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Study of Yield of Endoscopic Ultrasound: Fine Needle Aspiration Cytology in Patients with Solid Pancreatic Masses at S.M.S. Medical College, Jaipur

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Abstract
Solid masses of pancreas represent a variety of benign and malignant neoplasm of exocrine and endocrine tissue of pancreas. Endoscopic Ultrasound (EUS) is a relative new technology that employs endoscopic and high frequency ultrasound (US).
Keywords: *EUS-FNAB, Pancreatic Carcinoma.*

Introduction

Endoscopic Ultrasound (EUS) is relatively new technology that has been shown to be a highly sensitive method for the detection of pancreatic masses.[1] It is more sensitive than conventional computed tomography (CT) scan for detecting small pancreatic tumors (<3.0cm) and determining their resectability based on vessel invasion.[2] Early detection is important as tumor size is an independent predictor of improved prognosis.[3] EUS-guided fine-needle aspiration biopsy (EUSFNAB) is useful and accurate modality for characterizing lesions from the pancreas, lymph node, gastrointestinal tract wall, retro peritoneum, liver, biliary tree and adrenal glands.[4] EUS-FNAB can be performed on small lesions, offering an opportunity for early detection of tumors, the staging of malignancies and in some instances, helping to avoid unnecessary surgeries.

The reported results of pancreatic EUS-FNA vary in the range of 64–95% for sensitivity, 75–100% for specificity and 78–95% for diagnostic accuracy.[5] Several factors can affect the results of EUS-FNA, such as the experience of the endo-sonographer, the position of the endoscope, the diameter of the needle, the number of passes, and the presence of an onsite cytopathologist.[6] Furthermore, core biopsy specimens for assessing architectural features may be essential for diagnosing certain neoplasm, such as lymphomas and stromal cell tumors.[7] However cost and staffing limitations frequently limit the availability f an on-site cytopathologist at many centers.[8]

Although EUS is highly sensitive in detecting pancreatic solid masses, its ability to differentiate between inflammatory masses and malignant disease is limited.1with the advent of curvilinear echo endoscope stransgastric and transduodenal EUS-FNAB of the pancreas have become a reality.[9] EUS-with FNAB has become an important technique of gastroenterologists for the diagnosis of pancreatic adeno-carcinoma before chemotherapy and/ or surgery. EUS-FNAB, with its ability to obtain a tissue diagnosis, has increased the accuracy of EUS in the diagnosis of pancreatic adeno carcinoma. The diagnostic accuracy of EUS-FNAB was enhanced in prospective, multicenter studies and demonstrates that EUS-FNAB is a highly accurate diagnostic test for solid neoplasm of the pancreas.[10] The survival rate of patients with these tumors is extremely poor, with an overall 5- year survival rate of less than 5%, 12 making it one of the biggest "cancer killers".[13] Therefore early and accurate diagnosis is vital for improving the efficacy of therapeutic intervention. In the current study, we prospectively evaluated the cellular yield of EUS-FNAB in patients with solid pancreatic masses who were clinically suspected to have pancreatic carcinoma. We also evaluated the clinical significance of anatypical or suspicious cytologic diagnosis and investigated the causes of false-negative results with the aim to prospectively evaluate the yield of EUS-FNAB in the diagnosis of patients presenting with solid pancreatic lesion

Material

This descriptive type of prospective observational study conducted in Department of Pathology and Gastroenterology, S.M.S. Medical College Jaipur, Rajasthan from March 2017 to November 2018 in EUS-FNA specimens

Patients with solid pancreatic mass based on clinical results and/or other imaging studies Patients who required a tissue diagnosis or who failed other attempts by ERCP, CT-guided biopsy and/or US-guided biopsy were included in the current study. Patients had previously undergone chemotherapy or radiotherapy and Cystic lesion of pancreas were excluded.

