ORIGINAL ARTICLE

Indications for Endoscopic Ultrasound and Diagnosis on Fine-Needle Aspiration and Cytology

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ABSTRACT

Objective: To determine common indications for requesting Endoscopic Ultrasound (EUS) and to describe the diagnosis made after endoscopic ultrasound/Fine-Needle Aspiration and Cytology (FNAC) during two years at a tertiary gastrointestinal unit.

Study Design: Cross-sectional descriptive study.

Place and Duration of Study: The study was carried out in Gastrointestinal Department of Military Hospital, Rawalpindi, from March 2006 to February 2008.

Methodology: One hundred and eighty nine patients who underwent EUS during study period at Military Hospital were included in the study. Patients too ill (hypoxemic/hypotensive) to undergo procedure safely and those with complete esophageal blockage at upper end by tumour not allowing scope/EUS probe to advance beyond were excluded. EUS was done with Olympus Exera EUS 160, linear or radial scope, as required. EUS findings were recorded against indications as enlarged lymph nodes, tumour, staging, normal or incomplete. Fine-Needle Aspiration (FNA) was done as per findings on EUS using 21-22 G needle. An on-site cytopathologist made the provisional cytopathological diagnosis. Final cytology/histopathology report was given after review of slides by consultant histopathologists at Armed Forces Institute of Pathology (AFIP), Rawalpindi, and were documented as tuberculosis, malignancy, chronic pancreatitis or reactive hyperplasia. Data was analyzed for documentation of patients' age, gender, common indications, findings on EUS/FNAC, using SPSS version 10. Percentages and frequencies were calculated for the presence of these above-mentioned variables.

Results: Of the 189 patients, 145 (77%) were male and 44 (23%) female. Age was 18-80 years (mean 49 years). Major indications for referral were lymphadenopathy in 92 (49%), suspected growth pancreas in 57 (28%), growth of stomach in 20 (11%) and a heterogeneous group included esophageal, liver, retroperitoneal masses, rectal and other pathologies.

Findings on EUS included lymphadenopathy in 76, mostly in sub-carina and AP window. Mass in pancreas was seen in 36, followed by stomach tumour in 17 and esophagus in 9.

FNAC was done in 142 out of 189 patients. Final diagnosis out of 67 FNAC/histopathology of lymph nodes were tuberculosis in 26 and malignant lesions in 23. These included metastatic adenocarcinoma in 8, lymphoproliferative disorder in 7, metastatic squamous cell carcinoma in 5, small cell carcinoma in 2 and anaplastic in 1. Pancreatic tumours were adenocarcinoma in 16, poorly differentiated in 3 and neuroendocrine in 2. Stomach tumours were found in 11, and included lymphomas 5, GIST 3, carcinoids 2, metastatic choriocarcinoma 1 and adenocarcinoma in 1. Therapeutically, 3 celiac blocks and one pancreatic pseudocyst drainage was done.

Conclusion: The main indication of EUS and pathology of mediastinal and celiac nodes were metastatic malignancy and tuberculosis. Pancreatic adenocarcinoma was another common cause for asking EUS.

Key words: *Endoscopic ultrasound (EUS). EUS-Guided fine-needle aspiration (FNA). Tumour staging. Pancreatic tumour. Lymphadenopathy.*

INTRODUCTION

Ultrasound was considered to be one of the most important discoveries of the twentieth century, which revolutionized the field of diagnostic imaging. Advancement in endoscopy further facilitated diagnosis. Endoscopic Ultrasound (EUS) was developed in 1980 to overcome limitations of transabdominal ultrasound imaging of the pancreas caused by intervening gas and fat. It combines endoscopic visualization and high-frequency ultrasound. Over the past decade, EUS had steadily gained ground becoming an indispensable and complementary procedure in high volume tertiary Gastro Intestinal (GI) centres for patients with previously identified lesions of the gastrointestinal tract and surrounding organs including enlarged lymph nodes, the pancreas and biliary tree. EUS-guided Fine-Needle Aspiration (FNA) allows tissue diagnosis of not only suspected gastrointestinal lesions but also of extraluminal lesions. Besides tissue diagnosis, EUS has shown superiority to Computed Tomography (CT) for Tumour (T) and lymph node (N) staging of luminal and pancreaticobiliary malignancies. In a prospective multicentre study, results of EUS frequently resulted in a change in both subsequent work-up and therapy.[1]

