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Research Article

# Diagnostic Utility of Endoscopic Ultrasound-Guided Fine Needle Aspiration (EUS-FNA) Biopsy in Evaluating Primary and Metastatic Gastrointestinal Stromal Tumors (GIST)

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## Abstract

**Introduction:** GIST is the most common gastric mesenchymal tumour and is diagnosed on the basis of a combination of clinical and radiological features, with biopsy being considered the gold standard. EUS-guided FNA is a minimally invasive procedure which, in combination with rapid on site evaluation or ROSE, is increasingly being utilized to diagnose lesions within and around the gastrointestinal tract, and of the pancreas. In this study we aim to evaluate our experience in patients who were diagnosed with GIST on EUS-FNA.

**Material and Methods:** Thirteen patients [7 males, mean age 52 years] diagnosed with primary or metastatic GIST were diagnosed on EUS-FNA from January 2005 to June 2017 at Shaukat Khanum Memorial Cancer Hospital and Research Centre, Lahore, Pakistan were included in the study. Lesions were assessed using an Olympus linear array echo-endoscope. In each case part of the sampled material obtained using a 22-gauge EUS-FNA needle was smeared on glass slides, air-dried and then stained with Diff-Quik® stain for ROSE. One glass slide with smear was immediately dropped in 95% alcohol for Papanicolaou stain and the rest of the specimen was submitted for cell block in CytoLyt®. A trained cytopathologist was present in the procedure room for ROSE on Diff-Quik® stained slides. All slides and cell blocks were thoroughly examined and immunohistochemical (IHC) stains (CD117, DOG1, S100, Desmin and CK) were performed on the cell block material.

**Results:** The average size of the primary tumor in this study was 66.4 mm (range 30-120 mm) while metastatic tumors measured 15 mm each. Twelve tumours showed spindle cell morphology with only one mixed type. Mitoses were less than 5/10 HPF and no necrosis was seen. CD117 and DOG 1 were expressed in all thirteen cases.

**Conclusion:** Combining ROSE and IHC on cell-block material plays a vital role in confirming the diagnosis in both primary and metastatic GIST. Radiological findings can aid in risk assessment by documenting size and site. The diagnosis of GIST can be made confidently using EUS-FNA, even in resource-constraint settings.

**Keywords:** GIST; EUS-FNA; ROSE

## Introduction

Endoscopic ultrasound-guided fine needle aspiration (EUS-FNA) biopsy is a minimally invasive procedure which is commonly used for sampling submucosal lesions of the gastrointestinal (GI) tract, intraabdominal lymph nodes (coeliac, perigastric and porta hepatis) and pancreatic or peripancreatic masses. It has better diagnostic yield than endoscopic forceps biopsy, ultrasound (US) guided or EUS guided Trucut biopsy (TCB) especially when combined with rapid onsite evaluation (ROSE) [1-3].

GIST is the most common mesenchymal tumor of the GI tract, often found in a submucosal location, although intramural or extramural locations are not uncommon. The stomach is the most frequent site of involvement followed by the ileum, duodenum and rectum. GIST's may also present in a retroperitoneal location [5,6].

These lesions originate from the interstitial cells of Cajal or stem cell-like precursors and commonly show KIT and PDGFRA mutations, with occasional additional rare mutations. KIT (CD117) and DOG-1 immunohistochemical stains are commonly expressed markers. Histological features range from spindled to epithelioid morphology with respective architechural patterns [7-9].

Clinically these tumours can present with upper GI bleeding, manifested as either haematemesis or melaena, or both, with abdominal distention or with mass-effect. They have malignant potential irrespective of their site or size, with risk assessment being based upon location, size and mitotic count [10,11].

Complete surgical excision is the mainstay of treatment for GIST's. However, patients with unresectable tumours or distant metastases are usually offered KIT/PDGFRA tyrosine kinase Inhibitors (TKI's), such as Imatinib. Imatinib is an agent with activity against BCR-ABL, KIT and PDGFR alpha. Constitutive activation by mutated KIT is the hallmark of GIST. Imatinib inhibits KIT and can produce a partial or complete response. Availability of this targeted therapy makes accurate diagnosis essential [12-16].

Before the advent of EUS-FNA, diagnosis of GIST was made on surgical resection specimens or endoscopic biopsy. The diagnostic yield of endoscopic biopsy is limited due to the frequent submucosal or intramural location of this tumour [17-22]. The diagnostic accuracy of EUS-FNA is significantly improved by ROSE, which allows the pathologist to assess the sample in real time for adequacy, while also ensuring that additional tissue material can be obtained for ancillary studies, if required [23-27].