Plan of Procedure

H & E staining, Wet fix smear, Ethyl-alcohol (Fixation) - 5 minutes, Dry slide, Hematoxyline 5-7 minutes, Running water 5-7 minutes, Eosin - 30 second, Acetone – 3 jars (2 minutes in each jar), Xylene – 2 jars (2 minutes in each jar), Dry mount Giemsa staining

Dry Smear, Air Dry, Methanol (fixation) 5 minutes,1:10 (Giemsa stain: Distill water) mix pour on slide and rest for 20 minutes, Wash in running tap water till bluish colour appearance, Dry, Xylene dips – 2dip,Dry Mount

EUS-guided fine-needle aspiration of patients with solid pancreatic mass clinical/imaging was performed after exclusion criteria 80 Specimens was taken for analysis. Investigations applied staining done outcomes was analysed in terms of Proportion of - Malignant/ Suspicious for Malignancy/ Atypical/Benign.

Statistical analysis was performed with the SPSS, Trial version 23 for Windows statistical software package (SPSS inc., Chicago, il, USA) and Primer for the generation of descriptive and inferential statistics. The Categorical data were presented as numbers (percent). The quantitative data were presented as mean and standard deviation. The difference in proportion was analysed by using chi square test Statistical significance was set to $p < 0.05$.

Observation

Most of the patients were in the age group of 51 – 60 years (43.8%) followed by 41 – 50 years (27.5 %) and 61 – 70 years (21.3%). Only 3 (3.7%) patients were below the age of 40 years. Also only 3 (3.7%) patients were above the age of 70 years. The mean age of these patients with solid pancreatic mass was 55.48 ± 8.96 years ranging from 35 to 83 years. Most (61.2%) of these patients were male and only 31 patients (38.8%) were females.

Most of the female (45.2%) as well as male (42.9%) patients were in the age group of 51 – 60 years

followed by 41 – 50 years (32.3% of females and 24.5% of males). No significant difference was seen in the age distribution of pancreatic mass among male and female subjects (p=0.538).

EUS – FNAB suggested malignant lesion in most patients (68.8%) while benign legion was suggested in 21 (26.2%) patients. Four (5%) patients had suspicious finding on EUS – FNAB. Final diagnosis was made on basis of the histopathology findings. Most of the patients (83.8%) were finally diagnosed with malignant pancreatic mass and only 13 (16.2%) were diagnosed with benign pancreatic mass. Of the 4 suspicious lesions 3 turned out to be malignant and only 1 was benign.

Out of the 67 patients with malignant mass, 55 (82.1%) patients were correctly diagnosed by EUS – FNAB as malignant, while 9 (13.4%) were wrongly suggested as benign by EUS – FNAB and out of the 4 suspicious lesion 3 were malignant on final diagnosis. Out of 13 patients with benign pancreatic mass, 12 (92.3%) were correctly diagnosed to have benign lesion and one patient had suspicious finding. Sensitivity of 86.57% indicates that 86.57% malignant cases are correctly diagnosed as malignant by EUS FNAB and only 13.43% of malignant cases were missed by EUS FNAB. Specificity was found to be 92.31% which indicates that most (92.31%) of non-malignant cases were correctly excluded. i.e. 92.31% benign cases were correctly diagnosed as benign. A high PPV of 98.31% indicates that almost all cases suggested as malignant by EUS FNAB were finally diagnosed to be malignant. This is of great value for a clinician to immediately start treatment on positive finding on EUS FNAB. NPV was found to be low (57.14%) i.e. among patients suggested to have benign lesion by EUS FNAB, only 57.14% were finally diagnosed to have benign lesion, and rest 42.86% were wrongly suggested as benign. This implicates that if EUS FNAB finding suggests benign lesion, the patients need to be cautiously followed up as there is 42.86% chance that the lesion may turn up to be malignant. The overall diagnostic accuracy of EUS FNAB was found to be 88.5% i.e. 88.5% of pancreatic masses are correctly classified as malignant / benign by EUS FNAB adeno-carcinoma was the most common diagnosis in solid pancreatic masses found in 40 (50%) of patients. Most common benign finding was chronic pancreatitis found in 21 (26.2%) patients. Neuroendocrine carcinoma was found in 5 (6.3%) patients. Malignant epithelial and poorly differentiated metastatic carcinoma were reported in 3 (3.8%) pancreatic masses. Anaplastic giant cell carcinoma and spindle cell neoplasm were found in only 1 patient each. Suspicious for malignant finding on FNAC was reported in 4 patients.

