these diseases.

In this review, we focus on the establishment of an EUS-FNA service from a cytopathologist's perspective, the processing of FNA samples obtained through this procedure, and the advantages and limitations of EUS-FNA in the diagnosis of lesions of various organ systems.

Establishing a Service

EUS-FNA can yield diagnostic material that provides information to guide disease-specific therapeutic intervention. This technique also offers an opportunity to prevent unnecessary operative procedures. The usefulness of EUS-FNA depends on several factors that are critical to its success. In addition to the experience of the endoscopist, good lines of communication between the cytopathologist and the endoscopist, adequate sampling, adequate sample processing, accurate interpretation by the cytopathologist, and the ability to determine the need for additional samples required for ancillary studies are needed for effective diagnosis.

Sample Collection, Processing, and Diagnostic Yield

Needle Type and Sample Yield

To date, EUS-FNA samples have been obtained using 2 types of needles, marketed by GIP-Medizin Technik (Grassau, Germany) and Wilson-Cook (Winston-Salem, NC).[15-17] Fritscher-Ravens and colleagues[15] prospectively evaluated 2 types of needles (GIP and Wilson-Cook) in the analysis of 30 pancreatic lesions. They observed that inadequate results were obtained in 11% of cases using the GIP-Medizin Technik needle. In contrast, none of the samples obtained using the Wilson-Cook needle was inadequate. These investigators noted, however, that in 8 procedures, the Wilson-Cook needles broke the outer Teflon sheath or reinsertion of the stylet in the needle was not possible. Such problems were not encountered with the GIP-Medizin Technik needles.

Lesion Size and Yield of FNA

EUS alone is superior to other imaging modalities for detecting lesions, particularly small lesions. Because the detection of small lesions may offer the opportunity to improve patient prognosis or outcome by providing early detection, this is a major advantage. For example, a small (<3.0 cm) pancreatic carcinoma found on resected samples is an independent predictor of patient survival. The size range of the tumors that can be sampled effectively using EUS-FNA is broad.[18-20] In the experience of Jhala et al[21] with 125 EUS-FNAs, the size of the tumor (≤20 vs >20 mm) did not affect the yield of informative samples or the number of passes required to obtain a sample, irrespective of the location of the lesion (ie, pancreas, lymph nodes, liver, spleen, or adrenal gland).

Sample Preparation

Optimal specimen preparation is a key to accurate cytologic diagnosis. Therefore, it has been suggested by some that aspirated material should be processed by cytology personnel only.[22] In our laboratory, we use the following protocol to process samples obtained by EUS-FNA:

1. Slides are labeled appropriately and placed on a smooth surface.
2. After each aspirate, the FNA needle is advanced through the sheath and air is forced into the needle through an attached air-filled syringe.
3. Air-dried and alcohol-fixed smears are prepared.
4. After obtaining all passes, the needle is rinsed in CytoLyt (Cytyc, Boxborough, MA) or Hank's balanced-salt solution (GIBCO, Grand Island, NY) for ThinPrep (Cytyc) and cell-block preparations, respectively.
5. Air-dried smears stained with rapid Romanowsky are used for rapid interpretation and for assessment of sample adequacy.
6. Additional samples for ancillary studies such as flow cytometry and tumor marker analysis are obtained when necessary.

The choice of stain is an individual preference. The rapid Romanowsky and Papanicolaou stains are complementary stains and highlight different cellular details. Alcohol-fixed smears, cytocentrifuged preparations, ThinPrep preparations, or cell blocks may be used for immunohistochemical stains as needed. In our experience, cell blocks provide a better sample for performing immunohistochemical stains.

One of the advantages of EUS-FNA over other tissue sampling techniques is the ability to aspirate more than 1 site during the same procedure.[23,24] In our own experience during the last 5 years with 120 pancreatic FNAs, 2 or more sites were aspirated in 14 (15%) of 96 procedures performed using EUS-FNA, whereas only 1 site was aspirated in each of the 24 FNA specimens obtained percutaneously. If 2 or more sites are to be aspirated during the same procedure, the endoscopist should indicate the change of site to the pathologist at the time of aspiration to avoid errors in slide labeling and interpretation.

At all times, universal precautions should be observed to reduce the risk of iatrogenic infection of the patient and the operator. To our knowledge, iatrogenic infections have not been noted in patients who have undergone EUS-FNA.

DOI: 10.1309/MFRFJ0XYJLN8NVDP

Diagnostic Yield and the Role of the Pathologist in the Endoscopy Suite

For effective assessment of the EUS-FNA sample, it is important that a cytopathologist or an advanced trainee in cytopathology be present in the EUS suite during the procedure to discuss the case with the endoscopist. Such a discussion might reduce the number of nondiagnostic and atypical samples. On-site assessment of the adequacy of the specimen obtained by image-guided FNA reduces the rate of nondiagnostic samples.[25-27] Chang and colleagues[28] reported that adequate samples were obtained from all patients when a cytopathologist was present during the procedure, whereas inadequate samples were obtained from 29% of patients, necessitating second procedures, when on-site assessment was not available. In another study, Binmoeller and colleagues[29] attributed their low diagnostic yields to the absence of a cytopathologist to verify the adequacy of the specimens during the procedure. Similarly, Voss and colleagues[20] reported that when a cytopathologist was not present in the endoscopy suite, neuroendocrine tumor of pancreas was detected in only 7 (47%) of 15 cases. Jhala et al[30] reported that in the presence of a cytopathologist in the endoscopy suite, all pancreatic neuroendocrine tumors were identified correctly and adequate cells were obtained for ancillary studies. Erickson and colleagues[31] concluded from their study of 109 EUS-FNA procedures that the absence of a cytopathologist in the endoscopy suite would require an increased number of passes and increased endoscopy time and result in a 10% to 15% reduction in the rate of definitive cytologic diagnosis.

In addition, on-site evaluation of EUS-FNA samples helps obtain samples for ancillary studies such as immunohistochemical analysis,[30] bacterial cell cultures, flow cytometry, and gene rearrangement studies for unsuspected cases of lymphoma. Additional assessments such as these may enhance the diagnostic accuracy of the procedure, which, in turn, enhances the effectiveness of further patient management.

Assessment of Preliminary Diagnosis

In addition to on-site assessment of specimen adequacy, the on-site generation of a differential diagnosis and, if possible, a preliminary diagnosis further assists the treating physicians because additional studies to determine the nature of the lesion can be recommended and undertaken. The information generated also may assist in decisions regarding disease-specific therapeutic interventions and prompt and appropriate referrals to specialists. It should be noted, however, that the assessment of a preliminary diagnosis should be treated similarly to the implications of a diagnosis based on frozen sections in surgical pathology.

A recent report by Shin and colleagues[32] suggests that studies are needed to determine the effectiveness of providing on-site preliminary diagnoses for EUS-FNA samples. To determine the accuracy of providing on-site assessment, Jhala et al[33] prospectively evaluated 120 consecutive EUS-FNA procedures, including those of the pancreas, lymph nodes, spleen, hepatobiliary tree, and gastrointestinal tract, and found a 100% concordance rate for the diagnosis of malignant neoplasm (52/52 samples) between preliminary and final cytologic diagnosis with sensitivity, specificity, and positive and negative predictive values of 95%, 100%, 100%, and 92%, respectively. The high degree of concordance was noted even when compared with subsequent tissue diagnosis. These findings suggest that the on-site diagnosis of malignant neoplasm is accurate and provides an opportunity to institute disease- and stage-specific interventions promptly and for the physician to make timely referrals to appropriate specialists.

In many centers, EUS-FNA samples are obtained by the endoscopist and samples are sent in a fixative to the cytopathology laboratory for sample preparation. In other institutions, technologists and trainees in cytopathology go to the endoscopy suite and provide on-site assessment of sample adequacy. In a few centers, such as ours, cytopathologists go to the endoscopy suite and provide an on-site, prompt interpretation. These practices are governed largely by considerations of time, personnel, and cost. Since time and cost are major driving forces in a busy cytology practice, it is useful to facilitate the process by establishing interaction with the cytology laboratory such that arrangements for potential EUS-FNA cases are discussed with the cytopathologist in advance. It also is important that in institutions in which cytology personnel go to the endoscopy suite, they are called at the time when FNA is about to be performed.

Cost of Performing EUS-FNA Compared With Computed Tomography–Guided FNA and Surgery

Many investigators have attempted cost-benefit analysis of the use of EUS in comparison with other, more conventional modalities.[34-37] In a study to determine the least costly strategy for workup of patients with nonmetastatic pancreatic cancer, EUS-FNA ($15,938) emerged as the least costly staging strategy in comparison with computed tomography (CT)-guided FNA ($16,378) and surgery ($18,723).[34] This primarily reflected the accurate detection of nodal involvement using EUS-FNA, which obviated unnecessary surgery.[34] These results support the performance of EUS-FNA in patients with tumors that are thought to be resectable based on the findings of helical CT.

In a similar study, Harewood and Wiersema[38] compared the costs of EUS-FNA, CT-guided FNA, and surgery in the management of esophageal tumors. The authors assumed that the detection of tumor in celiac lymph nodes by EUS-FNA signified that they were unresectable. Their cost inputs were based on Medicare professional fees plus Medicare

DOI: 10.1309/MFRFJ0XYJLN8NVDP

facility fees. In their model, the cost for the management per patient for EUS-FNA was $13,811, compared with $14,350 for CT-guided FNA and $13,992 for surgery. Their analysis showed that EUS-FNA was the least costly option, provided the prevalence of celiac lymph node involvement is more than 16%; when the involvement of lymph nodes is 16% or less, surgery became the least costly modality for patient management.

Cost of FNA for Reimbursement of the Cytopathologist

The aforementioned analyses factor in the cost of performing the EUS-FNA only. For a busy cytology practice, the cost to the cytopathology laboratory is a major consideration. Layfield and colleagues[39] studied a series of 142 non–EUS-FNAs for which immediate, on-site evaluations were performed in a variety of clinical settings. The series included bronchoscopic, endoscopic, ultrasound-guided, and CT-guided biopsies. The authors studied the attendance time of the pathologist and correlated it with the target organ, guidance technique, and the nature of the aspirator. For purposes of comparison, the costs of the cytopathologist were calculated using the 80th percentile pay level of an associate professor with full-time clinical duties. Medicare rate schedules were used to calculate compensation. Including salary and benefits, the cytopathologist cost was approximately $88.83 per hour. With the exception of FNA performed in the clinic by the cytopathologist, the time costs exceeded compensation by $40 to $50 per procedure. From these data, it seems that intraprocedural consultations by cytopathologists for CT-guided, ultrasound-guided, bronchoscopic, or endoscopic procedures are compensated insufficiently by current Medicare compensation schedules using the *CPT* (*Current Procedural Terminology*) code 88172 for on-site evaluation.

Therefore, each cytopathology laboratory needs to determine the cost/benefit ratio, taking into account the reduction in the rate for nondiagnostic samples, the cost of providing on-site preliminary diagnosis, and the overall benefit to the patient.

Effectiveness of EUS-FNA

The pancreas and lymph nodes (intrathoracic and intra-abdominal) are the most common organs targeted in EUS-FNA.[23,24,28,32,33,40-42] EUS-FNA provides excellent cellular yield (86%-98%) and overall sensitivity (77%-95%), together with excellent specificity (96%-100%) and accuracy (79%-97%) rates for the diagnosis of malignant neoplasms[23,24,28,32,40-43] **Table 1**.

