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Comparison of Endoscopic Ultrasound-Guided Fine-Needle Aspiration with Fine-Needle Biopsy for Solid Gastrointestinal Lesions: A Randomized Crossover Single-Center study

Shivaraj Afzalpurkar[1] Vijay Kumar Rai[1] Nikhil Sonthalia[1] Gajanan Rodge[1] Awanesh Tewary[1] Mahesh Goenka[1]

[1] Institute of Gastrosciences and Liver, Apollo Multispeciality Hospitals, Kolkata, West Bengal, India

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Address for correspondence Mahesh Goenka, DM, Day Care, 4th Floor, Institute of Gastrosciences and Liver, Apollo Multispeciality Hospitals, 58 Canal Circular Road, Kolkata, West Bengal, 700054, India (e-mail: mkgkolkata@gmail.com).

Abstract

Background/Aims The purpose of this study was to compare the results of endoscopic ultrasound guided fine-needle aspiration (EUS-FNA) and fine-needle biopsy (FNB) performed at the same site in a single session in the same patient.

Methods Consecutive patients with solid gastrointestinal lesions referred for EUS evaluation underwent EUS-FNA and FNB using 22G needles with three and two passes, respectively, in the same session. Patients were randomized to one group having EUS-FNA first followed by EUS-FNB, while other group had EUS-FNB first followed by EUS-FNA.

Results Total 50 patients (31 male) of mean age 56.58 ± 14.2 years and mean lesion size of 2.6 (±2) cm were included. The Kappa agreement for final diagnosis for FNA and FNB was 0.841 and 0.61, respectively. The sensitivity and specificity of FNA versus FNB were 85.19 versus 62.96% and 100 versus 100%, respectively, in comparison with final diagnosis.

Conclusion Both EUS-FNA and FNB are equally safe when compared between the two techniques simultaneously in same lesion. EUS-FNA is better than FNB in terms of sensitivity, diagnostic accuracy, and tissue yield for solid GI lesion. However, the specificity and positive predictive value were equally good for both the modalities.

Keywords

- endoscopic ultrasound
- fine-needle aspiration
- fine-needle biopsy

Introduction

Endoscopic ultrasound (EUS) is now a widely used modality for identifying, characterizing, and sampling of various benign and malignant lesions of gastrointestinal (GI) tract and adjacent structures like pancreas, bile duct, and lymph nodes. EUS-guided tissue acquisition techniques play an important role in diagnosis of GI lesions. The yield of tissue acquisition depends upon the lesion size, location, sampling technique, needle size and type, availability of rapid onsite evaluation, and experience of the endoscopist as well as reporting pathologist. Tissue procurement techniques and tools have evolved significantly in last two decades. EUS-guided fine-needle aspiration (FNA) and fine-needle biopsy (FNB) are the useful tissue acquisition techniques for screening, diagnosis and staging of esophageal, gastric, pancreaticobiliary, rectal and lung diseases.[1]

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EUS-FNA is the validated tissue acquisition technique for pathological diagnosis of GI diseases. There is high variability in diagnostic yield with reported sensitivities, specificities and diagnostic accuracy in pancreatic neoplasms ranging from 64 to 95%, 75 to 100%, and 78 to 95%, respectively.[2] However, the diagnostic accuracy is lower for other lesions like mediastinal masses and GI stromal tumors.[3,4] The efficacy of FNA depends on the characteristics of the target tissue like site, size, surrounding organs, and availability of cytopathologist.[5,6] In order to overcome the drawbacks of FNA and to obtain the core tissue specimen for histological analysis, FNB needles were developed.[7] FNA shows tissue samples at the cellular level, while FNB reveals the true architecture of the tissue. The aim of this study was to compare the diagnostic accuracy of EUS-guided FNA with that of FNB for solid GI lesions by comparing the two techniques in the same lesion.

We did this study to compare sensitivity, specificity, positive, and negative predictive values (PPV and NPV) of FNA and FNB. In addition, comparison of diagnostic yield of FNA and FNB was done. We also compared the adverse effects of two techniques.

Material and Methods

Consecutive patients with solid lesions (pancreaticobiliary, lymph nodes, metastasis, submucosal lesions) referred for EUS evaluation to the gastroenterology department at our tertiary care hospital were included in the study between January 2019 and January 2021 after obtaining institutional ethics committee clearance.