Most of the benign pancreatic lesions were found in 51 – 60 years (46.1%) and 41 – 50 years (38.5%) age group. Most of the malignant pancreatic lesions were also found in 51 – 60 years (43.2%) and 41 – 50 years (25.4%). No significant difference was found in the age distribution of benign and malignant pancreatic lesions (0.754). Most of the benign pancreatic lesions were found in males (76.1%). Malignant pancreatic lesions were found more in males (58.2%) as compared to females (41.8%). No significant difference was found in the gender distribution of benign and malignant pancreatic lesions (p=0.339).

Table 01: Age distribution of patients with solid pancreatic masses

Age group (Years)	**No. of subjects**	**Percentage**
31-40 years	3	3.7
41-50 years	22	27.5
51-60 years	35	43.8
61-70 years	17	21.3
> 70 years	3	3.7
Total	**80**	**100**
Gender	**No. of subjects**	**Percentage**
Female	31	38.8
Male	49	61.2
Total	**80**	**100**
EUS-FNAB finding	**No. of subjects**	**Percentage**
Benign	21	26.2
Malignant	55	68.8
Suspicious	4	5
Total	**80**	**100**
Final diagnosis	**No. of subjects**	**Percentage**
Benign	13	16.2
Malignant	67	83.8
Total	**80**	**100**

Table 02: Final diagnosis of solid pancreatic masses according to age of patients

Age group (years)	Benign		Malignant		Total		P Value LS
	N	%	N	%	N	%	
31-40	0	0	3	4.5	3	3.7	0.754NS
41-50	5	38.5	17	25.4	22	27.5	
51-60	6	46.1	29	43.2	35	43.8	
61-70	2	15.4	15	22.4	17	21.3	
> 70	0	0	3	4.5	3	3.7	
Total	13	100	67	100	80	100	
Female	3	23.1	28	41.8	31	38.8	0.33NS
Male	10	76.1	39	58.2	49	61.2	
Total	13	100	67	100	80	100	

Table 03: EUS-FNAB results in relation to final diagnosis of patients with solid pancreatic masses

EUS-FNAB finding	Final diagnosis		Total Sensitivity	Diagnostic parameter Value (95% confidence interval)
	Malignant	Benign		86.57 % (76.03 – 93.67)
Malignant	55 (82.1%)	0	**Specificity**	92.31 % (63.97 – 99.81)
Benign	9 (13.4%)	12 (92.3%)	**Positive predictive value**	98.31 % (89.75 – 99.74)
Suspicious	3 (4.5%)	1 (7.7%)	**Negative predictive value**	57.14 % (41.58 – 71.41)
Total	67 (100%)	13 (100%)	**Diagnostic accuracy**	88.5 % (78.21 – 9.84)