The "gold standard" for these operating characteristics is based on a combination of surgical and/or clinical follow-up. Chhieng et al[18] and others[24,32,33] have noted that in many instances, a follow-up tissue confirmation for a cytologic diagnosis is not always available. In many cases, the cytologic diagnosis will provide the needed documentation for unresectable or metastatic malignant neoplasms or evidence of a benign lesion that does not need further surgical intervention. In such instances, cytology will be the only available tissue confirmation. Further biopsy, resection, or both are neither undertaken nor indicated.

The usefulness of EUS-FNA in various organ systems and the associated pitfalls in diagnostic interpretation are discussed in the following sections.

Pancreas

EUS is, in itself, a highly effective modality for detecting and staging pancreatic lesions. Therefore, it is used increasingly as the initial modality for evaluating pancreatic lesions. The overall accuracy of EUS is superior to CT scan and magnetic resonance imaging for detecting pancreatic lesions. It has been shown that EUS alone (94%) is more sensitive than

Table 1
Operating Characteristics of Endoscopic Ultrasound–Guided FNA Reported in the Literature

Reference	No. of FNAs	FNA Yields*	No. With Follow-up*	Sensitivity (%)	Specificity (%)	Accuracy (%)	False Negative*	False Positive (%)
Chang et al,[28] 1994	46	42 (91)	37 (80)	91	100	87	5 (14%)	0
Giovannini et al,[42] 1995	141	126 (89.4)	141 (100.0)	77	100	79	25 (12%)	0
Gress et al,[44] 1997	208	188 (90.4)	208 (100.0)	89	100	87	NS	NS
Wiersema et al,[24] 1997	554	524 (94.6)	474 (85.6)	86	99	89	6%	0
Bentz et al,[41] 1998	64	55 (86)	54 (84)	90	100	93	4 (7%)	0
Williams et al,[23] 1999	333	327 (98.2)	327 (98.2)	86	96	86	48 (15%)	
Chhieng et al,[18] 2002	103	97 (94.2)	93 (90.3)†	74 (95)†	100	83 (97)†	3 (3.5%)‡	0
Shin et al,[32] 2002	179	156 (87.2)	174 (97.2)	81.7	100	80.3	23 (13.2%)	0

FNA, fine-needle aspiration; NS, not specified.
* Data are given as number (percentage).
† Values in parentheses are those derived if atypical or "suspicious" diagnoses are considered diagnostic for malignancy.
‡ Nondiagnostic lesions and lesions with no follow-up were not included in the calculation.

DOI: 10.1309/MFRFJ0XYJLN8NVDP

CT scan (69%) and magnetic resonance imaging (83%) for detecting pancreatic lesions, especially when they are smaller than 3.0 cm.[45] In terms of staging, Gress and colleagues[46] reported overall accuracy rates for T and N staging as 85% and 72%, respectively, for EUS alone compared with 30% and 55%, respectively, for CT scans. These investigators also showed that EUS has an accuracy of 93% in the prediction of local resectability compared with an accuracy of only 60% for CT ($P < .001$).[46] The specificity of EUS is comparable to angiography for detecting vascular invasion. EUS, however, is more sensitive (86% vs 21%, respectively; $P = .0018$) and accurate (81% vs 38%) than angiography.[47]

FNA, ultrasound-guided or percutaneous, is a sensitive (81%-98%) and highly specific (99%-100%) modality for the diagnosis of pancreatic lesions.[20,48-56] EUS-FNA represents a recent addition to the armamentarium for the diagnosis of pancreatic diseases. The high degree of success with EUS-FNA of pancreatic lesions at our institution has resulted in a change in cytopathology practice for obtaining the initial diagnosis of pancreatic malignant neoplasms **Figure 1**. Similar changes at other institutions indicate a trend that seems to represent the evolving standard of care for the initial evaluation for pancreatic lesions.

The objectives of EUS-FNA of lesions of the pancreas are to obtain the initial diagnosis for a clinically suspicious malignant neoplasm, obviating the need for surgery for the purpose of obtaining tissue for diagnosis, and to obtain tissue confirmation of the diagnosis before surgical resection with curative intent or initiating adjuvant chemotherapy.

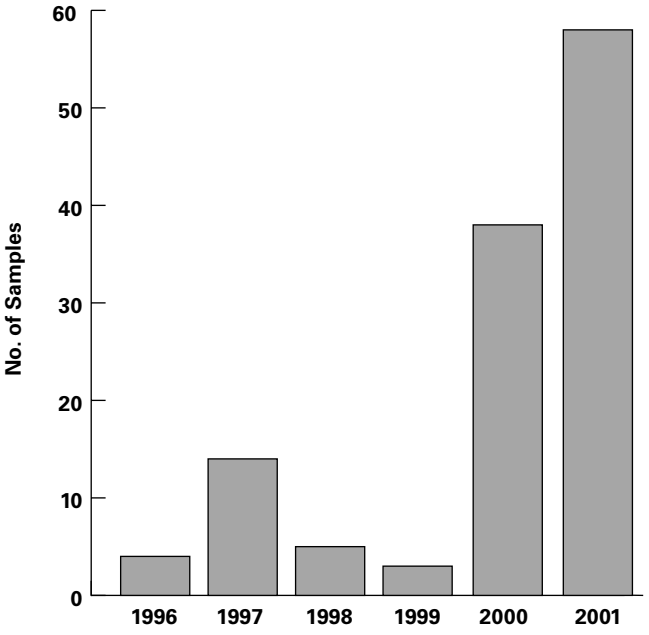

Figure 1 Frequency of fine-needle aspirations (FNAs) of the pancreas at the University of Alabama at Birmingham. Note the sharp increase in endoscopic ultrasound (EUS)–guided FNA of pancreas since the institution of the EUS-FNA service in 2000.

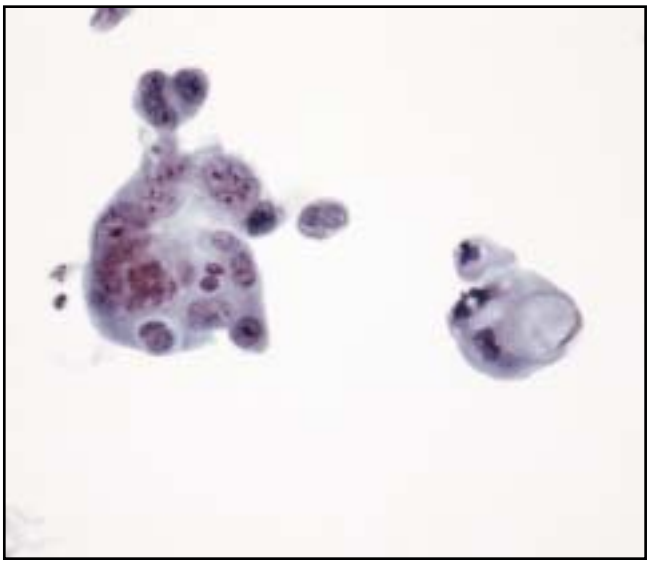

Image 1 ThinPrep (Cytyc, Boxborough, MA) preparation of endoscopic ultrasound–guided fine-needle aspiration sample from the pancreas showing large, single, pleomorphic cells with an increased nuclear/cytoplasmic ratio, some with prominent nucleoli, and a cell with mucin vacuole in the cytoplasm (Papanicolaou, ×40).

Pitfalls in the Evaluation of EUS-FNA of Pancreatic Lesions

Current diagnostic criteria for pancreatic adenocarcinoma **Image 1** have been well established and include increased cellularity; the predominance of 1 cell type; 3-dimensional groups (overlapping cells); a "drunken honeycomb" appearance; many pleomorphic single cells; tall cells with large nuclei (tombstones); and cells with an increased nuclear/cytoplasmic (N/C) ratio, irregular nuclear membrane, coarse and clumped chromatin, macronucleoli, and abnormal mitoses. These criteria have, however, been established using the extensive experience gained in the analysis of cell samples obtained by percutaneous[57] or intraoperative pancreatic FNA. Several issues must be taken into consideration in determining a diagnosis based on cells obtained by EUS-FNA.

Pancreatic Adenocarcinoma and Chronic Pancreatitis

1. A polymorphous cell population as opposed to predominance of cells of 1 type is one of the considerations WHEN evaluating specimens for pancreatic adenocarcinoma. With EUS-FNA, the pancreatic mass is approached from the gastrointestinal tract. The approach to the lesion in the pancreas using EUS varies with its topographic location. In addition, in EUS-FNA, as with percutaneous FNA, the needle passes through a background of chronic pancreatitis **Image 2** before reaching the target lesions. This may result

DOI: 10.1309/MFRFJ0XYJLN8NVDP

in additional cells being noted on the slide preparations and give the false impression of a polymorphous cell population. The approaches taken by the endoscopist to lesions in different locations in the pancreas and the cells that may be observed by a cytopathologist are listed in **Table 2**. Superficial glandular cells from the stomach using the transgastric approach are shown in **Image 3**.

2. Increased cellularity is one of the criteria used to distinguish well-differentiated adenocarcinoma from chronic pancreatitis. The cellularity of a sample is influenced by several factors, including operator technique and the anatomic location of the tumor. In an attempt to determine the differences in the cellularity of FNA samples of the pancreas obtained percutaneously or under EUS guidance, we evaluated 40 pancreatic FNA specimens (20 each percutaneous and EUS-FNA) and found that markedly cellular aspirates were seen more frequently with EUS-FNA (12/20) in comparison with percutaneous FNA (4/20) (unpublished observation). Similarly, Jhala et al[30] also demonstrated increased cellularity in FNA samples of pancreatic islet cell neoplasms **Image 4** using EUS guidance compared with those identified by CT scan. Some of the possible reasons for the increased cellularity of the samples obtained with EUS-FNA include the proximity to the lesion and the better visualization of the lesions. The on-site assessment of specimen adequacy during EUS-FNA may contribute further to the increased diagnostic yield on EUS-FNA of pancreatic lesions. Further studies are needed, however, to validate such assumptions. The use of cellularity as a criterion in the differentiation of chronic pancreatitis and well-differentiated adenocarcinoma should, therefore, be used with caution, especially when the samples have been obtained using EUS-FNA.

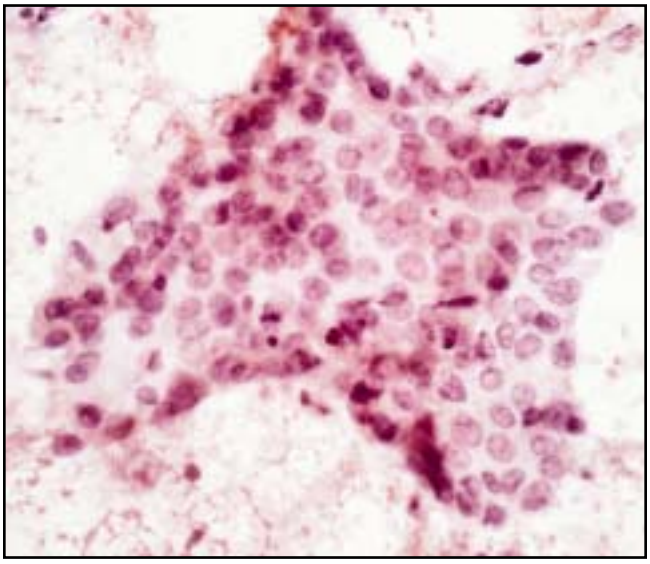

Image 2 Endoscopic ultrasound–guided fine-needle aspiration sample from a case of chronic pancreatitis that shows a cohesive 2-dimensional group of ductal epithelial cells. Individual cells show a preserved nuclear/cytoplasmic ratio and regular nuclear membrane (Papanicolaou, ×40).