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Endoscopic Ultrasound (EUS) had been shown to be a sensitive technique for the depiction of mediastinal lymph node enlargement in patients with lung cancer.[2,3] Although, several procedures had been available for obtaining biopsy specimens from mediastinal masses like mediastinoscopy, transbronchial fine-needle aspiration, VATS-video-assisted thoracoscopy, percutaneous puncture guided by computed tomography (CT) or open thorocotomy. Mediastinoscopy and thorocotomy had been invasive and hazardous. EUS offered a modality in which vascular structures could be identified with colour doppler and allow to biopsy lymph nodes in regions not easily accessible by mediastinoscopy i.e. the subaortic, subcarinal region and the inferior pulmonary ligament, the region around the left atrium and the artopulmonary window.[4]

The complex anatomy of pancreas makes its visualization and procurement of cytologic samples difficult. Pancreatic masses had been difficult to diagnose as malignant in the absence of clinical symptoms of advanced disease by imaging technique alone. Traditionally, Computed Tomography (CT)-guided Fine-Needle Aspiration (FNA) had been used for biopsy of the pancreas. However, this technique had risk of peritoneal dissemination of cancer cells and a false-negative rate of upto 20%.[5,6] Even ERCP brush cytology had a false-negative rate of nearly 30%.[7] Compared with other imaging modalities, the results of EUS-FNA of pancreatic masses had been excellent, with a sensitivity of 85-90% and a specificity of virtually 100%.[8-10] Surgeons aware of the role of EUS/FNAC had been expecting accurate diagnosis before embarking on surgery. Similarly, EUS had been used increasingly in various therapeutic procedures including management of pancreatic cancers.[11]

Unlike CT, EUS had been available only in a few academic centres and even fewer private-practice settings. Besides cost, EUS had been believed to be the most technically challenging endoscopic procedure and the images are more difficult to interpret than standard endoscopic images.

The present study was conducted to determine common indications for requesting Endoscopic Ultrasound (EUS) and to describe the diagnoses made after endoscopic ultrasound/fine-needle aspiration and cytology (FNAC).

METHODOLOGY

It was a cross-sectional descriptive study carried out at the Department of Gastroenterology, Military Hospital, Rawalpindi, from March 2006 to February 2008. Consecutive non-probability convenient sampling was done from general medical OPD, gastroenterology OPD and general medical wards. They included those referred for diagnosis/FNAC, staging of tumour and therapeutic procedures. Patients too ill (hypoxemic/hypotensive) to undergo procedure safely and those with complete esophageal blockage at upper end by tumour not allowing scope/EUS probe to advance beyond were excluded. Detailed history was taken, previous investigation reviewed, procedure was explained to the patients and informed consent was obtained. Baseline investigations including PT and INR were done. Indications were documented as per site of pathology, including lymph node, pancreas, stomach, esophagus and miscellaneous including liver, retroperitoneal and rectal pathology.

EUS was done with Olympus Exera EUS 160, linear or radial scope, as required. EUS was performed by a single trained operator and was observed by a second trained operator. EUS findings were recorded against indications as enlarged lymph nodes, tumour, staging, normal or incomplete. Fine-Needle Aspiration and Cytology (FNAC) was done as per findings on EUS using Olympus Endotherapy single use aspiration needle of 22 G width with needle length of 80 mm and working length of 1400 mm, minimum channel size 2.8 mm and maximum insertion portion diameter of 1.85 mm. Three to ten passes were performed, each one by moving the needle (back and forth) within the target.