Randomization

Patients underwent 22G EUS-FNA using a standard aspiration needle (Expect, Boston Scientific, Natick, MA, USA) and 22G EUS-FNB (Boston Scientific, Natick, MA, USA). The participants were randomized to one of the two groups: In first group, EUS-FNA was done first followed by EUS-FNB, while in the second group, EUS-FNB was performed first followed by EUS-FNA and so on.

All procedures were conducted with conscious sedation by intravenous propofol in left lateral decubitus position. All study procedures were performed by an experienced endoscopist using Olympus (United States) EU-ME2 EUS machine. Boston Scientific FNA needle of 22 gauze (Expect needle) was used for the procurement of cytological aspirates, whereas Boston Scientific FNB needle of 22 gauze (Acquire needle) was used for FNB. Three passes were made during FNA and two passes were made during FNB sampling in all study subjects. After identifying an avascular path and taking out the sheath from the endoscope, the needle was punctured into the mass under ultrasound vision. Subsequently, fanning technique (4×4) was used wherever feasible. No suction was used in our study. For FNB, the samples were analyzed by the pathologist blinded for the presence of histological core. The samples in which satisfactory assessment of histologic architecture is done were considered as optimal. Suboptimal specimens are those in which the quality of the core was inadequate or unsatisfactory for the assessment of histologic architecture. Cytology slides were assessed for cellularity and bloodiness of the sample and were classified as optimal or suboptimal.

One of the following methods was used to make a final diagnosis:

i. Definite evidence of malignancy on a surgical specimen.
ii. The diagnosis of malignant disease both on EUS-FNB or EUS-FNA and follow-up clinical/imaging.
iii. Confirm diagnosis of benign lesions with no evidence of malignancy on EUS-FNB or EUS-FNA and on clinical/imaging of at least 6 months' follow-up.

Statistical Analysis

Data was entered into Microsoft (MS) Excel data sheet and was analyzed using SPSS 22 version software. Categorical data and continuous data were represented in the form of frequencies/proportions and mean/standard deviation, respectively. Chi-squared test was used as test of significance for qualitative data. Agreement between two or more observers/between two or more methods or instruments and equipment was assessed by using Kappa statistics.[8–11] *p*-Value (probability that the result is true) of less than 0.05 was considered as statistically significant after assuming all the rules of statistical tests. MS Excel, SPSS version 22 (IBM SPSS Statistics, Somers, New York, United States) were used to analyze data.

Results

During the study period, 628 patients underwent EUS for various indications. Among them 52 patients underwent both EUS-guided FNA and EUS-guided FNB. Two patients had cystic lesions and were excluded. Hence, 50 patients among which 25 underwent EUS-FNA followed by EUS-FNB and remaining 25 underwent EUS-FNB followed by EUS-FNA were finally included in the analysis (►**Fig. 1**). The baseline characteristic of study population is depicted in ►**Table 1**. The predominant age group of patients involved in our study

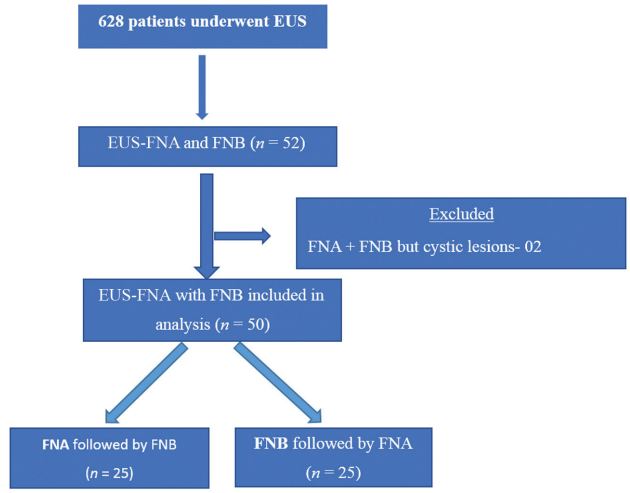

Fig. 1 Study flowchart. EUS-FNA, endoscopic ultrasound-fine-needle aspiration; FNB, fine-needle biopsy.