## Material and Method

This is a retrospective study which includes thirteen patients diagnosed with either primary or metastatic GIST on EUS-FNA from January 2005 to June 2017. Records for these patients were retrieved from the electronic medical record system of Shaukat Khanum Memorial Cancer Hospital and Research Centre, Lahore, Pakistan.

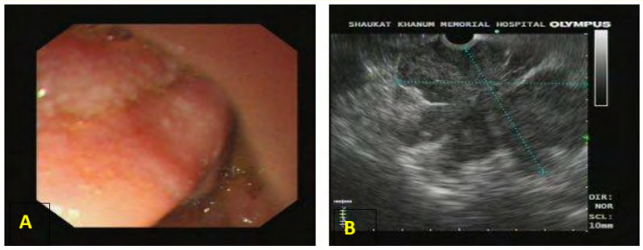



**Figure 1:** 1A: Endoscopic image of submucosal polyp within stomach. 1B) EUS showing a heterogenous hypoechoic lesion.

Lesions were initially evaluated using an Olympus linear array echo-endoscope (Figure 1A and 1B), after which a 22-guage EUS-FNA needle was used to obtain material for cytologic analysis, using a fanning technique, so as to sample all parts of the lesion. Using a small portion of the specimen from each pass, two smears were prepared, one smear was air dried and stained with Diff-Quik® stain for ROSE, the other smear was immediately fixed in 95% alcohol for Papanicolaou stain. The remaining specimen was submitted for cell block in CytoLyt®. A trained cytopathologist assessed the sampled material for specimen adequacy, initial diagnosis and need for ancillary studies.

All slides and cell blocks were analyzed and immunohistochemical (IHC) stains (CD117, DOG1, S100, Desmin and CK) were performed on the cell block material. IHC stain methodology is shown in table 1.

Clinical records for each were reviewed for presenting complaints, history of previous endoscopic or CT- guided trucut

| Antibody | CD 117 | DOG-1 | S 100 | Desmin | CK |
|---|---|---|---|---|---|
| Clone | Polyclonal | sp 31 | Polyclonal | DE-R-11 | AE1\ AE3 |
| Manufacturer | Dako | Roche | Roche | Roche | Leica |
| Dilution Method | 1: 400 | Ready to use | Ready to use | Ready to use | Ready to use |
| Antigen Retrieval | Heat-induced epitope | Heat-induced epitope | Heat-induced epitope | Heat-induced epitope | Heat-induced epitope |
| Buffer | EDTA; pH, 8.0 | EDTA; pH, 8.0 | EDTA; pH, 8.0 | EDTA; pH, 8.0 | EDTA; pH, 8.0 |
| Detection instrument | Bond Polymer | Ultraview DAB | Bond Polymer | Bond Polymer | Bond Polymer |
| Autostainer | Bond III | Ventana Benchmark XT | Bond III | Bond III | Bond III |
| Blocking Agent | $H_2O_2$ | $H_2O_2$ | $H_2O_2$ | $H_2O_2$ | $H_2O_2$ |

**Table 1:** Immunohistochemical stains methodology.

biopsies, neoadjuvant Imatinib therapy, surgical resection and patient follow up. All cases were correlated with pre-operative abdominal CT/ MRI scan and EUS for risk assessment (size and location). In addition, histological correlation was available in four cases.

## Results

### Clinical and radiological aspects

The records of thirteen patients (7 males and 6 females; mean age 52y, range 30-72 years) were reviewed. Patient details and clinical data are summarized in table-2. Barium meal examination suggested gastric submucosal lesions in six cases. Three cases were incidentally found on follow-up scans for pre-existing conditions including a case of endometrial cancer with a mass involving the greater curve of the stomach, a patient with laryngeal carcinoma presenting with a mass involving the duodenum and a patient with a history of menorrhagia who had an incidental mass adherent to the pancreatic head on CT abdomen and pelvis (Figure 2). Two cases of metastatic GIST were diagnosed, involving the abdominal wall and subcarinal lymph nodes. There were two patients who presented with huge abdominal masses arising from the ileum and retroperitoneum, respectively.

The average size of the primary tumor was 66.4 mm (range 30 – 120 mm) while metastatic tumours measured 15 mm each.

