**Original Article**

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# The Diagnostic Accuracy of Endoscopic Ultrasound-Guided Fine Needle Aspiration in Patients with Endoscopic Biopsy Negative Upper Gastrointestinal Lesions

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*[1,2,3] Substantial contributions to the conception or design of the work, Data collection , Review the study*
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**ABSTRACT**

**Objective:** To determine the diagnostic accuracy of endoscopic ultrasound guided (EUS) fine needle aspiration in patients who had inconclusive endoscopic biopsies of the same lesion.

**Methodology:** This retrospective study was conducted at Pak Emirates Military Hospital, Rawalpindi, Pakistan from January 2018 to July 2020. Patients who underwent EUS guided FNAC were screened. The FNAC results of patients satisfying the inclusion criteria were compared with either a surgical biopsy in patients in whom surgeries were done, while in the remaining patients, EUS FNAC results were compared with a 3 months radiological and/or 6 months clinical follow-up.

**Results:** The final diagnosis was defined based on the following criteria: (1) Malignant lesions (n=36), histopathologic diagnosis obtained based on surgery resected samples (n=18) or clinical diagnosis as neoplasm based on clinical follow-up of symptoms (n=30) or radiologic diagnosis based on imaging follow-up at 3 months (n=13) (2) Benign lesions (n=18), benign cytopathologic histopathologic findings and clinical follow-up with no evidence of malignant progression or metastasis. EUS-guided FNA cytology turned out to be malignant in 60 percent (n=36) of the specimens. 30 percent of the samples showed benign epithelial cytology (n=18) while in 10 percent of the cases (n=6), the tissue samples were deemed insufficient for cytological diagnosis. The accuracy came out to be 66.6 percent (n=10 were true negative), sensitivity 93.4 percent, and specificity 100 percent.

**Conclusion:** EUS guided-FNA cytology of the sub-mucosal upper GI lesions is highly sensitive and specific for upper GI lesions, which are negative on endoscopic biopsies.

**Keywords:** Endoscopic ultrasound (EUS), Fine needle aspiration cytology (FNAC), Diagnostic accuracy

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## Introduction

Certain gastrointestinal lesions like sub-mucosal stromal tumors, including (gastrointestinal stromal tumor (GIST), carcinoid tumors, lipomas, and diffuse gastric adenocarcinoma and lymphoma) are difficult to detect using traditional endoscopic forceps biopsies due to the tumor's position in deeper layers of the gastrointestinal tract.[1,2] About half of these deeper lesions are false negative on endoscopic biopsies. The yield of traditional forceps guided endoscopic biopsies can be enhanced if the endoscopist uses large, jumbo size forceps or, bite on bite technique or cold snare bulging lesions. Even with these techniques, the diagnostic yield of such lesions has been reported to be as low as 40%.[3] Furthermore, these approaches may increase the risk of bleeding and

perforation. Doctors must collect pathologic information in order to develop treatment protocols and make prognosis determinations. Endoscopic ultrasound-guided fine needle aspiration (EUS-FNA) was introduced into clinical practice in the 1990s, and it quickly displaced invasive risky procedures such as laparotomy and laparoscopy.

While histology is the "gold standard" for differentiating the various forms of subepithelial lesions, this assessment can only be performed using invasive techniques such as endoscopic mucosal resection, fine needle aspiration (FNA), or surgical resection. For the diagnosis of such lesions, newer, less invasive diagnostic methods have become available. Endoscopic ultrasound-guided fine-needle aspiration (EUS guided FNA) of gastrointestinal tract lesions is one such method that is thought to have a high diagnostic yield.[4-6] Limited studies have been done to evaluate the diagnostic accuracy of EUS guided FNA for submucosal upper GI lesions. EUS alone has also been used to study these lesions. Castro et al[7] found EUS alone to be extremely valuable in the initial diagnosis of subepithelial lesions, with 45 percent of patients requiring no additional testing.

EUS is a newer modality in Pakistan. Studies involving EUS-guided FNA for aiding in diagnosis of subepithelial lesions are lacking. Therefore, we conducted this study to evaluate the diagnostic yield of ultrasound-guided fine-needle aspiration in patients with endoscopic biopsies of the same lesions that were indeterminate.