Table 1 Baseline characteristics of study group

Characteristics		*n* (%)
Age	<40 years	5 (10)
	41–50 years	7 (14)
	51–60 years	19 (38)
	61–70 years	13 (26)
	>70 years	6 (12)
Gender	Female	19 (38)
	Male	31 (62)
Comorbidities	DM	24 (48)
	HTN	23 (46)
	Hypothyroidism	9 (18)
	CAD	6 (12)
	COPD	2 (4)
	NASH	1 (2)
	Others	2 (4)
	No comorbidities	10 (20)
Presenting symptoms	Fever	7 (14)
	Weight loss	20 (40)
	Jaundice	27 (54)
	Melena	1 (2)
	Dyspnea	3 (6)
	Dysphagia	1 (2)
	Chest tightness	1 (2)
Duration of symptoms	<3 months	21 (42)
	4–6 months	19 (38)
	7–12 months	9 (18)
	>12 months	1 (2)

Abbreviations: CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus; HTN, hypertension; NASH, nonalcoholic steatohepatitis.

was 51 to 60 years ($n = 19$, 38%). The majority of them were men ($n = 31$, 62%). Thirty-six percent ($n = 18$) of the patients had at least one comorbidity and 44% ($n = 22$) had multiple comorbidities with diabetes mellitus ($n = 24$, 48%) followed by hypertension ($n = 23$, 46%) being the most common. Duration of symptoms was less than 3 months in 21 (42%), 4 to 6 months in 19 (38%), 7 to 9 months in 3 (6%), 10 to 12 months in 6 (12%), and more than 12 months in only one patient (2%). In the study, 26 (52%) patients had lesions in the pancreas, 18 (36%) in the lymph nodes, and 6 (12%) at other sites. Among the patients with pancreatic masses, 14 (28%), 7 (12%), 4 (8%), and 1 (2%) patient had lesions in the head, body, uncinate process and tail of pancreas, respectively. Lymph node masses were seen in subcarinal nodes in 7 (14%), periportal nodes in 5 (10%), peripancreatic nodes in 4 (8%), and inferior mediastinal lymph nodes in 2 (4%) patients. Among the other remaining lesions, 3 lesions (6%) were located in gallbladder, 2 (4%) in the lower end of common bile duct, and 1 (2%) near the body of the stomach (►**Table 2**).

Table 2 Distribution of patients based on the site of lesion ($n = 50$)

Site		*n* (%)
Pancreas	Head	14 (28)
	Body	7 (14)
	Uncinate process	4 (8)
	Tail	1 (2)
Lymph nodes	Periportal	5 (10)
	Subcarinal	7 (14)
	Peripancreatic	4 (8)
	Inferior mediastinal	2 (4)
Others	Gallbladder	3 (6)
	Common bile duct	2 (4)
	Stomach	1 (2)

►**Fig. 2** shows distribution of FNA diagnosis. Benign lesions were more common ($n = 26$, 56%) than the malignant lesions ($n = 23$, 46%). Overall, adenocarcinoma (30%) was the most common finding followed by benign epithelial cells (20%). Other findings observed were inflammatory cells (14%), granulomatous inflammation (8%), reactive hyperplasia (4%), metastatic adenocarcinoma (4%), neuroendocrine tumor (6%), metastatic synovial sarcoma, spindle cell neoplasm, and GI stromal tumor (2% each). One patient had suboptimal specimen whose diagnosis could not be achieved by FNA. In cases where it was negative for malignancy on FNA, the pathologist reported them as benign cells, negative for malignancy, inflammatory cells, reactive hyperplasia, and granulomatous inflammation. In the study, most common diagnosis by FNB was adenocarcinoma (20%), followed by benign cells (10%), inflammatory mass (14%), and neuroendocrine tumor (6%). After tissue acquisition by FNB, it was found that 10 (20%) of the tissues were inadequate/suboptimal (►**Fig. 3**). By FNA, 46% were malignant lesions and 54% were benign lesions. By FNB, 34% were malignant lesions and 66% were benign lesions, and by final diagnosis, 54% and 46% were malignant and benign lesions, respectively (►**Table 3**). FNA had sensitivity of 85.19%, specificity of 100%, PPV of 100%, NPV of 85.19%, and diagnostic accuracy of 92% in comparison with final diagnosis for detecting malignant lesions (►**Table 4**). Kappa agreement between FNA and final diagnosis was 0.841 (almost perfect agreement). FNB had sensitivity of 62.96%, specificity of 100%, PPV of 100%, NPV of 69.7%, and diagnostic accuracy of 80% in comparison with final diagnosis for detecting malignant lesions. Kappa agreement between FNB and final diagnosis was 0.61 (substantial agreement). Out of 25 subjects who underwent FNA as first diagnostic procedure, 64% were malignant and 36% were benign. Similarly, out of 25 subjects who underwent FNB as first diagnostic procedure, 44% were malignant and 56% were benign. There was no significant difference in diagnosis and first investigation done ($p = 0.156$). FNA had tissue adequacy rate of 98%, whereas FNB had tissue adequacy rate of 80%. In