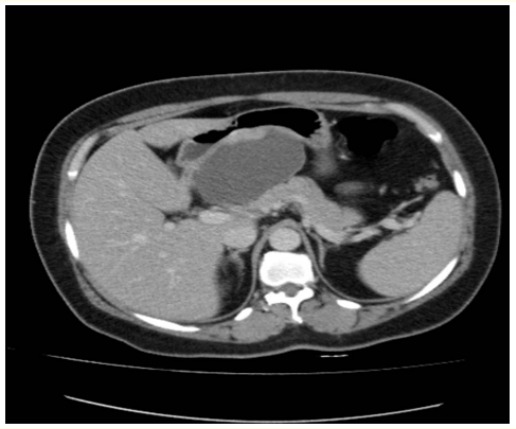


**Figure 2:** CT scan of the abdomen showing a cystic mass with a solid component attached to the pancreatic body.

Except for two gastric submucosal lesions which appeared homogenous, the remaining primary tumours had a heterogeneous echo-texture.

### Cytomorphological and Immunohistochemical findings

A preliminary diagnosis of spindle cell neoplasm with a probable differential of a GIST was made in 8 cases (61.5%). These included six gastric lesions, one duodenal lesion and an incidental abdominal wall nodule with a known history of GIST. Parameters recorded on Diff-Quik®, Pap-stained slides and H&E of cell block are shown in table-3. The majority of the smears (Diff-Quik® and Pap-stained) were hypercellular, comprising tight aggregates

with occasional discohesive tumour cell clusters. Cytomorphology showed uniform spindle-shaped cells with moderate cytoplasm and oval hyperchromatic nuclei showing a streaming effect (Figure 3A and 3B). One case exhibited a mixed spindled and epithelioid morphology (Figure 3C and 3D). Magenta colored fibrillary acellular material was also noted in the background of tumour nests (see Figure 5A). No necrosis or cytological atypia was noted. Cell blocks also showed similar morphology. Mitotic count was estimated on cell block sections (Figure 4A and 4B).

C-Kit (CD117) and DOG1 IHC stains showed strong cytoplasmic staining in tumour cells in all cases (Figure 5C and 5D). There was no immunoreactivity noted for S100, Desmin or Cytokeratin stains.

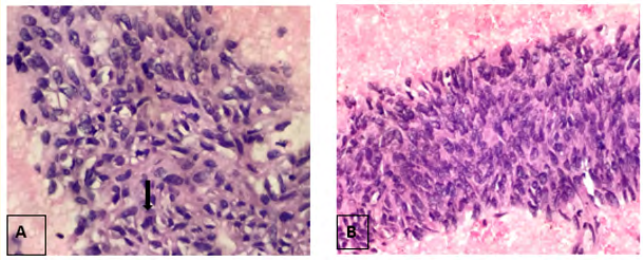



**Figure 4:** A) Cell block showing spindle cells with indistinct cytoplasm and darkly stained nuclei. Mitotic activity shown by black arrow. H&E, x 40 B) Cell block showing mixed spindle and epithelioid morphology. H&E, x 40.

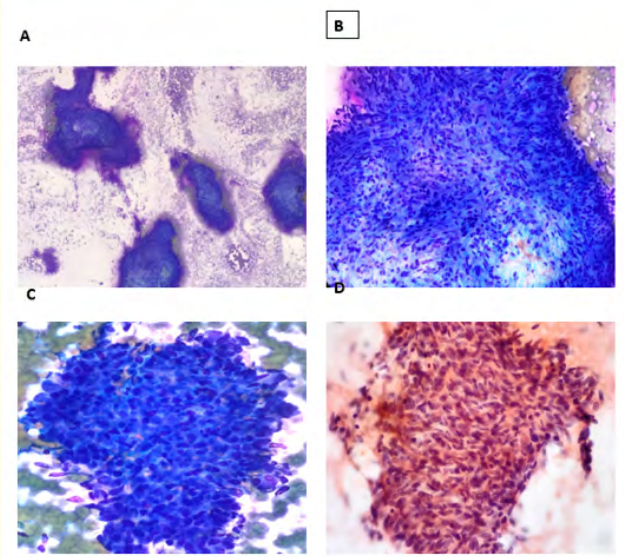



**Figure 3:** A) Markedly cellular smears showing large tumour nests. Diff-Quik® staining x 4. B) Spindle shaped tumour cells arranged in short fascicles with streaming effect. Diff-Quik® staining x 20. C&D) Mixed spindle and epithelioid cell morphology (Diff-Quik® and Pap staining x 40).