# Methodology

This retrospective study was conducted at Pak Emirates Military Hospital, Rawalpindi, Pakistan from Jan 2018 to July 2020 after the hospital ethical committee's approval.

All those patients above 18 years of age who underwent EUS guided FNAs of the lesions due to negative endoscopic forceps biopsy were enrolled in the study after taking informed consent. The sample size was calculated using the following formula[8] taking expected sensitivity as 87.3% with $\alpha = 0.05$ ; $\beta = 0.2$ and $\delta$ as 0.13 and came out to be at least 60 patients for this study.

For patients in whom the endoscopic forceps biopsy was diagnostic, EUS-FNA of the same lesion was not done and were excluded. Similarly, those patients with no surgical, radiological, or clinical outcome were also excluded from the study. In all patients, endoscopic forceps biopsies were taken with Cook, Olympus, or Pentax biopsy forceps, and more than five pieces were taken by a consultant gastroenterologist using a standard gastroscope (Olympus). The EUS-FNA examination of all patients was performed by one endo-sonographer using a linear probe echo-endoscope (Olympus) and a 22-gauge FNA needle (Cook). All the FNA samples were evaluated by rapid on-site specimen evaluation (ROSE) by a consultant cytopathologist. Furthermore, during the EUS examination, the lesion site, layer of origin, texture, tissue adequacy for FNA, and procedure-related complications were assessed. Figure 1a depicts an endoscopic view of such a lesion and figure 1b and 1c show EUS images of the same lesion and FNA needle in real time for obtaining the tissue sample. Figure 2 shows a cell block of an EUS-guided FNA sample while figure 3a and 3b show the histopathology of the surgically resected sample of the same lesion, confirming the diagnosis.

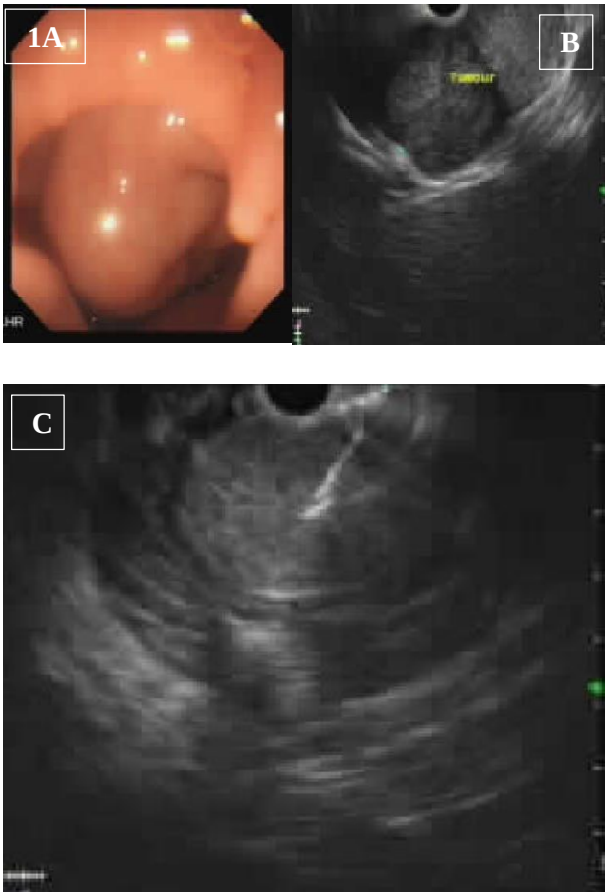


**Figure 1A, B and C: 1 A. endoscopic view of submucosal lesion, B: EUS showing same lesion, C: FNA needle inserted for cytology.**