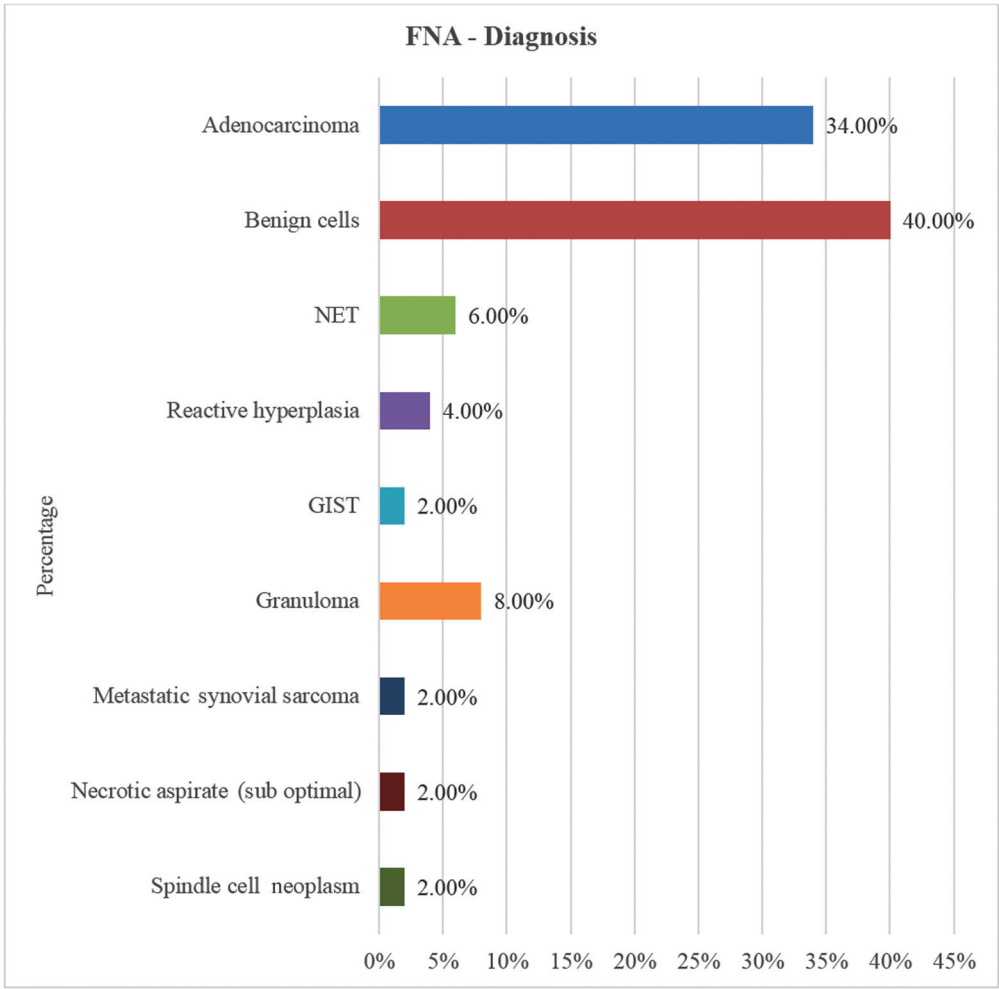

Fig. 2 Bar diagram showing fine-needle aspiration (FNA) diagnosis distribution. GIST, gastrointestinal stromal tumor, NET, neuroendocrine tumor.