3. Hypocellularity of the sample might result in a false-negative diagnosis. False-negative diagnoses may occur owing to technical difficulties, sampling error, or interpretive errors. A sampling error may result from the technical difficulty associated with reaching a small tumor. It also is possible that the marked desmoplasia of pancreatic adenocarcinoma might result in an inadequate specimen and/or an inconclusive diagnosis (ie, atypical or suggestive of malignancy), both of which require further investigations or repeated FNA. As discussed, we believe that the presence of a cytopathologist in the endoscopy suite at the time of the procedure helps ensure adequate diagnostic samples.

Cystic Pancreatic Lesions

The evaluation of cystic lesions of the pancreas poses a challenge for the radiologist, the endoscopist, and the pathologist.[47,58-60] In a study of 98 cystic lesions of the pancreas, Ahmad and colleagues[60] showed that EUS features alone could not be used to differentiate reliably between benign and malignant cystic lesions of the pancreas.

The cytologic features of various cystic lesions of the pancreas have been described.[61-66] Aspirates from microcystic adenomas yield hypocellular material with rare cuboidal cells with bland nuclei and pale cytoplasm. The neoplastic cells might stain with periodic acid–Schiff. Smears from mucinous cystic neoplasms may be moderately cellular and demonstrate abundant mucinous material. The glandular epithelial cells in this lesion are arranged in sheets and cohesive clusters. Most cells have benign nuclear features, but occasional cells may reveal focal, mild, nuclear atypia. Benign mucinous cystic lesions and cystadenocarcinoma cannot always be differentiated based on cytologic features alone. The key cytologic findings that support the

Table 2
Approaches for Performing Endoscopic Ultrasound–Guided Fine-Needle Aspiration From Various Topographic Locations in the Pancreas

Location of Lesion	Approach	Additional Cells
Head/uncinate	Transduodenal	Tightly cohesive glandular cells with honeycomb appearance and goblet cells
Body/tail	Transgastric	Parietal cells, superficial glandular cells (Image 3)

DOI: 10.1309/MFRFJ0XYJLN8NVDP

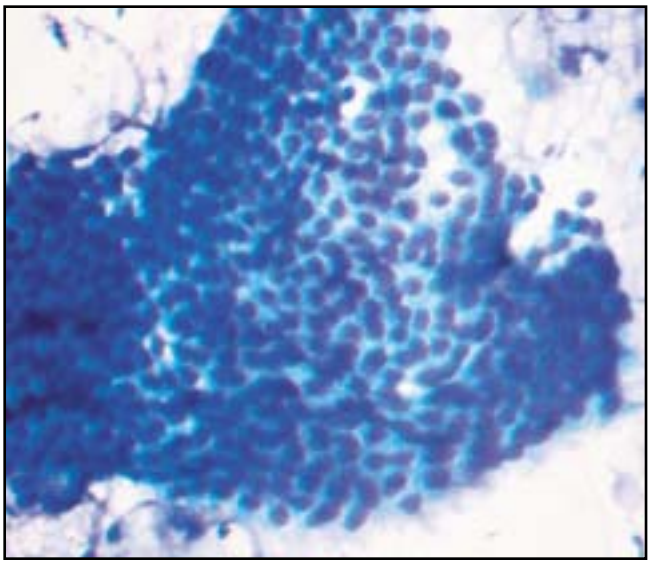

Image 3 Smear reveals cohesive superficial glandular cells of the stomach mucosa. The cells have a preserved nuclear/cytoplasmic ratio. These cells were obtained while aspirating a celiac lymph node using the transgastric approach (rapid Romanowsky, ×40).

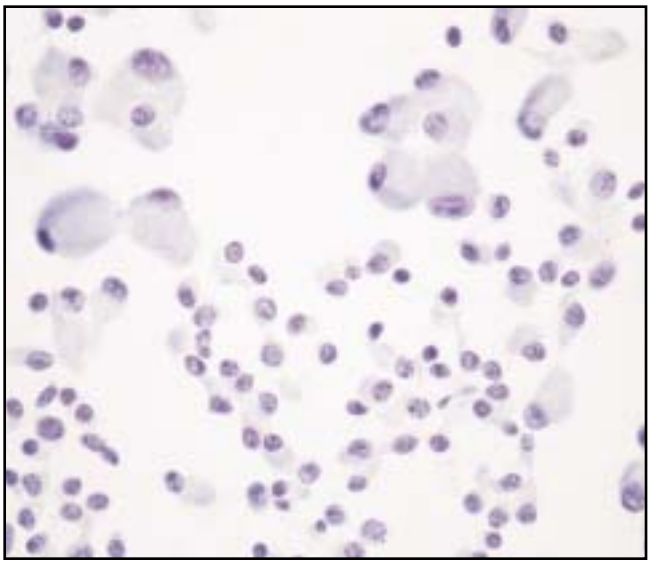

Image 4 This markedly cellular aspirate shows single cells with anisocytosis and eccentrically placed nuclei with evenly dispersed chromatin and occasional cells with conspicuous nucleoli obtained by endoscopic ultrasound–guided fine-needle aspiration of an islet cell tumor of the pancreas (Papanicolaou, ×20).

diagnosis of mucinous cystadenocarcinoma include moderate cellularity, loose clusters of cells, single cells, nucleoli, overt malignant nuclear features, and the presence of signet-ring cells.[67] Pancreatic pseudocysts can be distinguished from pancreatic cystic epithelial neoplasms by the predominance of histiocytes and inflammatory cells and an absence or paucity of epithelial cells. In addition, these lesions might not always be distinguished from intraductal papillary mucinous tumor (IPMT) of the pancreas and mucin-secreting adenocarcinoma of the pancreas.

We recently encountered 2 cases of IPMT. A definitive interpretation was possible based on cytologic features in 1 case, and a possibility of mucinous tumor was raised in the other. The features characteristic of IPMT include large papillary groups with fibrovascular core lying in pools of mucin **Image 5**. The neoplastic cells are columnar and show loss of cell polarity. A few single cells also might be seen. Individual cells might demonstrate a wide range of morphologic changes, from a preserved N/C ratio and a regular nuclear membrane to marked anisocytosis, an increased N/C ratio, and an irregular nuclear membrane with conspicuous nucleoli.

Cytology alone is considered an insensitive test for the analysis of cystic pancreatic lesions.[68] In 1 study, the sensitivity for detecting solid pancreatic lesions by FNA was 98%; this higher sensitivity for FNA diagnosis decreased to 62% when only cystic pancreatic lesions were analyzed.[55] Care must be taken to prevent potential interpretative errors

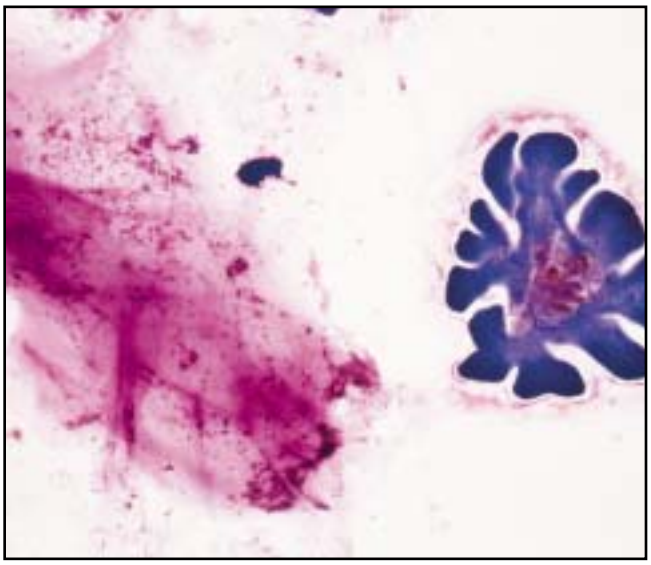

Image 5 The smear reveals pools of mucin and a large, cohesive group of epithelial cells with papillary arrangement; the sample was obtained by endoscopic ultrasound–guided fine-needle aspiration of an intraductal papillary mucinous tumor of the pancreas (rapid Romanowsky, ×10).

in the diagnosis of cystic pancreatic lesions that may arise owing to unique findings that are typical of samples obtained by EUS-FNA. An overinterpretation of duodenal or gastric mucosa in a pancreatic pseudocyst or microcystic serous cystadenoma may lead to an erroneous diagnosis of a mucinous cystic

DOI: 10.1309/MFRFJ0XYJLN8NVDP

lesion of the pancreas. In our practice, we report cystic lesions with increased mucin production and few epithelial cells without overt malignant features as cystic mucinous neoplasms.

To analyze cyst contents, carcinoembryonic antigen, amylase, CA125, and CA 19-9 have been used in the hope of increasing the sensitivity and specificity of the diagnosis, but their use has not become the standard of practice.[62,69] In a recent study, pancreatic tissues with noninvasive mucinous cystic neoplasms, irrespective of the degree of atypia, were positive for MUC5AC and negative for MUC1.[70] In contrast, the cases with an invasive component expressed MUC1. It therefore is possible that the expression pattern of the MUC antigens may provide useful information for the determination of the invasive potential of a cystic mucinous lesion.[70] More studies are needed, however, to evaluate the expression patterns of the MUC antigen in cytology samples and to assess their ability to differentiate between benign and malignant mucinous cystic lesions.

Pancreatic Neuroendocrine Cell Tumors (Islet Cell Tumors)

Islet cell tumors of the pancreas are aspirated infrequently. In the experience of Jhala et al,[30] the incidence of islet cell tumor is 4.6% (7/151) in pancreatic needle aspirates. A similar frequency of 3.3% (12/364) was noted by others.[56] A higher frequency, 8.8%, was noted when only solid pancreatic lesions were aspirated.[20] An accurate diagnosis of an islet cell tumor and its differentiation from pancreatic adenocarcinoma, acinar cell carcinoma, and solid cystic pancreatic carcinoma can be made based on an assessment of morphologic features and immunohistochemical analyses.[30,71,72] On-site assessment increases the diagnostic accuracy for the diagnosis of islet cell tumors by permitting immediate collection of additional material for ancillary studies.[30] In the absence of on-site assessment, the sensitivity for the detection of islet cell tumors decreases considerably.[20]

Metastatic or Disseminated Tumors

EUS-FNA also has been useful for the detection of metastatic malignant neoplasms. In our practice we have identified renal cell carcinoma[73] **Image 6**, a malignant lymphoma, and metastatic melanoma. The cytologic features for making a diagnosis of these tumors are well described in the literature.

Lymph Nodes

Many studies have noted the importance of performing EUS-FNA for mediastinal and intra-abdominal lymphadenopathy. Most of these studies have evaluated the use of EUS-FNA in the staging of malignant neoplasms of the lung, gastrointestinal tract, and pancreas. Determination of nodal metastasis by EUS-FNA has resulted in a change in preoperative staging that prevents unnecessary surgeries and a change in management strategies for primary malignant neoplasms of the lung, gastrointestinal tract, and pancreas.[6,74-81] EUS-FNA of deep-seated lymphadenopathy also is useful in the diagnosis of malignant lymphoma.

Cellular Yield and Technical Aspects

The technique used in performing EUS-FNA of deep-seated lymphadenopathy influences the cellularity of the sample obtained. Wallace and colleagues[82] found that the use of suction, compared with no suction, increased the cellularity of the specimen but also resulted in excessive blood in the sample, making interpretation difficult. The use of suction did not improve the likelihood of obtaining the correct diagnosis.[82] Similarly, the site of lymph node aspiration, edge or center, did not change the likelihood of obtaining a correct diagnosis. The same group of investigators also indicated that diagnostic material was obtained within the first 3 passes. It is, therefore, recommended that up to 3 passes of EUS-FNA, without the use of suction, should be performed and that the site of the enlarged lymph nodes that is most convenient be targeted.