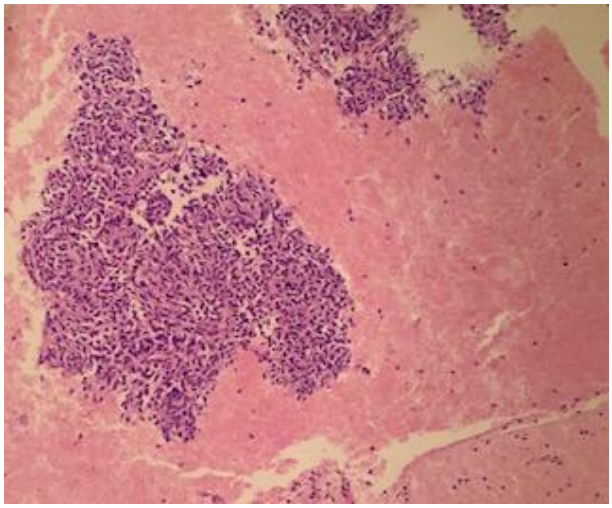

**Figure 2. Cell Block of EUS guided FNA, H&E 200X (clusters of spindle cells with uniform nuclei).**

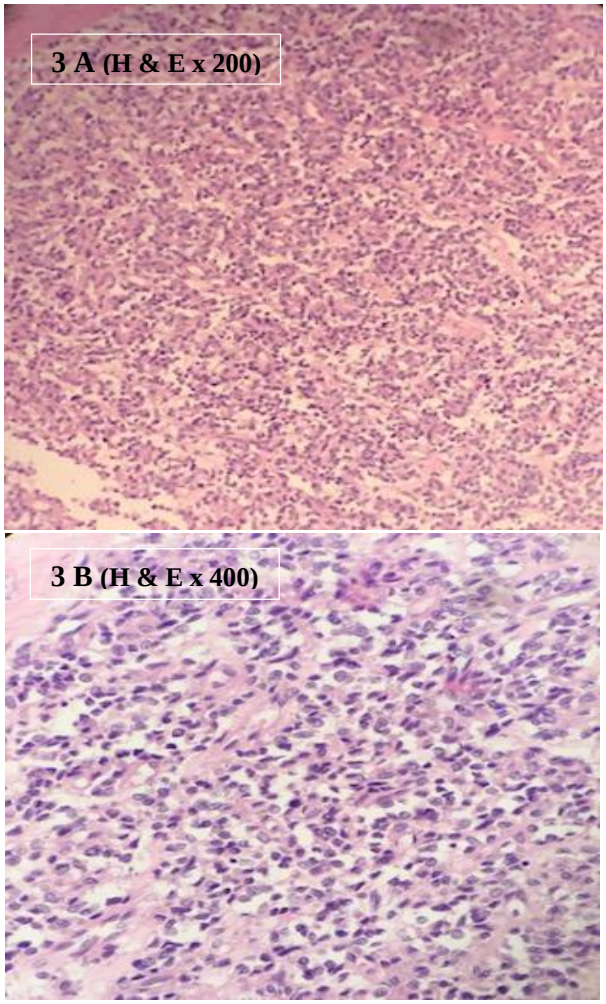


**Figure. 3A&3B (surgical specimen): H&E stained sections show spindle and epithelioid tumour cells with eosinophilic cytoplasm and predominantly uniform nuclei.**

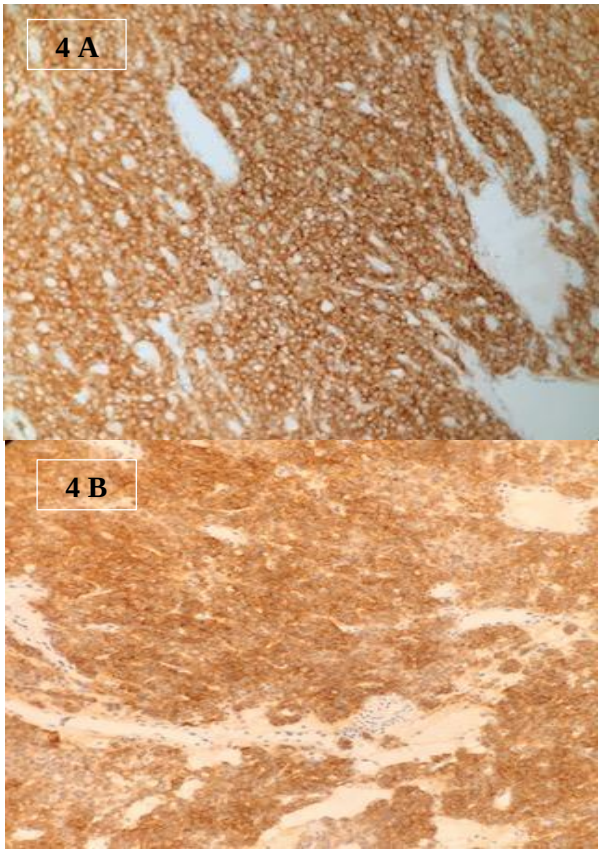


**Fig. 4a DOG1 immunohistochemical stain, 200X, 4b: CD117 immunohistochemical stain, 200X**

The demographics, including age, gender, clinical presentation, endoscopic appearance, endoscopic ultrasound appearance, and cytology, were studied.