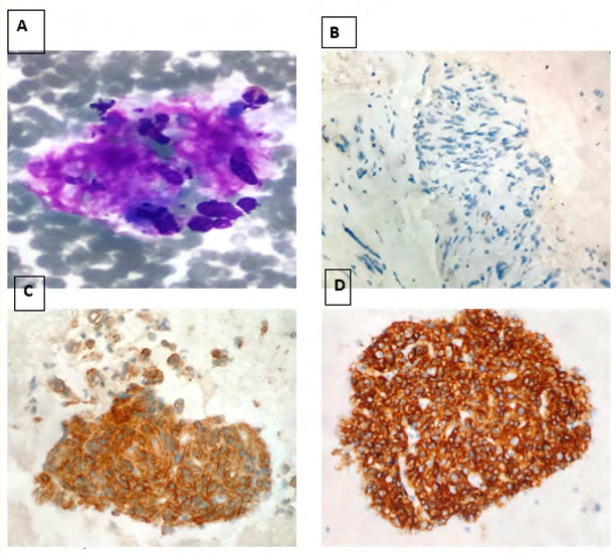
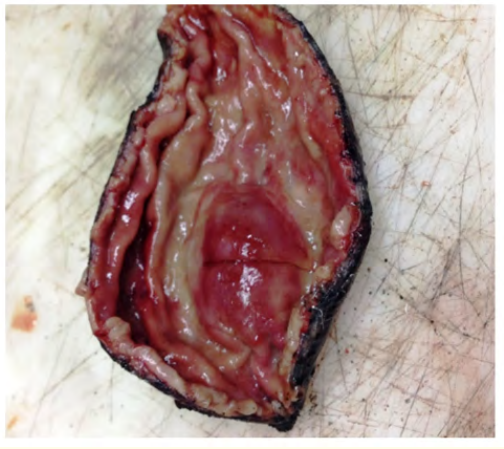



**Figure 5:** A) Smear showing fibrillary magenta coloured metachromatic material admixed with tumour cells. Diff-Quik® x 40 B) Negative SMA Stain C&D) Immunoreactivity of DOG 1 and CD117 stains performed on cell block sections x 40.

Four patients underwent subsequent surgical resection and were correlated with morphology, mitotic count and IHC findings (Figure 6 and 7). Mitotic count (<5/20HPF) was similar in all four surgical excision specimens. Size was correlated with preoperative radiology.



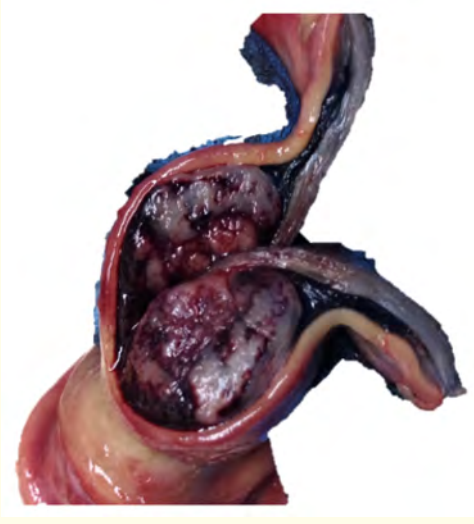


**Figure 6:** A) Gastric wall with a submucosal polyp B) Cross section of the gastric submucosal polyp showing a reddish-brown lesion with a lobulated cut surface.

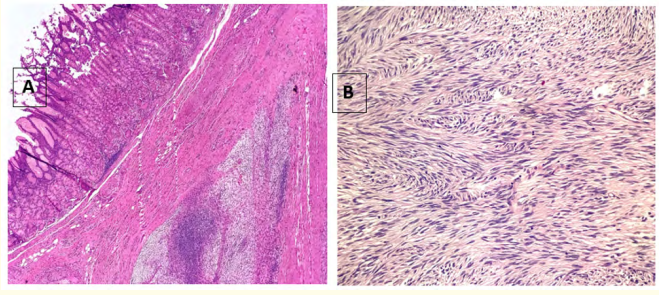



**Figure 7:** A) Gastric submucosal spindle cell lesion. H&E x 4 B) Spindle cells arranged in intersecting bundles and fascicles. H&E x 20.