Sample Collection

If the clinical information or the rapid interpretation of on-site cytology suggests malignant lymphoma, the endoscopist is asked to provide additional material for flow cytometric examination. The cells should be collected in RPMI 1640 solution for flow cytometric analysis or molecular genetic analysis. We have used Hank's balanced-salt solution as a transport medium, and collection in this solution has permitted subsequent analysis of aspirates by flow cytometry if required. Collection of samples in Hank's balanced-salt solution is associated, however, with the rapid loss of the viability of cells over a 24-hour period, which may decrease the yield of diagnostic cells for flow cytometric examination. We now routinely collect the samples in RPMI 1640 for a suspected lymphoma. In a series of 158 consecutive EUS-FNAs of lymph nodes, we correctly identified all 5 malignant lymphomas based on morphologic and flow cytometric analyses.

Mediastinal Lymphadenopathy

EUS-FNA has been useful in staging primary lung[83] and esophageal cancers,[75] in the diagnosis of benign conditions such as sarcoidosis,[84] and in the detection of primary mediastinal lesions such as paraesophageal bronchogenic cysts.[85] In a setting of known or suspected lung carcinoma, mediastinal lymphadenopathy may represent metastatic carcinoma. In patients with lymph node metastasis, surgery alone is unlikely to be curative and adjuvant therapy will be

DOI: 10.1309/MFRFJ0XYJLN8NVDP

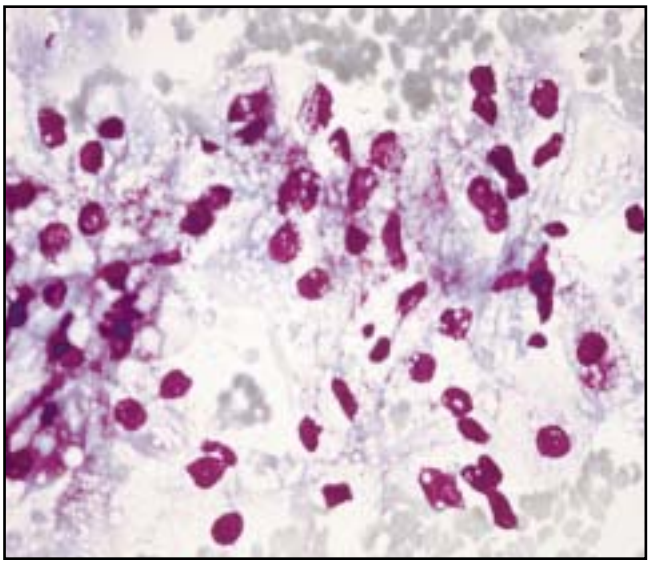

Image 6 Endoscopic ultrasound–guided fine-needle aspiration sample of the pancreas from a patient with history of renal cell carcinoma. The smear reveals group of cells with abundant clear cytoplasm and nuclei with nuclear membrane irregularity (rapid Romanowsky, ×40).

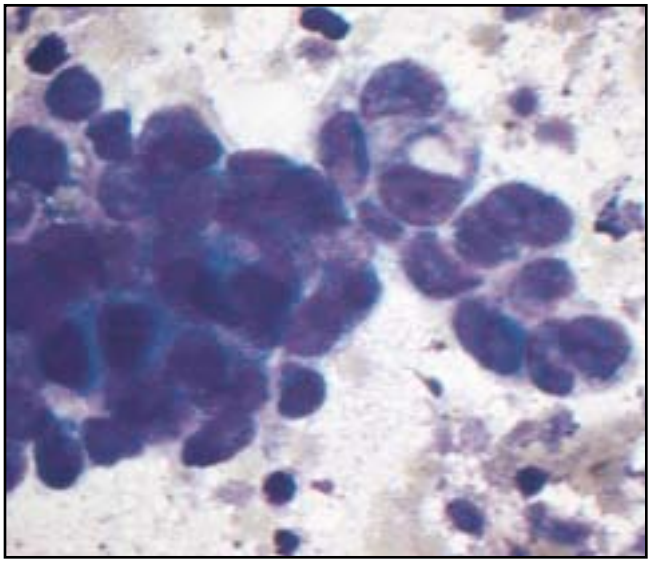

Image 7 A smear from aspiration of a celiac lymph node from a patient with esophageal carcinoma reveals a cohesive group of malignant cells with an increased nuclear/cytoplasmic ratio and metastatic adenocarcinoma cells; the sample is from a patient with a history of gastroesophageal carcinoma (rapid Romanowsky, ×40).

required. Currently, several nonsurgical techniques for obtaining tissue diagnosis, such as transbronchial needle aspiration and CT-guided aspiration, are used in most centers. Early studies have shown that transbronchial needle aspiration has wide ranging sensitivity (50%-91%), specificity (96%-100%), and overall accuracy (78%-91%) in the detection of metastatic lung carcinoma.[86,87] Similarly, CT-guided FNA of mediastinal nodes has a sensitivity ranging from 88% to 96%.[88,89] In comparison, it has been demonstrated consistently that EUS-FNA is a sensitive (96%), specific (100%), and accurate (97%-98%) modality for the detection of metastatic mediastinal malignant neoplasms.[74,90] It also has been demonstrated that EUS-FNA can accurately establish a primary diagnosis of metastasis when the results of other techniques have remained inconclusive. Thus, EUS-FNA might prevent the performance of more invasive procedures, such as thoracotomy or thoracoscopy and mediastinoscopy.[91] EUS-FNA has the added advantage of being capable of reaching the lower paraesophageal lymph nodes, aortopulmonary window, and posterior mediastinal nodes that are difficult to aspirate by other modalities.

Intra-abdominal Lymphadenopathy

Giovannini and colleagues[75] have shown that EUS-FNA is a highly sensitive (97%) and specific (100%) modality for the detection of celiac lymph node metastasis in patients with esophageal cancer. They also have shown that the detection of malignant neoplasms by using EUS-FNA modified the tumor staging in 77.5% of cases, resulting in the prevention of unnecessary surgery in 60% of the cases.[75] In an attempt to determine the clinical impact of FNA of celiac lymph nodes for M1a disease in esophageal carcinoma, Parmar and colleagues[92] showed that an EUS-FNA diagnosis positive for malignancy in a distant lymph node led to a change in management strategy and avoidance of unnecessary surgery. These authors also showed that EUS-FNA is superior to CT scan for diagnosing M1a disease. In addition, Eloubeidi and colleagues[81] demonstrated that detection of celiac lymphadenopathy by EUS is an independent predictor of survival in patients with esophageal cancer.

Our own experience with EUS-FNA of 158 lymph nodes shows that EUS-FNA is a highly sensitive (98.5%) and specific method (100.0%) for diagnosis with positive and negative predictive values of 100.0% and 98.8%, respectively. Our experience also shows that this modality is useful for the detection of metastatic carcinoma **Image 7** from the esophagus, pancreas, and lung. No false-positive diagnoses have been encountered.

Analysis of Lymph Nodes After Therapy

Jhala et al[93] describe experience with 11 patients with previous esophageal carcinoma who had lymphadenopathy following chemotherapy, radiation therapy, or both and who underwent EUS-FNA. The FNA specimens from these rapid Romanowsky–stained lymph nodes revealed predominantly pink, homogeneous, mucin-like material **Image 8**

DOI: 10.1309/MFRFJ0XYJLN8NVDP

with scattered, mixed lymphoid elements. In 1 case, groups of epithelial cells were noted in a background with marked mucinous change, giving an appearance of mucinous cystic neoplasm. The authors concluded that the knowledge of previous therapy and the absence of malignant cells in FNA specimens in these cases helped determine the correct diagnosis of therapy-associated change.

Pitfalls

One of the major pitfalls is overinterpretation of a lesion as positive for metastatic malignancy as a result of contamination of dysplastic cells when the needle traverses an area of high-grade dysplasia of the gastrointestinal tract mucosa. It is equally important that benign mucosal glandular cells in the aspirate of the lymph node not be overinterpreted as metastasis.

Gastrointestinal Tract

For cytologic diagnosis, endoscopic brushing is a useful modality for the detection of surface lesions; however, this modality is not useful for the diagnosis of submucosal lesions. EUS offers the advantages of direct visualization of the mucosal surface and accuracy in determining the extent and size of the submucosal lesion.[94] Therefore, EUS permits preoperative determination of the depth of tumor invasion, or T staging, as well as determination of the N status, providing valuable information concerning the TNM staging of gastrointestinal tract malignant neoplasms, including those of the esophagus[95-98] and stomach[98-100] and periampullary,[101,102] colorectal,[103] and anal canal tumors.[104] EUS also has been used to determine the extent of involvement and response to therapy of mucosa-associated lymphoid tissue (MALT) lymphomas of the stomach.[105-107]

Specifically, EUS-FNA has shown value in the following areas.

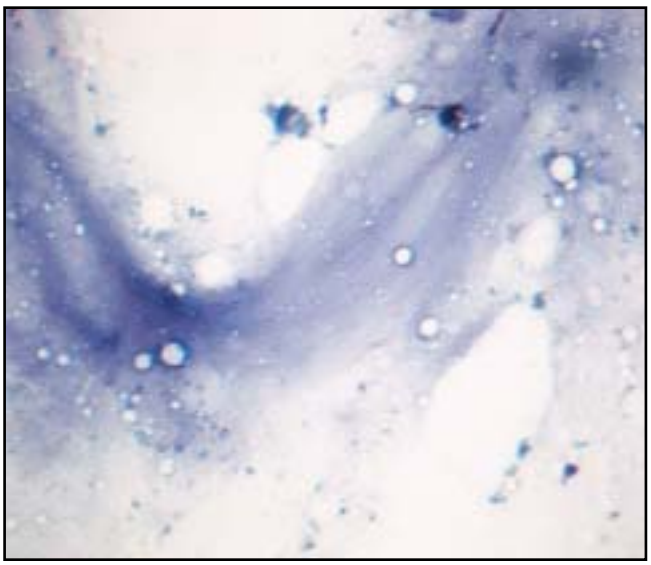

Image 8 This smear from a celiac lymph node aspirate obtained by endoscopic ultrasound–guided fine-needle aspiration in a patient treated with adjuvant chemotherapy and radiation therapy for esophageal carcinoma shows a paucicellular aspirate with large areas of myxoid change (rapid Romanowsky, ×10).

Detection of Foregut Cysts

One of the major differential diagnoses for a patient with a posterior mediastinal lesion, which might manifest with dysphagia, is a foregut cyst, which includes esophageal reduplication and bronchogenic cysts. These may be differentiated based on the presence of complete muscle wall, the type of lining epithelium, and results of the imaging studies. An esophageal reduplication cyst is a rare developmental anomaly that clinically and radiologically can mimic a neoplasm.

We have recorded 7 foregut cysts (bronchogenic cyst, 5; esophageal reduplication cyst, 2) that have been aspirated with EUS-FNA. Our experience shows that EUS-FNA is a useful and a safe nonsurgical modality for obtaining a diagnosis. The cytology of the cysts shows degenerated cell debris and hemosiderin-laden macrophages. In addition, these aspirates also might contain detached ciliated cell fragments, which can be demonstrated by both light and electron microscopy. The presence of numerous squamous cells supports the diagnosis of an esophageal reduplication cyst. The presence of numerous goblet cells with an absence of squamous cells supports the diagnosis of bronchogenic cyst.

Cytologic features alone are not pathognomonic for the diagnosis of a foregut cyst but can be used to rule out malignant neoplasm and help to support the diagnosis of foregut cyst when used in conjunction with imaging studies, including EUS findings.