The patients were then followed, and EUS-FNA cytology outcomes were compared with either a surgical biopsy in patients in whom surgeries were done, while in the remaining patients, EUS FNA results were compared with a 3 months' radiological and/or 6 months' clinical follow-up.

Statistical analysis was carried out using the SPSS software (version 20.0; SPSS, Chicago, IL, USA). Continuous variables were stated as a mean ± standard deviation, and categorical variables were computed as frequencies and percentages. Sensitivity, specificity, positive and negative predictive values were calculated manually.

## Results

We screened a total of 860 patients who underwent EUS-FNA; 60 patients met the inclusion criterion and were included in the report. The mean age of the participants was 51.75 years (range 18-80). 70% (n=42) of the

participants were male, and the most frequently seen clinical presentation was abdominal pain in 40% (n=24), accompanied by dysphagia in 33.3 percent (n=20), as seen in Table 1.

30% (n=18) of patients had esophageal lesions, 66.7 percent (n=40) had gastric lesions, and 3.3 percent (n=2) had duodenal lesions. On EUS 33.3% (n=20) of patients had a mass lesion, 30% (n=18) had thickened GI tract mucosa, 10% (n=6) had heterogeneous mass, 10 % (n =6) had homogenous mass appearance as reported in Table I.

**Table I: Descriptive statistics**

| Variable | **Frequency N (%)** |
|---|---|
| Age (mean ± SD*) | 51.75 ± 17.68 |
| Gender | |
| Female | 18 (30.0%) |
| Male | 42 (70.0%) |
| Clinical presentation | |
| Dysphagia | 20 (33.3%) |
| Vomiting | 16 (26.7%) |
| Abdominal pain | 24 (40.0%) |
| Location of lesion | |
| Esophageal | 18 (30%) |
| Gastric | 40 (66.7%) |
| Duodenal | 2 (3.3%) |
| Layers of origin | |
| Submucosa | 18 (30.0%) |
| Muscularis | 4 (6.7%) |
| Transmural | 14 (23.3%) |
| Extrinsic | 6 (10.0%) |
| Intrinsic | 2 (3.3%) |
| Mucosa | 16 (26.7%) |

EUS-FNA cytology revealed malignancy in 60% (n=36) of samples. In 30% (n=18), benign epithelial cytology was observed, while in 10% (n=6), the tissue samples were deemed insufficient for cytological diagnosis (Table II).

**Table II: EUS-FNA cytology diagnosis**

| Variable | **Frequency N (%)** |
|---|---|
| Cytology diagnosis | |
| Benign | **18 (30.0%)** |
| Benign epithelial cells | 14 (23.4%) |
| Candidiasis | 2 (3.3%) |
| Lipoma | 2 (3.3%) |
| Malignant | **36 (60.0%)** |
| Keratinizing SCCA* | 2 (3.3%) |
| Primary lung Adeno CA** | 2 (3.3%) |
| SCCA* | 6 (10.0%) |
| GIST*** | 14 (23.3%) |
| DLBCL~ | 2 (3.3%) |
| Adeno CA** | 10 (16.8%) |
| Inadequate tissue for diagnosis | **6 (10.0%)** |