## Patient follow up

Two patients were diagnosed in 2010 with GIST in the ileum and retroperitoneum. Both died during the initial stages of management. Neoadjuvant Imatinib therapy (oral dose 400mg once daily) was started in four patients diagnosed between 2012 and 2014, none of whom underwent surgical resection. Two of these had high-risk disease and metastases at presentation, and died within a year. The other two are still alive and on regular follow-up.

Two patients were diagnosed in 2017 with submucosal GIST and are currently on follow-up. Five patients have been lost to follow-up.

| Age/Sex | Clinical presentation | Site | Location | Ultrasonographic appearance | Size(EUS) mm |
|---|---|---|---|---|---|
| 45/F | Melaena | Stomach (Antrum) | Muscularis propria | Homogenous echotexture | 50 x 33 |
| 30/M | Epigastric burning and melaena | Stomach (Antrum) | Muscularis propria | Heterogeneous echotexture | 57 x 43 |
| 33/M | Palpable left hypochondrial mass | Duodenum | Muscularis propria | Heterogeneous echotexture | 67 x 62 |
| 58/M | Melaena and weight loss | Stomach (Antrum) | Muscularis propria | Heterogeneous echotexture | 70 x 67 |
| 44/F | Incidental mass on imaging | Pancreas (Head) | Peripancreatic tissue | Cystic with solid nodule | 57 x 49 |
| 71/F | Incidental mass on imaging | Stomach (fundus) | Muscularis propria | Heterogeneous echotexture | 30 x 25 |

| | | | | | |
|---|---|---|---|---|---|
| 63/F | Abdominal distention | Ileum | Muscularis propria | Heterogeneous echotexture | 120 x 100 |
| 72/M* | Chronic cough | Subcarinal lymph node | Cortex | Hypoechoic node | 15 x 10 |
| 59/F | Incidental | Stomach (Antrum) | Muscularis propria | Homogenous echotexture | 60 x 57 |
| 61/F* | Incidental nodule on imaging | Abdominal wall | Rectus muscle | Hypoechoic nodule | 15 x 15 |
| 62/M | Abdominal mass | Retroperitoneum | Peripancreatic tissue | Heterogeneous echotexture | 80 x 75 |
| 48/M | Abdominal distention | Ileum | Muscularis propria | Heterogeneous echotexture | 95 x 90 |
| 30/M | Epigastric mass | Stomach (Antrum) | Muscularis propria | Heterogeneous echotexture | 45 x 40 |

**Table 2:** Clinical Data of patients with primary and metastatic lesions of GIST.

*Cases with asterisks were diagnosed as metastatic lesions.

| | | |
|---|---|---|
| Cellularity | Marked<br>Moderate<br>Mild | 8 (61.6%)<br>4 (30.8%)<br>1 (7.6%) |
| Cell shape | Spindle<br>Epithelioid<br>Mixed | 12 (92.3%)<br>0<br>1 (7.7%) |
| Necrosis | Present<br>Absent | 0<br>13 |
| Mitoses* | Less than 5<br>5 to 10<br>More than 10 | 13<br>0<br>0 |
| Metachromatic material | Present<br>Absent | 8 (61.6%)<br>5 (39.4%) |

**Table 3:** Cytomorphological features assessed on smears and cell block material.

*Mitoses were counted on cell block material in 10hpf.

## Discussion

The diagnostic accuracy of EUS-FNA is well-established, perhaps nowhere more so than for evaluating otherwise hard-to-access submucosal lesions of the GI tract and for pancreatic masses. It helps in overcoming the limitations of CT-guided or endoscopic biopsies by introducing the needle from within close proximity of the lesion under EUS-guidance. Combining this modality with ROSE further improves its diagnostic accuracy [1,2].

Utilizing this approach has led to better sampling of GISTs in locations which are otherwise difficult to biopsy. In combination with clinical and radiological features, this has also helped in assessing the probable risk [7,10]. In our study most patients presented with melaena, together with signs of chronic anaemia and epigastric pain, details of which are shown in table 2. Three patients were provisionally suspected GIST, found incidentally on imaging carried out for other reasons.

Varying in cell morphology makes GIST difficult to diagnose. Indeed, in the past many GIST cases were thought to be mislabelled as smooth muscle neoplasms or gastric autonomic nervous system tumours (GANT's) [13,15]. It is well established now that GIST is a common mesenchymal tumour of the GI tract with a predilection for submucosal location, which involves the stomach, duodenum, ileum, rectum and oesophagus in descending order [6,11]. All GISTs have malignant potential, but the prognosis usually depends upon the site, size (both can be documented on radiology) and mitotic count estimated on biopsy specimens or on cell blocks. They are characterized by KIT or PDGFRA mutations and they respond well to Imatinib (TKI) therapy. This has activity against mutated KIT with a significant percentage of tumors showing complete or partial responses [11,17].