Gastrointestinal Stromal Tumors

Gastrointestinal stromal tumors (GISTs) usually are submucosal and cannot be detected by brush sampling or forceps biopsy. FNA is being used increasingly for the diagnosis of GIST.[108-113] EUS helps to determine the site, size, and extent of the lesion, with some of these features being useful for determining the malignant potential of this tumor. FNA samples from GISTs show hypercellular groups of spindled cells **Image 9** and, rarely, epithelioid cells. The spindled cells also show blunt-ended nuclei and might show nuclear angulations.

The major pitfall associated with EUS-FNA of GISTs is the aspiration of muscle cells from the wall of the gastrointestinal tract or smooth muscle tumors.[114] Since the definitive differentiation of GISTs from other spindle cell lesions influences subsequent therapy, every attempt should be made to

DOI: 10.1309/MFRFJ0XYJLN8NVDP

distinguish these lesions. A panel of immunohistochemical stains, including primary antibodies against c-kit (CD117), CD34, smooth muscle antigen, muscle-specific actin, and S-100, may be used to distinguish GISTs from muscle cells, smooth muscle tumors, and rare tumors, such as solitary fibrous tumors of the gastrointestinal tract.

MALT Lymphoma

EUS is useful for determining the characteristic wall thickness of the gastrointestinal tract. It has proven useful in determining the prognosis and predicting the therapeutic response of MALT lymphomas.[105-107] The diagnosis of gastrointestinal MALT lymphoma using EUS-FNA is more difficult; it is not always possible because morphologic examination forms the mainstay for diagnosis, and, therefore, these tumors have not been aspirated for the purpose of obtaining a definitive diagnosis. The detection of gastric MALT lymphoma requires characteristic morphologic changes, a high degree of clinical suspicion, and ancillary studies, including flow cytometry and analysis of immunoglobulins, gene rearrangements, or both.

We have encountered 1 case of gastric MALT lymphoma aspirated by EUS-FNA. The aspirate revealed only small, minimally atypical lymphocytes with clear cytoplasm admixed with plasma cells. This polymorphous lymphoid appearance means that it is difficult to differentiate MALT lymphoma from chronic gastritis. In such a scenario, the finding of significantly thickened gastric mucosa by EUS and the finding of light chain restriction by flow cytometry or immunoglobulin gene rearrangement analysis or the detection of bcl-10 nuclear staining[115] would support the diagnosis of MALT lymphoma over a diagnosis of chronic gastritis.

Uncommon Lesions

EUS-FNA is being used increasingly in the detection of some of the uncommon lesions of the gastrointestinal tract that previously were not detected by brush sampling. Endometriosis involving the gastrointestinal wall may manifest with bowel obstruction and require surgical intervention. EUS-FNA samples may become informative in the diagnosis of these lesions. The presence of endometrial gland and stroma and macrophages with or without evidence of hemorrhage would support the correct recognition of endometriosis by EUS-FNA **Image 10**.

Hepatobiliary Tree

Liver

CT scans and ultrasound have been used to detect and guide the collection of FNA samples from hepatic masses.[116-119] Several studies have explored the usefulness of EUS in the diagnosis of hepatic lesions and its ability to promote early intervention. It has been reported that EUS is able to identify hepatic lesions in cases in which a previous CT scan had failed to detect a lesion.[120] As is the case in the lesions of other organs, however, EUS alone cannot differentiate

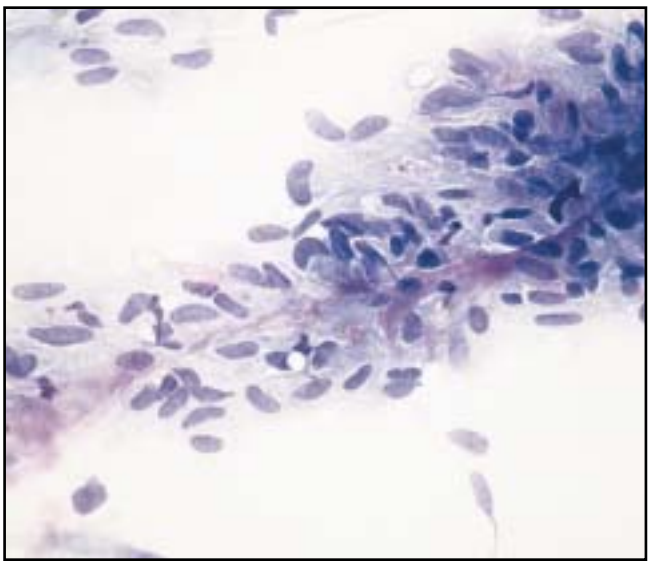

Image 9 The cellular aspirate from a gastrointestinal stromal tumor obtained from a duodenal mass reveals sheets of spindled cells with wispy cytoplasm. The nuclei are elongated with some showing nuclear angulation (rapid Romanowsky, ×20).

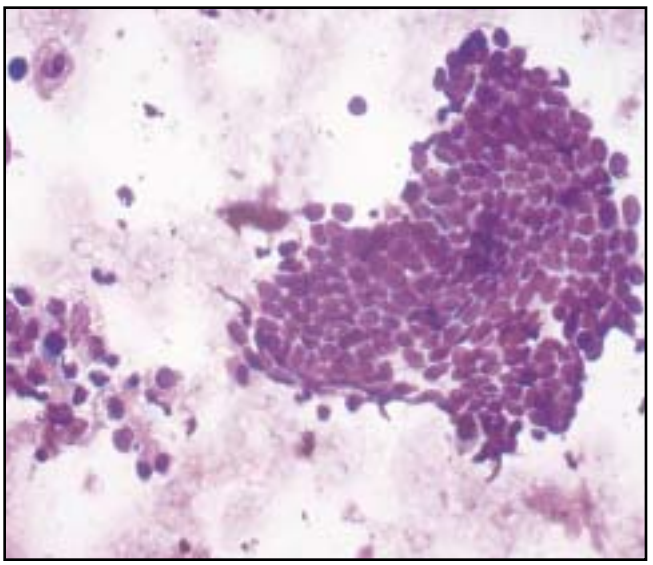

Image 10 Endoscopic ultrasound–guided fine-needle aspiration sample from a patient with a history of endometriosis and a mass in the bowel wall reveals tightly cohesive, small glandular cells reminiscent of endometrial cells. In addition, macrophages, some with pigment, also are identified (rapid Romanowsky, ×20).

DOI: 10.1309/MFRFJ0XYJLN8NVDP

between malignant and benign conditions.[121] In a multi-institutional study, EUS-FNA increased the diagnostic accuracy in 89% of cases in which previous percutaneous FNA was nondiagnostic.[121] In another study, EUS-FNA led to the early detection of hepatocellular carcinoma, resulting in its early resection.[122]

These studies show that EUS-FNA might have a valuable role in the detection of primary and metastatic malignant neoplasms of the liver **Image 11**. EUS-FNA of the liver might have a complication rate of 4%, with the reported complications including death, bleeding, fever, and pain.[121]

Biliary Tree and Gallbladder

EUS is a valuable alternative to endoscopic retrograde cholangiopancreatography (ERCP) and is increasingly studied for initial evaluation of the biliary tree. Erickson and Garza[35] found that performing EUS with FNA as the initial modality for evaluation of obstructive jaundice obviates the need for about 50% of ERCPs. They also showed that the use of EUS as an initial modality for the evaluation of biliary tree lesions substantially reduced costs ($1,007-$1,313 per patient). In addition, some investigators have noted that in cases in which ERCP-guided bile duct brushing proved inconclusive, EUS-FNA successfully provided information that led to a definitive diagnosis of malignant neoplasm.[123] In our experience, we obtained a diagnosis of malignant neoplasm **Image 12** in 4 cases using EUS-FNA when diagnostic cells could not be obtained by ERCP-guided bile duct brushing. As is the case with bile duct brushings, EUS-FNA of the biliary tract might show epithelial cells with marked reactive changes in patients with cholangitis and stent placement, and these cells mistakenly might be judged to be malignant. The presence of many single cells would, however, favor a diagnosis of malignant neoplasm.

Gallbladder

EUS-FNA may be used for obtaining samples to rule out malignant neoplasms of the gallbladder. This has not been investigated previously by others.

We have encountered 3 patients who have undergone EUS-FNA of the gallbladder (4 samples). In all cases, we encountered malignant cells in a background of marked acute inflammatory response. The presence of a marked acute inflammatory response led to an inconclusive diagnosis of atypia in 2 cases. No complications, including bile leakage, have been noted in our series. However, further studies are needed to demonstrate cytologic features and the safety of performing FNA of gallbladder lesions.

Spleen

FNA of the spleen has proven useful for the detection of malignant non-Hodgkin lymphoma, metastatic carcinoma,

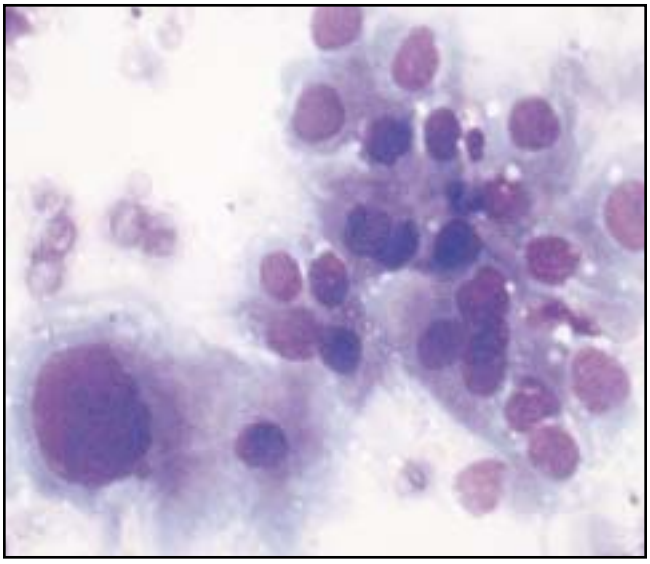

Image 11 This smear from a patient with history of pancreatic carcinoma was aspirated from liver lesions (adenocarcinoma metastatic to the liver). The cells show marked pleomorphism with anisocytosis. Individual cells show an enlarged nucleus with an altered nuclear/cytoplasmic ratio. Nuclear membrane irregularity is noted in the large cells (rapid Romanowsky, ×40).

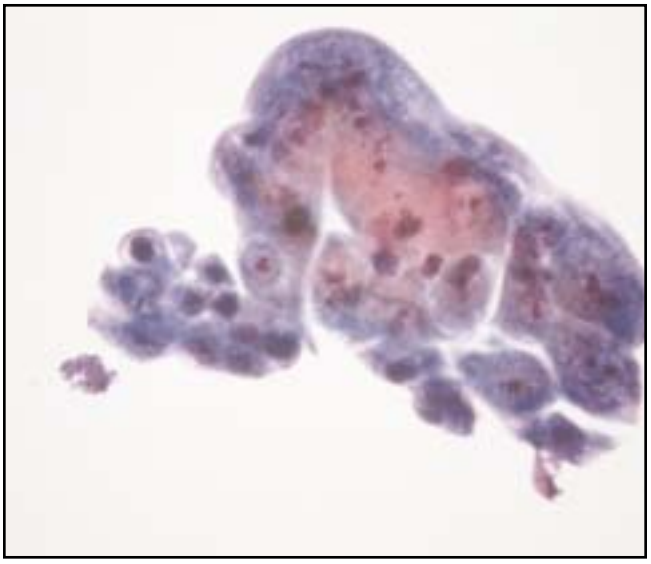

Image 12 This ThinPrep (Cytyc, Boxborough, MA) sample was obtained by endoscopic ultrasound–guided fine-needle aspiration of a mass in the second portion of the biliary duct. The cells show loosely cohesive groups with occasional single cells. A marked variation in cell size is noted. Individual cells reveal an altered nuclear/cytoplasmic ratio, prominent nucleoli, and an irregular nuclear membrane. This aspirate is from a patient with cholangiocarcinoma (Papanicolaou, ×40).