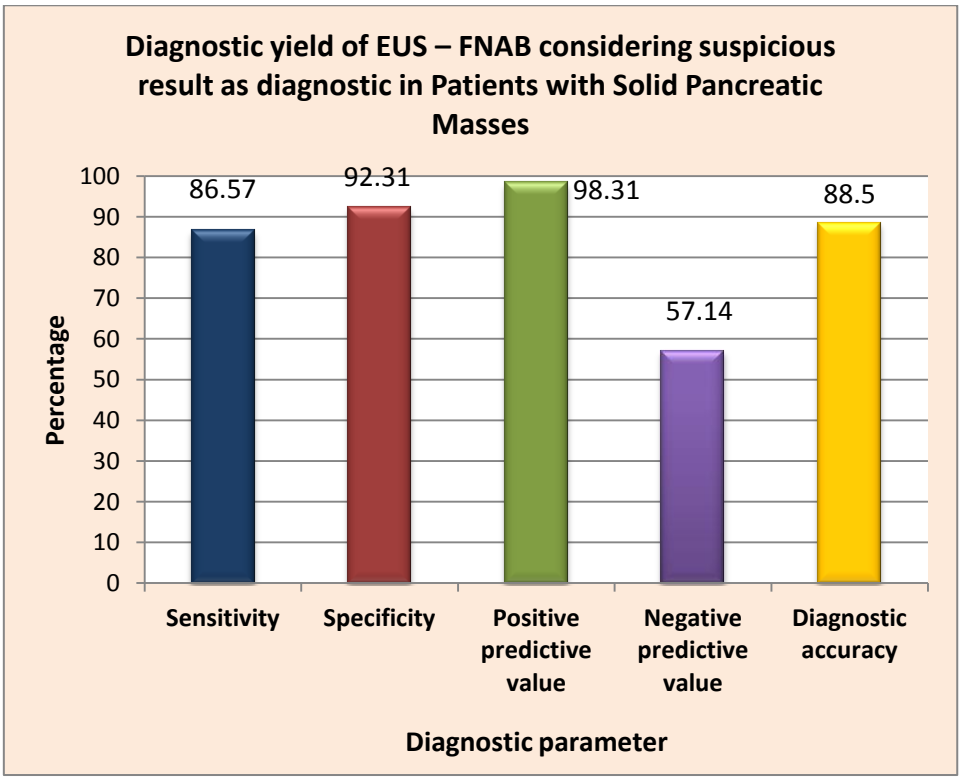

Fig. 1: Diagnostic Yield of EUS –FNAB considering suspicious result as diagnostic in patients with solid pancreatic masses

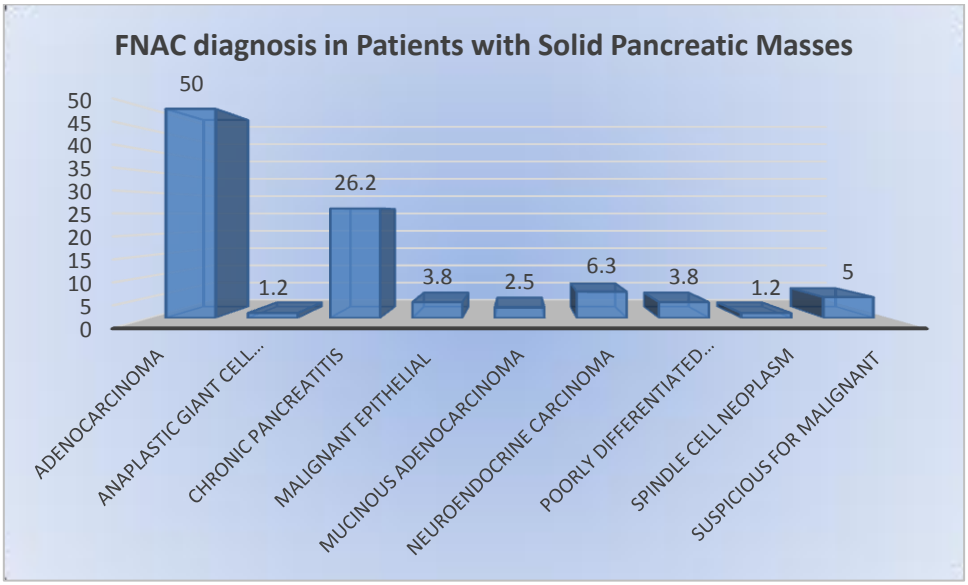

Fig. 2: Final diagnosis of Solid Pancreatic Masses

Discussion

This is laboratory based descriptive type of observational study conducted in the Department of Pathology and Gastroenterology, S.M.S. Medical College Jaipur, Rajasthan on EUS-FNA specimens received in Pathology Department of SMS Medical College Jaipur on 80 Patients with Solid Pancreatic Masses with the aim to contribute to the advancement of management for pancreatic cancer patients by improving the detection and diagnostic results.