The aspirate was placed onto glass slides and half were air dried and were stained using Diffquick method and half slides were wet fixed in absolute alcohol. Samples were also taken where required for cell blocks into 10% formalin saline solution and PCR for *Mycobacterium tuberculosis* and immunochemistry where indicated.

An on-site cytopathologist was present from Armed Forces Institute of Pathology (AFIP), Rawalpindi, and air dried slides were reviewed for adequacy of tissue and provisional cytopathological diagnoses were made in GI department. Samples taken for tissue block and wet slides were taken to AFIP. Final cytology/histopathology report was given after review of slides by consultant histopathologists and review of tissue taken for PCR/immunochemistry at AFIP, Rawalpindi.

Therapeutic procedures were done there and than where indicated. Further investigations and work-up like ERCP with stenting, surgical and or oncology consultation were planned where required. Data was analyzed using SSPS version 10, percentages and frequencies were determined for various variables (common indications and diagnosis).

RESULTS

Of the 189 patients who underwent EUS; 145 (77%) were males and 44 (23%) females. Age ranged from 18 to 80 years with mean of 49 years. Maximum referrals were by gastroenterologists followed by pulmonologists and thoracic surgeons. Major indications with which patients were referred for EUS are shown in Figure 1.

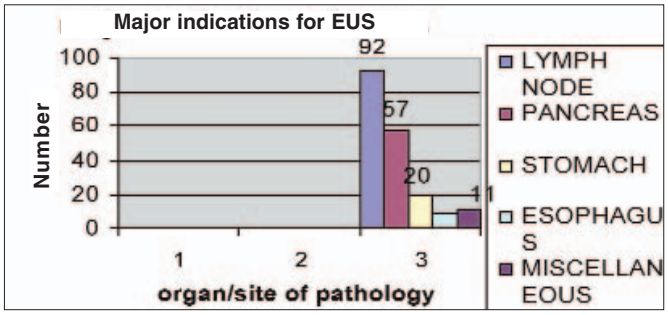

Figure 1: Major indications for EUS as per site of pathology.

Evaluation of lymphadenopathy including mediastinal/ para aortic or celiac detected by chest X-ray, ultrasound abdomen or CT scan chest or abdomen needing FNA/tissue diagnosis was the major indication for EUS in 49% cases. Abnormal pancreatic imaging (mass lesion, fullness or prominence of pancreatic head on ultrasound or CT abdomen) in 28% cases was the second largest reason for requesting EUS. This was followed by tumours of stomach in 11% cases, lacking diagnosis on routine biopsy on upper GI endoscopy or needing layer analysis or staging. Heterogeneous group included tumours of esophagus in 9 cases and space occupying lesions of liver in 7 cases and retroperitoneal masses in 2 cases and rectal tumour in one.

Common findings on EUS are shown in Table I.

Enlarged lymph nodes involving subcarina, AP window and para aortic regions of various sizes were the most common findings on EUS and FNAC was done in most cases. Masses in pancreas were the second common finding and FNAC was done accordingly. In certain cases, there was no abnormality detected on EUS despite suspicion clinically on the basis of initial investigation, and were advised further work-up or follow-up. Tumours in stomach were the third largest group and FNAC was done in 13 cases. This was followed by tumours of esophagus and FNAC was done in 5 cases. Incomplete procedure included situations like tight stricture esophagus or grade IV varices where procedure was not considered safe.

Table I: EUS findings against clinical indications.