DOI: 10.1309/MFRFJ0XYJLN8NVDP

sarcoidosis, infectious conditions, and extramedullary hematopoiesis.[124-128] Percutaneous FNA of the spleen is highly specific (100%) and yields an overall accuracy of 84.9% to 88% for needle aspirates. When combined with needle biopsy, the accuracy increases to 90.3%.[125,127,129] It has been noted that the diagnostic accuracy of splenic FNA can be increased by obtaining samples for flow cytometry.[130] It has been suggested by some, however, that a potential risk for increased bleeding contributes to the lack of use of FNA of the spleen in the United States.[128,131]

The use of EUS-FNA in the spleen has not been studied. We have encountered 3 cases of EUS-FNA for splenic lesions. In our experience, EUS-FNA yielded cellular samples and an accurate diagnosis in 2 of 3 cases. In these 2 cases, the morphologic features of the cells, in conjunction with immunohistochemical stains and/or flow cytometric examination, helped in the correct interpretation of large B-cell malignant non-Hodgkin lymphoma. The third case proved to be a false-negative diagnosis because the morphologic features of the cells and the flow cytometric findings could not conclusively establish the diagnosis of malignant non-Hodgkin lymphoma. Our preliminary experience suggests that judicious use of EUS-FNA might permit the detection of unsuspected neoplasms, the determination of a preoperative diagnosis of splenic lesions, or both. It should be stressed, however, that further studies are needed to determine the safety and efficacy of this modality in the detection of splenic lesions.

Adrenal Glands

EUS can detect adrenal gland lesions and can effectively obtain FNA samples from the left side. We have obtained samples from 7 cases, of which 2 demonstrated carcinoma. In our experience, no complications were noted following EUS-FNA. This modality is useful for detecting metastatic malignant neoplasms to the adrenal gland, especially from the lung.

Samples from normal adrenal glands reveal single cells or small aggregates. The cells usually are uniform; however, anisocytosis sometimes can be noted. The nuclei generally have regular nuclear membranes. Some cells may reveal conspicuous nucleoli. The cytoplasm may be eosinophilic, foamy. or rich in lipids. Since the cytoplasm frequently is disrupted, naked nuclei often are identified, with lipid vacuoles **Image 13** noted in the background.

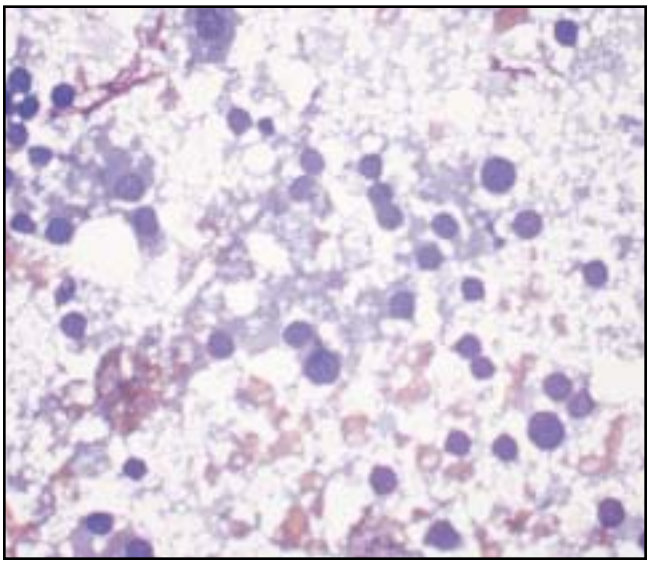

Image 13 A sample obtained by endoscopic ultrasound–guided fine-needle aspiration of the left adrenal gland reveals individual cells, some without cytoplasm, lying in the lipid rich background. The cytoplasm of cells reveals lipid vacuolation. The nuclei are small and round with a regular nuclear membrane (rapid Romanowsky, ×20).

Future Directions and Summary

FNAs are being used increasingly to obtain samples for molecular tests, including determinations of k-*ras, p53,* and *DPC4* activity[132]; clusterin expression[133]; c-*kit* mutations[112,134]; gene rearrangement studies[135]; and telomerase activity.[136,137] The increased usefulness of molecular techniques for the early detection and prognostication of tumors potentially will increase the usefulness of powerful modalities such as EUS-FNA that can provide samples from deep-seated lesions.

EUS is a powerful modality that promises to change practice patterns related to deep-seated malignant neoplasms in coming years. This modality requires that cytopathologists become an integral part of the patient management team, and the protocols concerning management will reflect this. While the diagnostic criteria for the majority of lesions are not affected, the cytopathologist should be aware of the limitations and pitfalls of this technique when evaluating samples obtained by EUS-FNA.

From the Departments of [1]Pathology and [2]Gastroenterology, University of Alabama at Birmingham.

[*] The first 2 authors contributed equally to the writing of this article.

Address reprint requests to Dr Nirag C. Jhala: Division of Anatomic Pathology, KB526, University of Alabama at Birmingham, 1922 6th Ave S, Birmingham, AL 35249.

References

1. Lux G, Heyder N, Lutz H, et al. Endoscopic ultrasonography: technique, orientation and diagnostic possibilities. *Endoscopy.* 1982;14:220-225.

DOI: 10.1309/MFRFJ0XYJLN8NVDP

2. Dimagno EP, Regan PT, Clain JE, et al. Human endoscopic ultrasonography. *Gastroenterology.* 1982;83:824-829.
3. Hunt GC, Faigel DO. Assessment of EUS for diagnosing, staging, and determining resectability of pancreatic cancer: a review. *Gastrointest Endosc.* 2002;55:232-237.
4. Pfau PR, Chak A. Endoscopic ultrasonography. *Endoscopy.* 2002;34:21-28.
5. Shimizu S, Tada M, Kawai K. Use of endoscopic ultrasonography for the diagnosis of colorectal tumors. *Endoscopy.* 1990;22:31-34.
6. Yasuda K, Cho E, Nakajima M, et al. Diagnosis of submucosal lesions of the upper gastrointestinal tract by endoscopic ultrasonography. *Gastrointest Endosc.* 1990;36:S17-S20.
7. Nickl NJ, Cotton PB. Clinical application of endoscopic ultrasonography. *Am J Gastroenterol.* 1990;85:675-682.
8. Rosch T, Lorenz R, Suchy R, et al. Colonic endoscopic ultrasonography: first results of a new technique. *Gastrointest Endosc.* 1990;36:382-386.
9. Wiersema MJ, Chak A, Kopecky KK, et al. Duplex Doppler endosonography in the diagnosis of splenic vein, portal vein, and portosystemic shunt thrombosis. *Gastrointest Endosc.* 1995;42:19-26.
10. Wilson SR, Thurston WA. Gastrointestinal sonography. *Curr Opin Radiol.* 1992;4:69-77.
11. Matre K, Odegaard S, Hausken T. Endoscopic ultrasound Doppler probes for velocity measurements in vessels in the upper gastrointestinal tract using a multifrequency pulsed Doppler meter. *Endoscopy.* 1990;22:268-270.
12. Becker D, Strobel D, Bernatik T, et al. Echo-enhanced color- and power-Doppler EUS for the discrimination between focal pancreatitis and pancreatic carcinoma. *Gastrointest Endosc.* 2001;53:784-789.
13. Wiersema MJ, Hawes RH, Tao LC, et al. Endoscopic ultrasonography as an adjunct to fine needle aspiration cytology of the upper and lower gastrointestinal tract. *Gastrointest Endosc.* 1992;38:35-39.
14. Vilmann P, Jacobsen GK, Henriksen FW, et al. Endoscopic ultrasonography with guided fine needle aspiration biopsy in pancreatic disease. *Gastrointest Endosc.* 1992;38:172-173.
15. Fritscher-Ravens A, Topalidis T, Bobrowski C, et al. Endoscopic ultrasound–guided fine-needle aspiration in focal pancreatic lesions: a prospective intraindividual comparison of two needle assemblies. *Endoscopy.* 2001;33:484-490.
16. Fritscher-Ravens A, Sriram PV, Topalidis T, et al. Endoscopic ultrasonography–guided fine-needle cytodiagnosis of mediastinal metastases from renal cell cancer. *Endoscopy.* 2000;32:531-535.
17. Bhutani MS, Suryaprasad S, Moezzi J, et al. Improved technique for performing endoscopic ultrasound guided fine needle aspiration of lymph nodes. *Endoscopy.* 1999;31:550-553.
18. Chhieng D, Jhala D, Jhala N, et al. Endoscopic ultrasound–guided fine-needle aspiration biopsy: a study of 103 cases. *Cancer.* 2002;96:232-239.
19. Vazquez-Sequeiros E, Norton ID, Clain JE, et al. Impact of EUS-guided fine-needle aspiration on lymph node staging in patients with esophageal carcinoma. *Gastrointest Endosc.* 2001;53:751-757.
20. Voss M, Hammel P, Molas G, et al. Value of endoscopic ultrasound guided fine needle aspiration biopsy in the diagnosis of solid pancreatic masses. *Gut.* 2000;46:244-249.
21. Jhala N, Eltoum I, Chhieng D, et al. Endoscopic ultrasound guided fine needle aspiration is a powerful tool for diagnosis of small deep-seated lesions: analysis of 125 lesions [abstract]. *Acta Cytol.* 2002;46:1013.
22. Logrono R, Waxman I. Interactive role of the cytopathologist in EUS-guided fine needle aspiration: an efficient approach. *Gastrointest Endosc.* 2001;54:485-490.
23. Williams DB, Sahai AV, Aabakken L, et al. Endoscopic ultrasound guided fine needle aspiration biopsy: a large single centre experience. *Gut.* 1999;44:720-726.
24. Wiersema MJ, Vilmann P, Giovannini M, et al. Endosonography-guided fine-needle aspiration biopsy: diagnostic accuracy and complication assessment. *Gastroenterology.* 1997;112:1087-1095.
25. Civardi G, Fornari F, Cavanna L, et al. Value of rapid staining and assessment of ultrasound-guided fine needle aspiration biopsies. *Acta Cytol.* 1988;32:552-554.
26. Stewart CJ, Stewart IS. Immediate assessment of fine needle aspiration cytology of lung. *J Clin Pathol.* 1996;49:839-843.
27. Santambrogio L, Nosotti M, Bellaviti N, et al. CT-guided fine-needle aspiration cytology of solitary pulmonary nodules: a prospective, randomized study of immediate cytologic evaluation. *Chest.* 1997;112:423-425.
28. Chang KJ, Katz KD, Durbin TE, et al. Endoscopic ultrasound–guided fine-needle aspiration. *Gastrointest Endosc.* 1994;40:694-699.
29. Binmoeller KF, Thul R, Rathod V, et al. Endoscopic ultrasound–guided, 18-gauge, fine needle aspiration biopsy of the pancreas using a 2.8 mm channel convex array echoendoscope. *Gastrointest Endosc.* 1998;47:121-127.
30. Jhala D, Eloubeidi M, Chhieng DC, et al. Fine needle aspiration biopsy of the islet cell tumor of pancreas: a comparison between computerized axial tomography and endoscopic ultrasound–guided fine needle aspiration biopsy. *Ann Diagn Pathol.* 2002;6:106-112.
31. Erickson RA, Sayage-Rabie L, Beissner RS. Factors predicting the number of EUS-guided fine-needle passes for diagnosis of pancreatic malignancies. *Gastrointest Endosc.* 2000;51:184-190.
32. Shin HJ, Lahoti S, Sneige N. Endoscopic ultrasound–guided fine-needle aspiration in 179 cases. *Cancer.* 2002;96:174-180.
33. Jhala D, Eloubeidi M, Chhieng D, et al. Accuracy of preliminary malignant diagnosis on endoscopic ultrasound guided fine needle aspiration: analysis of 120 cases [abstract]. *Acta Cytol.* 2001;45:859.
34. Harewood GC, Wiersema MJ. A cost analysis of endoscopic ultrasound in the evaluation of pancreatic head adenocarcinoma. *Am J Gastroenterol.* 2001;96:2651-2656.
35. Erickson RA, Garza AA. EUS with EUS-guided fine-needle aspiration as the first endoscopic test for the evaluation of obstructive jaundice. *Gastrointest Endosc.* 2001;53:475-484.
36. Harewood GC, Wiersema MJ, Edell ES, et al. Cost-minimization analysis of alternative diagnostic approaches in a modeled patient with non–small cell lung cancer and subcarinal lymphadenopathy. *Mayo Clin Proc.* 2002;77:155-164.
37. Harewood GC, Wiersema MJ. Cost-effectiveness of endoscopic ultrasonography in the evaluation of proximal rectal cancer. *Am J Gastroenterol.* 2002;97:874-882.
38. Harewood GC, Wiersema MJ. A cost analysis of endoscopic ultrasound in the evaluation of esophageal cancer. *Am J Gastroenterol.* 2002;97:452-458.
39. Layfield LJ, Bentz JS, Gopez EV. Immediate on-site interpretation of fine-needle aspiration smears: a cost and compensation analysis. *Cancer.* 2001;93:319-322.