the study among those with malignant lesions, 77.8% had size of lesion more than 2cm and 22.2% had size of lesion less than 2cm and among those with benign lesions, 43.5% had more than 2cm lesions, and 56.5% had less than 2cm lesions. There was significant association between size of lesion and final diagnosis ($p = 0.013$). With increase in size, malignancy rates also increased. Representative histology images of the study patients are shown in ►**Fig. 4**. EUS-FNA from enlarged peri-pancreatic lymph nodes of a patient who presented with chronic pain abdomen and significant weight loss showed granulomatous inflammation (►**Fig. 4A**) and EUS-FNB revealed epithelioid cell granuloma in the same patient (►**Fig. 4B**). EUS-FNA and FNB of peripancreatic lymph nodes of another patient were consistent with the diagnosis of metastatic adenocarcinoma (►**Fig. 4C** and **D**).

In this study, the overall adverse events were noted in 14% patients. Mild self-limited bleeding was seen in 6%, hypotension in 4%, and mild acute pancreatitis in remaining 4% of study group. Among malignant lesions, 3.7% each had acute pancreatitis, hypotension, and mild bleeding. Among benign lesions, 4.3% each had acute pancreatitis, hypotension and 8.7% had mild bleeding. There was no significant difference in adverse events between malignant and benign lesions ($p = 0.625$). There was no significant difference whether FNA or FNB was done first

Discussion

EUS-guided tissue acquisition technique is a multistep procedure that involves assessment of indications, proper selection of needles, and adequate skill to perform the procedure. There are different needle sizes (19-gauze, 22-gauze, 25-gauze), different types (FNA, FNB), and different techniques (use of stylets, suction, fanning). There are different trials and studies that are conducted to compare the diagnostic performances of different needle sizes and types for endoscopic ultrasound-guided sampling of solid GI lesions. It is always challenging to make an accurate diagnosis of solid pancreatic masses discovered on abdominal imaging. There are many studies conducted in the recent past for comparison of EUS-FNA and FNB in solid lesions like pancreatic masses, lymph nodes, and intra-abdominal mass. Most of the studies have compared FNA and FNB in different patients with different sizes of lesions. There are very few studies that compared both the modalities of EUS tissue acquisition (FNA and FNB) in a single lesion and at a single point of time.