Clinical indication	Findings	Number	Percentage
Lymph node Enlargement (n=92)	Enlarged	79	41.80
	Normal EUS	8	4.23
	Incomplete	5	2.64
Pancreatic lesions (n=57)	Mass or tumour	45	23.81
	Normal EUS	10	5.30
	Incomplete	2	1.06
Stomach tumour for FNAC/staging (n=20)	Tumour/FNA staging	20	10.58
Esophagus tumour for FNAC/staging (n=9)	Tumour/FNA staging	9	4.76
Miscellaneous (n=11)	SOL liver	5	2.64
	Retroperitoneal	3	1.59
	Masses/rectal incomplete	3	1.59
Total		189	100

On the basis of on-site pathology and detailed evaluation in laboratory by experienced histo-pathologists, the final diagnosis established are shown in Table II.

Table II: Final diagnosis on FNAC/cytopathology.

FNAC	Diagnosis	Number	Percentage
Lymph node	Tuberculosis	26	13.76
	Malignancy	23	12.17
	Reactive hyperplasia	15	7.94
Pancreas	Malignancy	21	11.11
	Chronic pancreatitis	7	3.70
Stomach	Malignancy	12	6.35
	Reactive hyperplasia	1	0.53
Esophagus	Malignancy	5	2.64
Miscellaneous	Liver tumour	2	1.06
	Retroperitoneal sarcomas	2	1.06
	Non-diagnostic/inadequate	22	11.64
	FNAC not done/indicated	47	24.86
	Missing	6	4.17
Total		189	100

FNA was done in 142 patients out of 189. Tuberculosis was seen in 26 patients and malignancy was present in 23 patients in whom FNAC was done for enlarged lymph nodes. These were metastatic adenocarcinoma in 8, lymphoproliferative disorder in 7, metastatic squamous cell carcinoma in 5, small cell carcinoma in 2 and anaplastic in 1. Pancreatic tumours were adeno-carcinoma in 16 out of 36 FNAC done for pancreatic masses, poorly differentiated carcinoma in 3 and neuroendocrine tumour in 2. Seven patients out of 36 had changes consistent with chronic pancreatitis and eight were non-diagnostic.

Stomach tumours were found in 12 out of 17 FNAC done for stomach tumours, and included 5 lymphomas, 3 GIST, 2 carcinoids, 1 metastatic choriocarcinoma and 1 adenocarcinoma.

FNAC was not done in 47 cases. These were patients referred for therapeutic procedure, staging or where clinically suspected pathology was not found on EUS, or procedure was technically incomplete or unsafe. Non-diagnostic aspirate was defined as atypical or scanty cells lacking clear histological diagnosis. These cases were followed-up including repeat EUS and other procedures as indicated and two of them turned out to have lymphoma, one on cervical lymph node biopsy and second on thorocoscopy.

Rectal EUS was done in one patient with carcinoma prostate having growth in rectum. Therapeutically, three celiac blocks and one pseudocyst drainage were done. None of the patients had complications of haemorrhage or pancreatitis after FNA.

DISCUSSION

Endoscopic ultrasound is now widely accepted technique to establish the identity of masses/suspicious lesions detected in almost any location in gastrointestinal tract and surrounding organs including

enlarged lymph nodes. By virtue of its diagnostic accuracy, especially with FNAC and safety profile, EUS had been superior to many currently available imaging modalities and biopsy/FNAC options.

Evaluation of suspected lymph nodes enlargement were the major indication for EUS in this study and malignancy and tuberculosis common underlying aetiology. Several similar studies had used EUS guided transmural FNA of lymph nodes adjacent to gastrointestinal tract to establish cytopathological diagnosis. Wiersema *et al.* demonstrated that EUS guided FNA biopsy was diagnostic in 07 patients with mediastinal lesions, in which visualization by CT was not possible or prior non-surgical biopsy techniques were unsuccessful.[13] Silvestri *et al.* reported 89% accuracy for EUS guided FNA of abnormal mediastinal lymph nodes enlargement.[4] Similarly, Ravens *et al.* demonstrated malignancy in 9 out of 16 patients, evaluated for mediastinal masses, in the remaining 7 patients, the aspirated samples revealed a benign lesion including tuberculosis.[14] Similarly, the assessment of regional and distant lymph nodes in a patient with a gastrointestinal malignancy had always been critical in the staging process. EUS features suggestive of malignant lymph nodes had included size greater than or equal to 1 centimeter, hypoechoic echotexture, rounded shape and well-defined borders. Use of EUS guided FNAC enhanced the ability to differentiate benign from malignant infiltration and should be considered in all patients with suspicious lymph nodes prior to surgery.