DOI: 10.1309/MFRFJ0XYJLN8NVDP

40. Gress FG, Hawes RH, Savides TJ, et al. Endoscopic ultrasound–guided fine-needle aspiration biopsy using linear array and radial scanning endosonography. *Gastrointest Endosc*. 1997;45:243-250.
41. Bentz JS, Kochman ML, Faigel DO, et al. Endoscopic ultrasound–guided real-time fine-needle aspiration: clinicopathologic features of 60 patients. *Diagn Cytopathol*. 1998;18:98-109.
42. Giovannini M, Seitz JF, Monges G, et al. Fine-needle aspiration cytology guided by endoscopic ultrasonography: results in 141 patients. *Endoscopy*. 1995;27:171-177.
43. Jhala D, Chhieng D, Jhala N, et al. A prospective evaluation of the yield of endoscopic ultrasound guided fine needle aspiration in 103 consecutive lesions [abstract]. *Acta Cytol*. 2001;45:860.
44. Gress FG, Savides TJ, Sandler A, et al. Endoscopic ultrasonography, fine-needle aspiration biopsy guided by endoscopic ultrasonography, and computed tomography in the preoperative staging of non–small-cell lung cancer: a comparison study. *Ann Intern Med*. 1997;127:604-612.
45. Muller MF, Meyenberger C, Bertschinger P, et al. Pancreatic tumors: evaluation with endoscopic US, CT, and MR imaging. *Radiology*. 1994;190:745-751.
46. Gress FG, Hawes RH, Savides TJ, et al. Role of EUS in the preoperative staging of pancreatic cancer: a large single-center experience. *Gastrointest Endosc*. 1999;50:786-791.
47. Ahmad NA, Kochman ML, Lewis JD, et al. Endosonography is superior to angiography in the preoperative assessment of vascular involvement among patients with pancreatic carcinoma. *J Clin Gastroenterol*. 2001;32:54-58.
48. Hajdu EO, Kumari-Subaiya S, Phillips G. Ultrasonically guided percutaneous aspiration biopsy of the pancreas. *Semin Diagn Pathol*. 1986;3:166-175.
49. Smith EH, Bartrum RJ Jr, Chang YC, et al. Percutaneous aspiration biopsy of the pancreas under ultrasonic guidance. *N Engl J Med*. 1975;292:825-828.
50. Bret PM, Nicolet V, Labadie M. Percutaneous fine-needle aspiration biopsy of the pancreas. *Diagn Cytopathol*. 1986;2:221-227.
51. Al-Kaisi N, Siegler EE. Fine needle aspiration cytology of the pancreas. *Acta Cytol*. 1989;33:145-152.
52. Kocjan G, Rode J, Lees WR. Percutaneous fine needle aspiration cytology of the pancreas: advantages and pitfalls. *J Clin Pathol*. 1989;42:341-347.
53. Schramm H, Urban H, Arnold F, et al. Intrasurgical pancreas cytology. *Pancreas*. 2002;24:210-214.
54. Cohen MB, Egerter DP, Holly EA, et al. Pancreatic adenocarcinoma: regression analysis to identify improved cytologic criteria. *Diagn Cytopathol*. 1991;7:341-345.
55. Sperti C, Pasquali C, Di Prima F, et al. Percutaneous CT-guided fine needle aspiration cytology in the differential diagnosis of pancreatic lesions. *Ital J Gastroenterol*. 1994;26:126-131.
56. David O, Green L, Reddy V, et al. Pancreatic masses: a multi-institutional study of 364 fine-needle aspiration biopsies with histopathologic correlation. *Diagn Cytopathol*. 1998;19:423-427.
57. Robins DB, Katz RL, Evans DB, et al. Fine needle aspiration of the pancreas: in quest of accuracy. *Acta Cytol*. 1995;39:1-10.
58. Shiraishi M, Tokashiki H, Samura H, et al. Avoiding an overdiagnosis of pancreatic pseudocysts. *Hepatogastroenterology*. 2001;48:1758-1761.
59. Jones EC, Suen KC, Grant DR, et al. Fine-needle aspiration cytology of neoplastic cysts of the pancreas. *Diagn Cytopathol*. 1987;3:238-243.
60. Ahmad NA, Kochman ML, Lewis JD, et al. Can EUS alone differentiate between malignant and benign cystic lesions of the pancreas? *Am J Gastroenterol*. 2001;96:3295-3300.
61. Sperti C, Cappellazzo F, Pasquali C, et al. Cystic neoplasms of the pancreas: problems in differential diagnosis. *Am Surg*. 1993;59:740-745.
62. Pinto MM, Meriano FV. Diagnosis of cystic pancreatic lesions by cytologic examination and carcinoembryonic antigen and amylase assays of cyst contents. *Acta Cytol*. 1991;35:456-463.
63. Laucirica R, Schwartz MR, Ramzy I. Fine needle aspiration of pancreatic cystic epithelial neoplasms. *Acta Cytol*. 1992;36:881-886.
64. Cappellari JO. Fine-needle aspiration cytology of a pancreatic lymphoepithelial cyst. *Diagn Cytopathol*. 1993;9:77-81.
65. Granter SR, DiNisco S, Granados R. Cytologic diagnosis of papillary cystic neoplasm of the pancreas. *Diagn Cytopathol*. 1995;12:313-319.
66. Logrono R, Vyas SH, Molina CP, et al. Microcystic adenoma of the pancreas: cytologic appearance on percutaneous and endoscopic ultrasound–guided fine-needle aspiration: report of a case. *Diagn Cytopathol*. 1999;20:298-301.
67. Dodd LG, Farrell TA, Layfield LJ. Mucinous cystic tumor of the pancreas: an analysis of FNA characteristics with an emphasis on the spectrum of malignancy associated features. *Diagn Cytopathol*. 1995;12:113-119.
68. Brugge WR. Role of endoscopic ultrasound in the diagnosis of cystic lesions of the pancreas. *Pancreatology*. 2001;1:637-640.
69. Lewandrowski KB, Southern JF, Pins MR, et al. Cyst fluid analysis in the differential diagnosis of pancreatic cysts: a comparison of pseudocysts, serous cystadenomas, mucinous cystic neoplasms, and mucinous cystadenocarcinoma. *Ann Surg*. 1993;217:41-47.
70. Luttges J, Feyerabend B, Buchelt T, et al. The mucin profile of noninvasive and invasive mucinous cystic neoplasms of the pancreas. *Am J Surg Pathol*. 2002;26:466-471.
71. al-Kaisi N, Weaver MG, Abdul-Karim FW, et al. Fine needle aspiration cytology of neuroendocrine tumors of the pancreas: a cytologic, immunocytochemical and electron microscopic study. *Acta Cytol*. 1992;36:655-660.
72. Labate AM, Klimstra DL, Zakowski MF. Comparative cytologic features of pancreatic acinar cell carcinoma and islet cell tumor. *Diagn Cytopathol*. 1997;16:112-116.
73. Eloubeidi MA, Jhala D, Chhieng DC, et al. Multiple late asymptomatic pancreatic metastases from renal cell carcinoma: diagnosis by endoscopic ultrasound–guided fine needle aspiration biopsy with immunocytochemical correlation. *Dig Dis Sci*. 2002;47:1839-1842.
74. Wiersema MJ, Vazquez-Sequeiros E, Wiersema LM. Evaluation of mediastinal lymphadenopathy with endoscopic US–guided fine-needle aspiration biopsy. *Radiology*. 2001;219:252-257.
75. Giovannini M, Monges G, Seitz JF, et al. Distant lymph node metastases in esophageal cancer: impact of endoscopic ultrasound–guided biopsy. *Endoscopy*. 1999;31:536-540.
76. Reed CE, Mishra G, Sahai AV, et al. Esophageal cancer staging: improved accuracy by endoscopic ultrasound of celiac lymph nodes. *Ann Thorac Surg*. 1999;67:319-322.
77. Wiersema MJ. Identifying contraindications to resection in patients with pancreatic carcinoma: the role of endoscopic ultrasound. *Can J Gastroenterol*. 2002;16:109-114.
78. Mortensen MB, Pless T, Durup J, et al. Clinical impact of endoscopic ultrasound–guided fine needle aspiration biopsy in patients with upper gastrointestinal tract malignancies: a prospective study. *Endoscopy*. 2001;33:478-483.