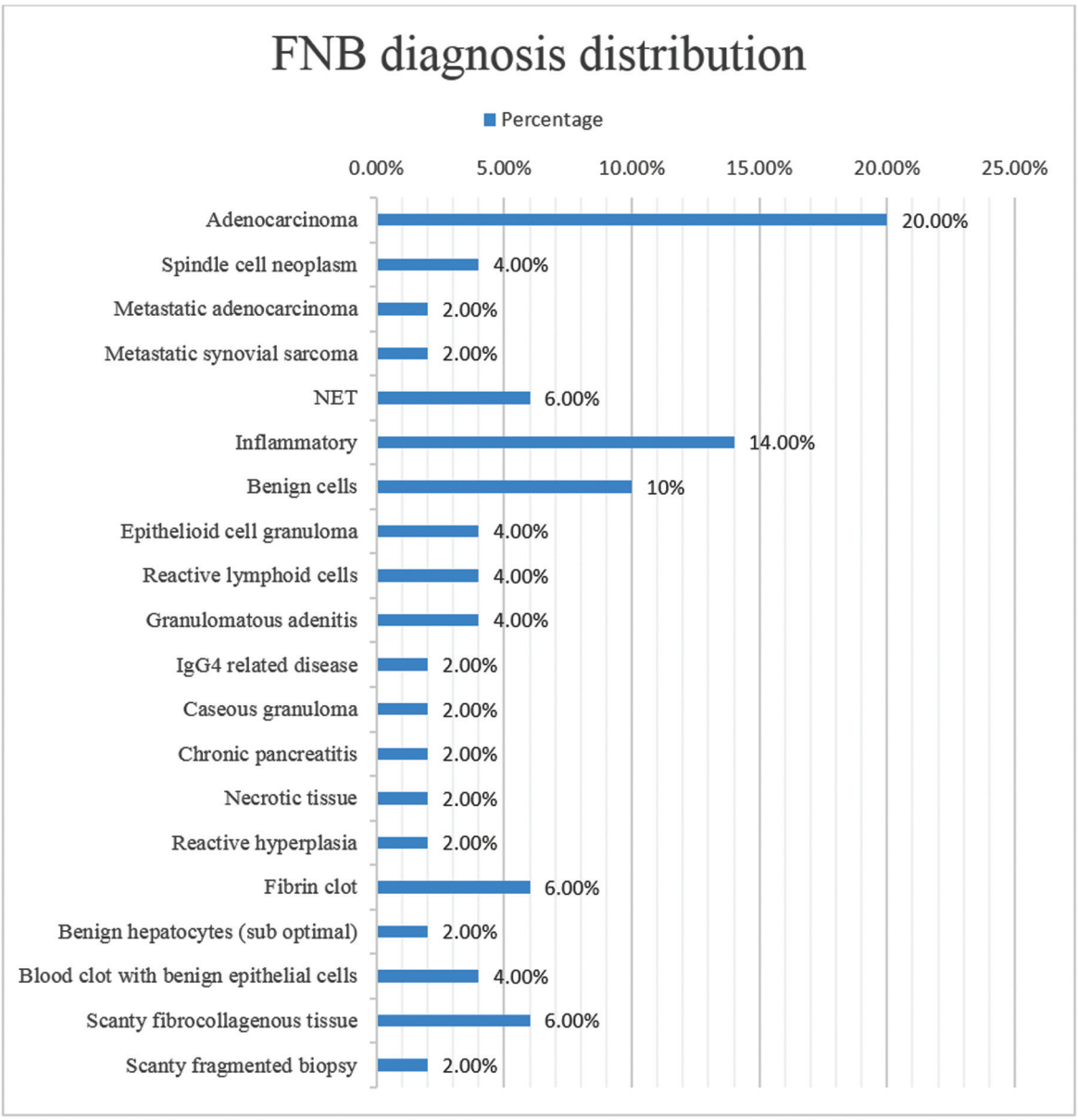

Fig. 3 Bar diagram showing fine-needle biopsy (FNB) diagnosis distribution. IgG4, immunoglobulin G 4; NET, neuroendocrine tumor.

Table 3 FNA, FNB, and final diagnosis distribution

		Number	Percentage
FNA	Malignant	23	46.0
	Benign	27	54.0
FNB	Malignant	17	34.0
	Benign	33	66.0
Final diagnosis	Malignant	27	54.0
	Benign	23	46.0

Abbreviations: FNA, fine-needle aspiration; FNB, fine-needle biopsy.

In our study, different types of solid lesions were included. Accordingly, 52% had pancreatic mass, 36% had lymph-node enlargement, and 12% had other lesions (gallbladder, bile duct and stomach mass). In a similar study by Altonbary et al pancreatic lesions were 58%, lymph node masses of 20%, and other intraabdominal lesions of 22%.[12]

The diagnostic accuracy of EUS-FNA for solid lesions varies from 78 to 95%.[12] Bang et al[13] in 2012 conducted a randomized controlled trial (RCT) on EUS-FNA versus FNB in 56 pancreatic lesions using 22 G needle and found that the overall diagnostic accuracy and sample adequacy was equivalent. In a similar RCT by Alatwai[14] in 2015 found that the sample adequacy was equivalent with both FNA and FNB needles, but the diagnostic yield was higher with FNB needle (84 vs. 90%). In a meta-analysis (of 4 RCTs and 11 observational studies) by Khan et al[15] in 2017, it was found that the overall diagnostic accuracy and sample adequacy were equivalent. In the recently conducted RCTs, the diagnostic accuracy of both FNA and FNB was equivalent.[16]

Table 4 Validity of FNA and FNB in diagnosis of malignant lesions in comparison with final diagnosis

Parameter	Validity of FNA (range)	Validity of FNB (range)
Sensitivity	85.19% (67.52–94.08)	62.96% (44.23–78.47)
Specificity	100% (85.69–100)	100% (85.69–100)
PPV	100% (85.69–100)	100% (81.57–100)
NPV	85.19% (67.52–94.08)	69.7% (52.66–82.62)
Diagnostic accuracy	92% (81.16–96.85)	80% (66.96–88.76)
Cohen's kappa (unweighted)	0.841 (0.57–1.12)	0.61 (0.35–0.87)

Abbreviations: FNA, fine-needle aspiration; FNB, fine-needle biopsy; NPV, negative predictive value; PPV, positive predictive value.