In our current study, most of the patients were in the age group of 51 to 60 years (43.8%) followed by 41 to 50 years (27.5 %) and then 61 to 70 years (21.3%).

Only 3 (3.7%) patients were below the age of 40 years and only 3 (3.7%) patients were above the age of 70 years. The mean age of these patients with solid pancreatic mass was 55.48 ± 8.96 years ranging from 35 years to 83 years. This finding was similar with studies by Veronika Gagovic (2012)14 mean age of 66 years, Faming Zhang (2016)15with mean age 65.6±12.5 years, Yang et al (2015)16mean age 61.8±11.4 years, Robert A et al (2016)17mean patient age was 67.3 years (±9.5 years), i.e. most of cases were observed in elder age group of the population.

Most of these (61.2%) patients were male and only 31 patients (38.8%) were females. Veronika Gagovic (2012)14out of 144 patients 73 were male (51%) Faming Zhang (2016)15also observed the similar observation in the study of 241 patients 133 male (55.19%) Yang et al (2015)16 80.95% were males, Robert A et al (2016)1762% males i.e. male preponderance was observed in cases of pancreatic cancer.

Most of the female (45.2%) as well as male (42.9%) patients were in the age group of 51 – 60 years followed by 41 – 50 years (32.3% of females and 24.5% of males respectively). No significant difference was seen in the age distribution of pancreatic mass among male and female subjects (p=0.538).

In our study, most of the benign pancreatic lesions were found in 51- 60 years (46.1%) and 41 – 50 years (38.5%) age group. Most of the malignant pancreatic lesions were also found in 51 – 60 years (43.2%) and 41 – 50 years (25.4%). No significant difference was found in the age distribution of benign and malignant pancreatic lesions (P =0.754).

Veronika Gagovic (2012)14 There was no significant difference in age (P=0.0675) or sex (P=0.3595) between patients who had adenocarcinoma versus NPPA.

In our study patients presenting with solid pancraetic lesion found that 67% of the lesions were located in head of the pancreas, 15% were located in the uncinate, 13% were located in the body and 5% were located in the tail.

According to Mohamad A. Eloubeidi et al (2003)18, in evaluating the yield of EUS-FNAB in the diagnosis of patients presenting with solid pancreatic lesions found that 65% of the lesions were situated in the head of pancreas, 12% of it were located in the uncinate, 17% in the body and 6% in the tail.

According to Guilia A Zamboni et al (2009)19, 63.0% of the lesions were located in head or uncinate process of the pancreas and 35.2% of the lesions were located in the body or tail of the pancreas. Among these lesions ultrasound-guided fine-needle aspiration cytologic sampling had 99.4% sensitivity, 100% specificity, and 99.4% accuracy.

EUS – FNAB suggested malignant lesion in most patients (68.8%) while benign lesion was suggested in 26.2% patients. Four (5%) patients had suspicious findings on EUS – FNAB.

Final diagnosis was made on basis of the histopathology findings. Most of the patients (83.8%) were finally diagnosed with malignant pancreatic mass and only 13 (16.2%) were diagnosed with benign pancreatic mass. Of the 4 suspicious lesions 3 turned out to be malignant and only 1 was benign.

According to Sean D. Paulsen et al (2005)20, 92 of 107 masses analyzed to have true-positive results. Histopathologic analysis of the core samples revealed 76 biopsy samples sufficient for a diagnosis of pancreatic ductal adenocarcinoma

M Vossetal (2000)21EUS-FNAB was feasible in 90 patients (adenocarcinomas, n = 59; neuroendocrine tumours, n = 15; various neoplasms, n = 6; pancreatitis, n = 10), and analysable material was obtained in 73.