DOI: 10.1309/MFRFJ0XYJLN8NVDP

79. Zhang Q, Nian W, Zhang L, et al. Endoscopic ultrasonography assessment in preoperative staging for carcinoma of ampulla of Vater and extrahepatic bile duct. *Chin Med J (Engl)*. 1996;109:622-625.
80. Eloubeidi MA, Wallace MB, Reed CE, et al. The utility of EUS and EUS-guided fine needle aspiration in detecting celiac lymph node metastasis in patients with esophageal cancer: a single-center experience. *Gastrointest Endosc*. 2001;54:714-719.
81. Eloubeidi MA, Wallace MB, Hoffman BJ, et al. Predictors of survival for esophageal cancer patients with and without celiac axis lymphadenopathy: impact of staging endosonography. *Ann Thorac Surg*. 2001;72:212-220.
82. Wallace MB, Kennedy T, Durkalski V, et al. Randomized controlled trial of EUS-guided fine needle aspiration techniques for the detection of malignant lymphadenopathy. *Gastrointest Endosc*. 2001;54:441-447.
83. Wallace MB, Silvestri GA, Sahai AV, et al. Endoscopic ultrasound–guided fine needle aspiration for staging patients with carcinoma of the lung. *Ann Thorac Surg*. 2001;72:1861-1867.
84. Mishra G, Sahai AV, Penman ID, et al. Endoscopic ultrasonography with fine-needle aspiration: an accurate and simple diagnostic modality for sarcoidosis. *Endoscopy*. 1999;31:377-382.
85. Lim LL, Ho KY, Goh PM. Preoperative diagnosis of a paraesophageal bronchogenic cyst using endosonography. *Ann Thorac Surg*. 2002;73:633-635.
86. Schenk DA, Bower JH, Bryan CL, et al. Transbronchial needle aspiration staging of bronchogenic carcinoma. *Am Rev Respir Dis*. 1986;134:146-148.
87. Shannon JJ, Bude RO, Orens JB, et al. Endobronchial ultrasound–guided needle aspiration of mediastinal adenopathy. *Am J Respir Crit Care Med*. 1996;153:1424-1430.
88. Akamatsu H, Terashima M, Koike T, et al. Staging of primary lung cancer by computed tomography–guided percutaneous needle cytology of mediastinal lymph nodes. *Ann Thorac Surg*. 1996;62:352-355.
89. Protopapas Z, Westcott JL. Transthoracic needle biopsy of mediastinal lymph nodes for staging lung and other cancers. *Radiology*. 1996;199:489-496.
90. Fritscher-Ravens A, Soehendra N, Schirrow L, et al. Role of transesophageal endosonography–guided fine-needle aspiration in the diagnosis of lung cancer. *Chest*. 2000;117:339-345.
91. Larsen SS, Krasnik M, Vilmann P, et al. Endoscopic ultrasound guided biopsy of mediastinal lesions has a major impact on patient management. *Thorax*. 2002;57:98-103.
92. Parmar KS, Zwischenberger JB, Reeves AL, et al. Clinical impact of endoscopic ultrasound–guided fine needle aspiration of celiac axis lymph nodes (M1a disease) in esophageal cancer. *Ann Thorac Surg*. 2002;73:916-921.
93. Jhala D, Eloubeidi M, Eltoum I, et al. Cytology of lymph nodes in patients status post chemo- and/or radiation therapy with esophageal cancer: a potential diagnostic pitfall. *Acta Cytol*. 2002;46:98-99.
94. Shen EF, Arnott ID, Plevris J, et al. Endoscopic ultrasonography in the diagnosis and management of suspected upper gastrointestinal submucosal tumours. *Br J Surg*. 2002;89:231-235.
95. Scotiniotis IA, Kochman ML, Lewis JD, et al. Accuracy of EUS in the evaluation of Barrett's esophagus and high-grade dysplasia or intramucosal carcinoma. *Gastrointest Endosc*. 2001;54:689-696.
96. Richards DG, Brown TH, Manson JM. Endoscopic ultrasound in the staging of tumours of the oesophagus and gastro-oesophageal junction. *Ann R Coll Surg Engl*. 2000;82:311-317.
97. Heidemann J, Schilling MK, Schmassmann A, et al. Accuracy of endoscopic ultrasonography in preoperative staging of esophageal carcinoma. *Dig Surg*. 2000;17:219-224.
98. Tio TL, Coene PP, Schouwink MH, et al. Esophagogastric carcinoma: preoperative TNM classification with endosonography. *Radiology*. 1989;173:411-417.
99. Grimm H, Binmoeller KF, Hamper K, et al. Endosonography for preoperative locoregional staging of esophageal and gastric cancer. *Endoscopy*. 1993;25:224-230.
100. Yucel C, Ozdemir H, Isik S. Role of endosonography in the evaluation of gastric malignancies. *J Ultrasound Med*. 1999;18:283-288.
101. Chen CH, Tseng LJ, Yang CC, et al. Preoperative evaluation of periampullary tumors by endoscopic sonography, transabdominal sonography, and computed tomography. *J Clin Ultrasound*. 2001;29:313-321.
102. Chen CH, Tseng LJ, Yang CC, et al. The accuracy of endoscopic ultrasound, endoscopic retrograde cholangiopancreatography, computed tomography, and transabdominal ultrasound in the detection and staging of primary ampullary tumors. *Hepatogastroenterology*. 2001;48:1750-1753.
103. Bhutani MS, Nadella P. Utility of an upper echoendoscope for endoscopic ultrasonography of malignant and benign conditions of the sigmoid/left colon and the rectum. *Am J Gastroenterol*. 2001;96:3318-3322.
104. Giovannini M, Bardou VJ, Barclay R, et al. Anal carcinoma: prognostic value of endorectal ultrasound (ERUS): results of a prospective multicenter study. *Endoscopy*. 2001;33:231-236.
105. Nakamura S, Matsumoto T, Suekane H, et al. Predictive value of endoscopic ultrasonography for regression of gastric low grade and high grade MALT lymphomas after eradication of *Helicobacter pylori*. *Gut*. 2001;48:454-460.
106. Caletti G, Fusaroli P, Togliani T, et al. Endosonography in gastric lymphoma and large gastric folds. *Eur J Ultrasound*. 2000;11:31-40.
107. Pavlick AC, Gerdes H, Portlock CS. Endoscopic ultrasound in the evaluation of gastric small lymphocytic mucosa-associated lymphoid tumors. *J Clin Oncol*. 1997;15:1761-1766.
108. Ando N, Goto H, Niwa Y, et al. The diagnosis of GI stromal tumors with EUS-guided fine needle aspiration with immunohistochemical analysis. *Gastrointest Endosc*. 2002;55:37-43.
109. Ballo MS, Guy CD. Percutaneous fine-needle aspiration of gastrointestinal wall lesions with image guidance. *Diagn Cytopathol*. 2001;24:16-20.
110. Boggino HE, Fernandez MP, Logrono R. Cytomorphology of gastrointestinal stromal tumor: diagnostic role of aspiration cytology, core biopsy, and immunochemistry. *Diagn Cytopathol*. 2000;23:156-160.
111. Gu M, Ghafari S, Nguyen PT, et al. Cytologic diagnosis of gastrointestinal stromal tumors of the stomach by endoscopic ultrasound–guided fine-needle aspiration biopsy: cytomorphologic and immunohistochemical study of 12 cases. *Diagn Cytopathol*. 2001;25:343-350.
112. Li SQ, O'Leary TJ, Sobin LH, et al. Analysis of KIT mutation and protein expression in fine needle aspirates of gastrointestinal stromal/smooth muscle tumors. *Acta Cytol*. 2000;44:981-986.

DOI: 10.1309/MFRFJ0XYJLN8NVDP

113. Seidal T, Edvardsson H. Diagnosis of gastrointestinal stromal tumor by fine-needle aspiration biopsy: a cytological and immunocytochemical study. *Diagn Cytopathol.* 2000;23:397-401.
114. Fu K, Eloubeidi M, Jhala NC, et al. Diagnosis of gastrointestinal stromal tumors by endoscopic ultrasound–guided fine needle aspiration: a potential pitfall. *Ann Diagn Pathol.* 2002;6:294-301.
115. Du MQ, Diss TC, Dogan A, et al. Clone-specific PCR reveals wide dissemination of gastric MALT lymphoma to the gastric mucosa. *J Pathol.* 2000;192:488-493.
116. Granados R, Aramburu JA, Murillo N, et al. Fine-needle aspiration biopsy of liver masses: diagnostic value and reproducibility of cytological criteria. *Diagn Cytopathol.* 2001;25:365-375.
117. Logrono R, Rampy BA, Adegboyega PA. Fine needle aspiration cytology of hepatobiliary cystadenoma with mesenchymal stroma. *Cancer.* 2002;96:37-42.
118. Das DK. Cytodiagnosis of hepatocellular carcinoma in fine-needle aspirates of the liver: its differentiation from reactive hepatocytes and metastatic adenocarcinoma. *Diagn Cytopathol.* 1999;21:370-377.
119. Cohen MB, Haber MM, Holly EA, et al. Cytologic criteria to distinguish hepatocellular carcinoma from nonneoplastic liver. *Am J Clin Pathol.* 1991;95:125-130.
120. Nguyen P, Feng JC, Chang KJ. Endoscopic ultrasound (EUS) and EUS-guided fine-needle aspiration (FNA) of liver lesions. *Gastrointest Endosc.* 1999;50:357-361.
121. tenBerge J, Hoffman BJ, Hawes RH, et al. EUS-guided fine needle aspiration of the liver: indications, yield, and safety based on an international survey of 167 cases. *Gastrointest Endosc.* 2002;55:859-862.
122. Bogstad J, Vilmann P, Burcharth F. Early detection of recurrent hepatocellular carcinoma by endosonographically guided fine-needle aspiration biopsy. *Endoscopy.* 1997;29:322-324.
123. Fritscher-Ravens A, Broering DC, Sriram PV, et al. EUS-guided fine-needle aspiration cytodiagnosis of hilar cholangiocarcinoma: a case series. *Gastrointest Endosc.* 2000;52:534-540.
124. Venkataramu NK, Gupta S, Sood BP, et al. Ultrasound guided fine needle aspiration biopsy of splenic lesions. *Br J Radiol.* 1999;72:953-956.
125. Civardi G, Vallisa D, Berte R, et al. Ultrasound-guided fine needle biopsy of the spleen: high clinical efficacy and low risk in a multicenter Italian study. *Am J Hematol.* 2001;67:93-99.
126. Rajwanshi A, Gupta D, Kapoor S, et al. Fine needle aspiration biopsy of the spleen in pyrexia of unknown origin. *Cytopathology.* 1999;10:195-200.
127. Lishner M, Lang R, Hamlet Y, et al. Fine needle aspiration biopsy in patients with diffusely enlarged spleens. *Acta Cytol.* 1996;40:196-198.
128. Silverman JF, Geisinger KR, Raab SS, et al. Fine needle aspiration biopsy of the spleen in the evaluation of neoplastic disorders. *Acta Cytol.* 1993;37:158-162.
129. Siniluoto T, Paivansalo M, Tikkakoski T, et al. Ultrasound-guided aspiration cytology of the spleen. *Acta Radiol.* 1992;33:137-139.
130. Bonifacio A, Goldberg RE, Patterson BJ, et al. Flow-cytometry–enhanced fine-needle aspiration biopsy of the spleen. *Can Assoc Radiol J.* 2000;51:158-162.
131. Moriarty AT, Schwenk GR Jr, Chua G. Splenic fine needle aspiration biopsy in the diagnosis of lymphoreticular diseases: a report of four cases. *Acta Cytol.* 1993;37:191-196.
132. van Heek T, Rader AE, Offerhaus GJ, et al. K-*ras*, *p53*, and *DPC4* (*MAD4*) alterations in fine-needle aspirates of the pancreas: a molecular panel correlates with and supplements cytologic diagnosis. *Am J Clin Pathol.* 2002;117:755-765.
133. Jhala D, Jhala N, Eloubeidi M, et al. Clusterin expression in pancreatic adenocarcinoma and chronic pancreatitis. *Mod Pathol.* 2002;15:288A.
134. Rader AE, Avery A, Wait CL, et al. Fine-needle aspiration biopsy diagnosis of gastrointestinal stromal tumors using morphology, immunocytochemistry, and mutational analysis of c-kit. *Cancer.* 2001;93:269-275.
135. Galindo LM, Garcia FU, Hanau CA, et al. Fine-needle aspiration biopsy in the evaluation of lymphadenopathy associated with cutaneous T-cell lymphoma (mycosis fungoides/Sézary syndrome). *Am J Clin Pathol.* 2000;113:865-871.
136. Suehara N, Mizumoto K, Tanaka M, et al. Telomerase activity in pancreatic juice differentiates ductal carcinoma from adenoma and pancreatitis. *Clin Cancer Res.* 1997;3:2479-2483.
137. Suehara N, Mizumoto K, Kusumoto M, et al. Telomerase activity detected in pancreatic juice 19 months before a tumor is detected in a patient with pancreatic cancer. *Am J Gastroenterol.* 1998;93:1967-1971.

DOI: 10.1309/MFRFJ0XYJLN8NVDP

HOLOGIC®

First and Only FDA Cleared
Digital Cytology System

Genius™ Cervical AI

Genius™ Review Station

Genius™ Digital Imager

Empower Your Genius With Ours

Make a Greater Impact on Cervical Cancer
with the Advanced Technology of the
Genius™ Digital Diagnostics System

Click or Scan
to discover more

genius™
DIGITAL DIAGNOSTICS