In our study, we reviewed thirteen patients with GIST - eleven primary and two metastatic lesions. All of these were diagnosed

using EUS-guided FNA in conjunction with the clinical context and radiological features. This allowed not only diagnosis, but also risk stratification. All procedures were performed by an experienced gastroenterologist with an average of two FNA-needle passes per patient (range 1-3). Upon ROSE, a differential diagnosis including GIST was made in 8 (61.5%) cases, later confirmed by IHC. Five (38.5%) cases were called spindle cell lesions on ROSE and later diagnosed as GISTs after IHC stains [22,28].

ROSE of material obtained during the procedure has tremendously improved the sensitivity of EUS-guided FNA [36-39]. However, comparison of adequacy rates by based on the presence or absence of an on-site cytopathologist is beyond the scope of this article.

Cellularity of the smears we obtained was compared with a study by Chatzipantelis., *et al*. [29], who reported 17 cases of gastric GIST only on EUS-FNA. Smears were markedly or moderately cellular in 14 (82.3 %) and 3 (17.4%) cases respectively, compared to our study which showed similar cellularity in 8 (61.6%) cases and 4 (30.8%) cases, respectively. 1 (7.6%) case in our study was paucicellular, because of the cystic nature of the lesion, requiring a total of four passes.

Technicalities of the procedure were also documented and compared with other studies utilizing EUS-FNA. Needle gauge, average number of passes, sample adequacy and procedural complications were all compared and are listed in Table-4 [29,31].

Typical cytological features of GIST (fascicles of spindle cells with streaming effect, cells with oval vesicular nuclei and indistinct cytoplasm) were present in 12 cases. Additionally, fibrillary metachromatic material was seen in 8 cases. These results were also compared with studies carried out by Chatzipantelis., *et al*. and Gu., *et al*. (see Table-5) [29,30].

Immunohistochemical stain (CD117, DOG-1) positivity was seen in all cases, which confirmed the diagnosis on EUS-FNA, whereas others [29,30,33] used CD117 (c-kit) and CD 34 IHC only in order to diagnose GIST, and did not use DOG-1 stain.

| | **Current study** | **Chatzipantelis., *et al*.** | **Tamura., *et al*.** |
|---|---|---|---|
| Needle size | 22-G | 22-G | 19/22-G |
| Mean number of passes | 2 | 3 | 3 |
| Sample adequacy | 13/13 (100%) | 17/17 (100%) | 28/32 (87.5%) |
| Diagnostic accuracy | 13/13 (100%) | 17/17 (100%) | 28/32 (87.5%) |
| Complications | 0 (haematoma) | Not documented | 1 |

**Table 4:** EUS-FNA procedural results comparison.

| | **Current study** | **Chatzipantelis., *et al*.** | **Gu., *et al*.** |
|---|---|---|---|
| No. of cases (n) | n = 13 | n = 17 | n = 12 |
| Cell morphology | Spindle 12(92.3%)<br>Epithelioid 0(0%)<br>Mixed 1(7.7%) | 15(88.23%)<br>0<br>2(11.8%) | 12(100%)<br>0<br>0 |
| Metachromatic material | Present 8(61.6%) | 17(100%) | 12(100%) |
| Necrosis | Absent | Absent | Absent |
| Mitosis | <5 mitoses /25hpf in all cases | <5 mitoses /50hpf in all cases | <5 mitoses /50hpf in all cases |

**Table 5:** Comparison of cytomorphological features of different studies.

## Conclusion

In this era of advanced precision medicine, EUS- FNA is a very effective and safe method which provides superior efficacy in evaluation of submucosal and extra-intestinal lesions as compared to conventional methods.

Using EUS-FNA with ROSE is a minimally invasive means of diagnosing both primary as well as metastatic GIST, which also allows for risk assessment of GIST.

This study confirms that utilizing ROSE not only improves the diagnostic yield but is also associated with fewer needle passes and significantly fewer inadequate samples, hence increasing the overall accuracy of EUS-FNA.

Prospective studies are still required to evaluate the utility of these combined approaches and how they can be used not only to diagnose other malignancies using EUS-FNA but also to document clinical stage, where applicable.

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