Robert A et (2016)17the cumulative yield after repeat EUS-FNA for definite pancreatic adenocarcinoma was 7 (16%).

Faming Zhang (2016)15 Pancreatic adenocarcinoma was the final diagnosis in 87.6% of patients.

Out of the 67 patients with malignant mass, 55 (82.1%) patients were correctly diagnosed by EUS – FNAB as malignant, while 9 (13.4%) were wrongly suggested as benign by EUS – FNAB and out of the 4 suspicious lesion 3 were malignant on final diagnosis. Out of 13 patients with benign pancreatic mass, 12 (92.3%) were correctly diagnosed to have benign lesion and one patient had suspicious finding.

Diagnostic yield of EUS – FNAB is considering suspicious result as non-diagnostic in patients with Solid Pancreatic Masses. Specificity was found to be 100% Sensitivity of 82.09% PPV of 100% NPV was found to be low 52%. This implicates that if EUS FNAB finding suggests benign lesion, the patients need to be cautiously followed up as there is 48% chance that the lesion may turn up to be malignant. The overall diagnostic accuracy of EUS FNAB was found to be 88.5% i.e. 88.5% of pancreatic masses are correctly classified as malignant / benign by EUS FNAB.

Diagnostic yield of EUS – FNAB is considering suspicious result as diagnostic in Patients with Solid Pancreatic Masses where Sensitivity of 86.57% Specificity 92.31% and PPV of 98.31%.

According to Mohamad A. Eloubeidi et al (2003)18, of all the solid pancreatic masses, 72 yielded true positive results, 23 yielded true-negative results, and 4 yielded false-negative results. Hence, sensitivity, specificity, PPV, and NPV of EUS-FNAB for pancreatic solid masses were 94.7% (95% CI, 89.7–99.8%), 100%, 100%, and 85.2% (95% CI, 71.8–98.6%), respectively.

According to Gavin C Harewood et al (2002)22, FNA had 90% sensitivity for malignancy, 50% specificity for benign disease and 84% accuracy. Similarly among 36 patients with negative ERCP tissue samplingresults for EUS FNA which were 94%, 67% and 92% respectively.

According to Sukru Mehmet Erturk et al (2005)23, Among small masses, the diagnostic rate and sensitivity for biopsies guided using CT (100% and 100%, respectively) were not significantly different from those for biopsies guided using endoscopic sonography (90.9% and 93.8%, respectively). For large masses, the diagnostic rate & sensitivity (96.6% & 92.3% respectively) for biopsies guided using CT were not significantly different from those for biopsies guided using endoscopic sonography (83.3% and 50%, respectively).

According to P. Thomas Cherian et al (2010)24, there were 78 pancreatic lesions, of which 65 were true positives (TP), 11 true negatives (TN) and two FN, giving an overall accuracy of 97% (76/78). Of nine periampullary lesions, 2 were TP, 6 were TN and 1 was FN, giving an overall accuracy of 89% (8/9). The sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and accuracy of EUS-FNA for pancreatic and periampullary lesions combined were 96%, 100%, 100% [95% confidence interval (CI) 95–100%], 85% (95% CI 62–97%) and 97%, respectively.

NPV was found to be low (57.14%) i.e. among patients suggested to have benign lesion by EUS FNAB, only 57.14% were finally diagnosed to have benign lesion, and rest 42.86% were wrongly suggested as benign. This implicates that if EUS FNAB finding suggests benign lesion, the patients need to be cautiously followed up as there is 42.86% chance that the lesion may turn up to be malignant.

The overall diagnostic accuracy of EUS FNAB was found to be 88.5% i.e. 88.5% of pancreatic masses are correctly classified as malignant / benign by EUS FNAB.