***Squamous cell carcinoma, ** Carcinoma, *** Gastrointestinal stromal tumor, Diffuse large B-cell lymphoma.**

The final diagnosis was defined based on the following criteria: (1) Malignant lesions (n=36), histopathologic diagnosis obtained based on surgery resected samples (n=18) or clinical diagnosis as neoplasm based on clinical follow-up of symptoms (n=30) or radiologic diagnosis based on imaging follow-up at 3 months (n=13) (2) Benign lesions (n=18), benign cytopathologic histopathologic findings and clinical follow-up with no evidence of malignant progression or metastasis. The EUS-FNA cytology was compared with the gold standard surgical biopsies in 30% (n=18), 17 out of 18 patients' surgical specimen diagnoses were in agreement to the EUS-FNA cytology, while one patient had inadequate tissue on EUS-FNA. Imaging was suggestive of GIST in this patient, and upon surgical excision, GIST was confirmed. 50 % (n=30) of the patients had clinical follow up at 6 months while radiological follow up at three months was available in 43% (n=13) of the patients.16 % (n=5) of the patients were lost to follow up. 10 patients, who had malignant FNA cytology, had progressive disease on follow up CT at three months, as well as clinically after 6 months. Two patients had benign FNA cytology, remained stable on follow-up CT as well as clinically, while one patient had inadequate EUS-FNA sample. Among the patients who were lost to follow up, one had adenocarcinoma of pulmonary origin; one had candidiasis, one revealed benign epithelial cytology and in one patient, the sample was not adequate.

The diagnostic yield was 66.6% (n=10 were true negative). Sensitivity was 93.4 %, while specificity was 100%. Positive predictive value came out to be 100% and negative predictive value was 82.1%, as shown in Table III.

**Table III: Outcomes of endoscopic ultrasound- fine needle aspiration**

| Variable | **Frequency N (%)** |
|---|---|
| Sensitivity | 93.4% |
| Specificity | 100.0% |
| Positive predictive value | 100.0% |
| Negative predictive value | 82.1% |
| Diagnostic Yield | 66.6% |

# Discussion

EUS guided-FNA is now considered a gold standard for pancreatic mass lesions, abdominal and mediastinal lymph nodes, because of its high, sensitivity, specificity, diagnostic yield and overall safety. Extensive work has been done on this, and is available in the literature.[9-14]

Certain sub-mucosal upper GI lesions like GIST, schwannoma, lipoma, lymphoma, and adenocarcinoma are located in deeper layers. They are usually stenotic, and thus, are difficult to diagnose with conventional endoscopic forceps biopsies, which have a very high false-negative rate, necessitating more invasive surgical biopsies for tissue diagnosis.[1-3] Previous studies done on EUS-FNA for submucosal upper GI lesions have shown variable results.

Wu A et al.[15] described the diagnostic yield of EUS to be 60%, while H.J. Sung et al.[16] reported a diagnostic yield of 87 %. In literature limited work has been done to assess the usefulness and diagnostic accuracy of EUS guided FNA in upper GI lesions which are negative on endoscopic forceps biopsies. We, therefore, conducted this study to find the diagnostic yield, sensitivity, specificity, positive and negative predictive values, as well as the complications associated with the procedure.

The outcomes of our study showed a diagnostic yield of 66.6% (n=10 were true negative). Sensitivity was 93.4 %, while specificity was 100%. The positive predictive value came out to be 100% and negative predictive value was 82.1%. None of the patients had any procedure-related complications like bleeding, perforation or infection. The results of our study were highly comparable with the other two studies published in literature, having similar objectives. H.H. Okasha et al. reported sensitivity of 96.8%, specificity of 89.1%, PPV of 92.4%, NPV of 95.3%, and accuracy of 93.6%.[17] And similarly, Zargar *et al*. in a large study concluded that the diagnostic accuracy of EUS-FNA (94%) was significantly greater than the accuracy of endoscopic mucosal forceps biopsy (87%).[18]

All of our patients who underwent EUS guided FNA had ROSE by a consultant cytopathologist, which increases diagnostic yield by up to 20 %. This also lowers the chances of inadequate tissue sampling and reduces the overall time of procedure by making limited numbers of passes.[19-21]

30%(n=18) patients had surgical resection of a tumor and the histopathology results when compared with EUS FNA, the tissue diagnoses were similar in 88.88% (n=8) patients and one had an inadequate sample on EUS FNA, which came out to be a GIST on surgical specimen. Similarly the clinical and radiological follow up was also highly compatible with EUS guided-FNA cytology diagnosis. This concluded that EUS guided-FNA cytology of the sub-mucosal upper GI lesions is highly sensitive and specific in diagnosis. Additionally, ROSE increased the diagnostic outcomes. The retrospective nature and relatively small sample size are the main limitations of our study.

# Conclusion

For upper GI lesions, which are negative on endoscopic biopsies, EUS FNA should be considered as the procedure of choice owing to its high specificity and sensitivity.

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