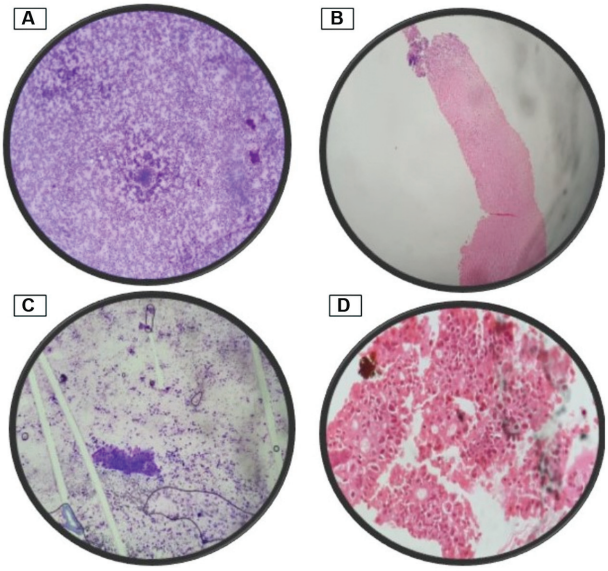

Fig. 4 Endoscopic ultrasound-fine-needle aspiration (EUS-FNA) from enlarged peri pancreatic lymph nodes of a patient who presented with chronic pain abdomen and significant weight loss showed granulomatous inflammation (**A**) and EUS-FNB revealed epithelioid cell granuloma granulomatous inflammation in the same patient (**B**). EUS-FNA and fine-needle biopsy (FNB) of peri pancreatic lymph nodes of another patient were consistent with the diagnosis of metastatic adenocarcinoma (**C and D**). Hematoxylin and eosin staining was used and depicted in low and medium power magnification.

We performed both EUS-FNA and EUS-FNB in solid GI lesions in a same patient and in same session. There are very few such articles in the literature. JH Jun et al[17] in 2018 (published as abstract) and Asokkumar et al[17] in 2019 published the RCT in which both FNA and FNB are performed at the same site in the same session. JH Jun et al performed EUS-FNA and FNB in pancreatic, liver, and retroperitoneal lesions in 47 patients. The diagnostic sensitivity, specificity, PPV, NPV, and accuracy of EUS-FNA and EUS-FNB were as follows: 70 versus 82.5%, 100 versus 100%, 100 versus 100%, 36.84% versus 50.00%, and 74.47 versus 85.11%, respectively. In the other study by Asokkumar et al,[17] both FNA and FNB of pancreas, stomach, lymph nodes, and other abdominal masses were performed in 36 patients. They found that the histological core tissue obtained by EUS-FNB was more frequent than EUS-FNA (97 vs. 77%, $p = 0.03$). Diagnostic adequacy and yield of the histological tissue were similar between EUS-FNB and EUS-FNA (81 vs. 64%, $p = 0.19$).

In our study, in comparison to the final diagnosis out of 27 malignant lesions, on FNA 85.2% were malignant and 14.8% were benign (false negative) and out of 23 benign lesions, 100% were benign. There was significant association between FNA diagnosis and final diagnosis. FNA had sensitivity of 85.19%, specificity of 100%, PPV of 100%, NPV of 85.19%, and diagnostic accuracy of 92% in comparison with final diagnosis for detecting malignancy. Previously published studies on sampling of solid pancreatic masses using EUS-FNA have reported sensitivity and specificity of 85 to 95% and 95 to 98%, respectively, and diagnostic accuracy of 78 to 95%.[14,18]

Certain neoplasms such as lymphoma, neuroendocrine tumors, stromal tumors, well-differentiated adenocarcinoma of the pancreas, and immunoglobulin G-4 auto-immune pancreatitis require histological exams to assess tissue architecture and cell morphological changes in order to formulate a more accurate diagnosis.[19,20]