Our study observed that the adenocarcinoma was the most common diagnosis in solid pancreatic masses found in 40 (50%) of patients. Most common benign finding was chronic pancreatitis found in 21 (26.2%) patients. Neuroendocrine carcinoma was found in 5 (6.3%) patients. Malignant epithelial and poorly differentiated metastatic carcinoma were reported in 3 (3.8%) pancreatic masses. Anaplastic giant cell carcinoma and spindle cell neoplasm were found in only 1 patient each. Suspicious for malignant finding on FNAC was reported in 4 patients.

Similar observation was found in the study conducted by M Voss et al (2000)21, which found that EUS-FNAB was feasible in 90 patients (adenocarcinomas, as 59; neuroendocrine tumours, as 15; various neoplasms, as 6; pancreatitis, n = 10), and analyzable material was obtained in 73. Tumour size (> or <25 mm in diameter) did not influence the ability to obtain informative biopsy samples. Diagnostic accuracy was 74.4% (adenocarcinomas, 81.4%; neuroendocrine tumours, 46.7%; other lesions, 75%; $p<0.02$). Overall, the diagnostic yield in all 99 patients was 68%.

According to Sean D. Paulsen et al (2005)20 who observed that 92/ 107 masses analyzed to have true-positive results. Histopathology analysis of the core samples revealed 76 biopsy samples sufficient for a diagnosis of pancreatic ductal adenocarcinoma. Benign biopsy findings cannot be used to exclude the presence of a neoplasm, and repetition of a biopsy should be considered if there is high clinical suspicion of malignancy.

Veronika Gagovic (2012)14there were 21 patients (11%) with initial FNA suspicious for malignancy who required a second attempt at tissue acquisition via repeat EUS-FNA, EUS-guided core biopsy or confirmed pathology based on surgical resection specimen. Out of 21 patients, 11 confirmed NPPA neoplasms, while 10 as primary pancreatic adenocarcinoma.

In this study we observed that most of the benign pancreatic lesions were found in males (76.1%). Malignant pancreatic lesions were found more in males (58.2%) as compared to females (41.8%). No significant difference was found in the gender distribution of benign and malignant pancreatic lesions ($p=0.339$).

Carlo Fabbri et al (2014)25 found that the overall sensitivity, specificity, positive predictive value, negative predictive value, and accuracy were 80%, 100%, 100%, 40%, and 82%, respectively. They have suggested that EUS–FNB of small pancreatic lesions using a 22-gauge ProCore needle is effective and safe which supports our hypothesis that EUS–FNB is highly useful in establishing the nature of small pancreatic lesions.

Alexandra Kalogeraki et al (2016)26EUS-FNAB shows the sensitivity, specificity and accuracy of EUS-FNAB for pancreatic lesions range from 64% to 94%, 71% to 100% and 78% to 95% respectively. In different studies retrieved from PUBMED database since last 5 years, the sensitivity, specificity, positive predictive value, negative predictive value and accuracy of EUS-FNA for pancreatic solid masses were reported to be as 78 to

95%, 75%-100%, 98%-100%, 46%-80% and 78%-95%, respectively. There was no improvement of the efficacy of EUS-FNA even though new equipment and procedures have been developed.

Mohamed Malak et al (2016)27 observed the Sensitivity, specificity and accuracy were 98.9%, 93.3% and 98.1% for EUS-FNA.

Jeremy Wang et al (2018)28they found that there were no significant differences in sensitivity between EUS-FNA and CT-FNA specimens (73.7% vs. 88.9%, p = 0.33). They observed that EUS-guided FNA is as sensitive as CT-guided FNA in diagnosing pancreatic NETs, but its main advantage is in the diagnosis of smaller pancreatic NETs in the head of the pancreas.

Conclusion

EUS-FNAB is a safe and highly effective method for securing tissue diagnosis in patients with suspected pancreatic carcinoma. Almost all patients with suspicious cytology were subsequently proven to harbor cancer in the current study. Newer strategies, such as the addition of ancillary studies (e.g., tumor markers), are needed to further improve the yield and minimize suspicious and false-negative results. Patients with suspicious EUS-FNAB aspirates warrant further clinical evaluation.

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