The most important application of EUS in hepatobiliary disease included visualization and staging of obstructing pancreatic or distal biliary neoplasms with the simultaneous capacity for EUS ultrasound-guided fine-needle aspiration for cytologic diagnosis. It was the second largest indication in this study after lymph node evaluation with pancreatic adenocarcinoma being the major underlying cause. This is similar to another study by Fabbri *et al.* in Italy, who performed EUS in 210 patients in 3 years following abnormal pancreatic imaging and 139 had FNA with cytopathology results of pancreatic adenocarcinoma in 79.[15] They concluded that EUS/FNA is minimally invasive and highly accurate for tissue diagnosis in solid pancreatic tumours. Similarly, Touchefeu *et al.* from France reported that EUS/FNA was able to provide definite histological evidence of malignancy in 33 out of 70 patients with suspicion of pancreatic cancer over 2 years.[16] EUS has an important role in guiding a biopsy needle into lesions that are too small to be identified by CT/MRI or too well encased by surrounding vascular structures to safely allow percutaneous biopsy.

Chang *et al.* in a series of 44 patients demonstrated that EUS-FNA had an accuracy rate of 95% for pancreatic lesions and 88% for lymph nodes and reduced the number of unnecessary surgical explorations by identifying patients with surgically incurable disease.[17]

EUS can also detect biliary obstruction, with a sensitivity and specificity that are comparable with those of Magnetic resonance cholangiopancreatography with additional advantage of FNAC.[18-20] EUS may be most useful in circumstances in which the patient is felt to be at high risk for complications of endoscopic retrograde or percutaneous transhepatic cholangiography.

Evaluation of gastric malignancy was the third major group in this study. EUS is superior to CT in determining the depth of wall invasion by gastric carcinoma. It can also detect perigastric spread and local lympha-denopathy that may not be apparent on CT. EUS has demonstrated 83-88% accuracy for determining depth of invasion compared with 35% accuracy for CT. For determining nodal involvement, EUS is 66-72% accurate compared with 45% accuracy for CT.[21] EUS can distinguish lymphoma from carcinoma. It is a useful technology for evaluating possible GIST lesions due to their submucosal localization and recent studies have worked out characteristics for differentiating features suggestive of benign or malignant behaviour in GIST.[22,23] Although, EUS is safe modality but still diagnostic EUS carries the same risks of sedation, and perforation as diagnostic endoscopy. The addition of FNA to EUS has introduced the potential for additional complications of hemorrhage, infection and pancreatitis. Bleeding due to EUS-FNA is rare but can be lethal, if a major vessel is lacerated.[24] This complication has not been reported with linear array ultrasound endoscopes that are currently used for FNA. However, pancreatitis following EUS-FNA of the pancreas has been reported in less than 1% of cases.[25] None of these patient had pancreatitis following the procedure which is comparable to another study by Fabbri *et al.*[15]

Therapeutic procedures were few in this study. Rectal EUS was done in only one patient. Similarly, staging of chest malignancy before surgery was not referred. Pre-surgical down-sizing and follow-up EUS is another underutilized area in the local set-up, which can be improved by increased awareness and utilization of EUS.

CONCLUSION

The main pathology of mediastinal and celiac nodes in the studied cases were metastatic malignancy and tuberculosis. Pancreatic evaluation was another common cause for asking EUS and adenocarcinoma was the most frequent finding. The diagnostic yield of malignancy at this centre was well within accepted rates reported in literature. Therapeutic indications were limited.

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