To overcome such issues, it was proposed to use EUS-FNB. The needles are designed in such a way that it enhances the flexibility and also helps in collecting core biopsy samples. In our study, in comparison to the final diagnosis, out of 27 malignant lesions 63% were malignant and 37% were benign (false negative) in FNB, and out of 23 benign lesions, 100% were benign in FNB samples. The association between FNB diagnosis and final diagnosis was statistically significant. FNB had sensitivity of 62.96%, specificity of 100%, PPV of 100%, NPV of 69.7%, and diagnostic accuracy of 80% in comparison with final diagnosis for detecting malignant lesions. One of the reasons for less sensitivity of FNB was significant resistance while advancing the needle in four patients that leads to inadequate tissue sample (other reasons could be difficult location/vascularity of tumor, etc.). Similar lower sensitivity of FNB needle was noted in two studies published earlier.[21,22]

For procuring the adequate sample using the biopsy needle, size of the lesion plays a very important role. In our study, the median ± standard deviation size of the lesions was 2.6 (±2) cm. Among those with malignant lesions, 77.8% had size of lesion more than 2cm and 22.2% had size of lesion less than 2cm, and among those with benign lesions, 43.5% had more than 2cm lesions and 56.5% had less than 2cm lesions. There was significant association between final diagnosis and the size of lesion. With increase in size, malignancy rates also increased. In the recent RCT by

Asokkumar et al[17] published in 2019, similar diagnostic accuracy between FNA and FNB was reported and it was mainly due to the larger mean size (3.8 ± 2.0 cm) of the lesions. They did not assess the performance of EUS-FNB and EUS-FNA in smaller (<2 cm) lesions. Therefore, in our study one of the reasons for lower diagnostic yield and tissue adequacy rate of EUS-FNB may be the small median size of the lesions making it difficult to procure the sample.

In our study, sensitivity of both FNA and FNB was highest for pancreatic lesions (88.2 and 70.6%) followed by lymph nodes (80 and 60%) and other lesions of the GI tract (80 and 40%). However, the specificity for FNA and FNB was 100% for malignant lesions irrespective of the site. Vanbiervliet et al in 2014 in a randomized crossover study showed that FNB (ProCore) is inferior to FNA in the diagnosis of pancreatic masses.[21] In another study by Strand et al in the same year also concluded that EUS-guided 22-gauge FNA is superior to core biopsy needle in the evaluation of solid pancreatic neoplasms.[22]

In this study, only mild adverse events like self-limited bleeding, hypotension, and mild acute pancreatitis were noted. There was no significant difference in adverse events between malignant and benign lesions. Since both EUS-FNA and FNB were done in each patient, it is difficult to corroborate the complications with the single procedure (FNA or FNB). In a previous comprehensive nationwide retrospective study, the incidence of adverse events in EUS tissue acquisition (EUS-FNA/FNB) was relatively low.[23] In the retrospective study by Hamada et al, the most common adverse events were infection and pancreatitis.[24]

The limitations of our study were as follows. It was done in a heterogeneous sample (as lesions of pancreas, lymph nodes, biliary system, and stomach were included). There was no single gold standard investigation used in this study to compare FNA and FNB. Rapid onsite evaluation was not done in the study due to unavailability. The number of passes used were limited (3 for FNA and 2 for FNB) and tissue macroscopic onsite evaluation of the tissue sample was not done after each pass. Finally, assessment of tissue adequacy of FNB samples needing immunohistochemistry was not done.

To conclude, Both EUS-FNA and FNB are equally safe. When compared between the two techniques in same lesion at the same time, EUS-FNA is better than EUS-FNB in terms of sensitivity, diagnostic accuracy, and tissue yield for solid GI lesion. However, the specificity and PPV were equally good for both the modalities. There was no significant difference whether EUS-FNA was performed first or FNB.

Authors' Contributions

SA, MG, and VR helped in conceptualization and project administration. GR, SA, and AT contributed in data curation. NS and GR helped in formal analysis. VR and SA helped in investigation. MG, VR, and SA contributed to methodology. MG, VR, and SA helped in providing resources. VR and MG supervised the study. MG, VR, and GR helped in validation. MG and VR contributed to visualization. SA, MG, NS, and GR helped in review and editing. All the authors helped in writing-original draft.

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Conflict of Interest

None declared.

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