EUS-FNA Biopsy for Pancreatic Mass

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ABSTRACT

Objective: To assess both solid and cystic pancreatic lesions using endoscopic ultrasound (EUS), and the effect of endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA) in patient management.

Study Design: Descriptive study.

Place and Duration of the Study: Department of Gastroenterology, Division of Internal Diseases, Sivas Cumhuriyet University Hospital, Sivas, Turkiye, from January 2018 to 2022.

Methodology: Patients with pancreatic mass, who underwent EUS-FNA were inducted in the study. EUS-FNA was performed using a 22-gauge needle *via* both transgastric and transduodenal routes. The size of the pancreatic lesion, its location, and whether there was SMA or CA invasion were evaluated on CT and EUS scans. Biopsy results of 64 patients who received EUS-FNA due to pancreatic lesions were considered. The results were divided into malignancy or benign pathology.

Results: A total of 64 cases were compared. Crosstable Chi-square analysis showed a statistically significant difference between CT and EUS ($p < 0.001$). EUS-FNA results revealed that out of the 64 patients with pancreatic mass detected in EUS, 46 had adenocarcinoma, 7 were negative for malignancy, 4 had intraductal papillary mucinous neoplasia (IPMN), 3 had neuroendocrine tumour (NET), 2 had lymphoma, and 2 had solid pseudopapillary neoplasia (SPN). In the 2-year follow-up of the seven patients who were negative for malignancy in EUS-FNA, there were no clinical, laboratory or imaging findings indicating pancreatic malignancy or distant metastasis.

Conclusion: Tissue sampling through EUS-FNA has minimal side effects and remains useful in managing preoperative patients with resectable or suspicious pancreatic masses.

Key Words: *Pancreatic cancer, Abdominal CT, Endoscopic ultrasound (EUS), Ultrasound-guided fine-needle aspiration (EUS-FNA).*

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INTRODUCTION

Pancreatic masses can take on different forms, such as solid or cystic, and can be either benign or malignant. Solid masses typically include ductal adenocarcinoma, which makes up 90% of pancreatic malignancies, and neuroendocrine tumours.[1] However, chronic focal pancreatitis may mimic the appearance of malignancy.[2] It is crucial to differentiate between these types of lesions and malignant lesions. With regard to cystic lesions in the pancreas, malignant cysts account for 10-15% of all cystic masses and 1-5% of all pancreatic malignancies.[3]

Pancreatic lesions are typically identified using endoscopic ultrasound (EUS) or computerised tomography (CT). EUS is more sensitive in detecting pancreatic mass lesions or pancreatic adenocarcinoma, particularly in cases where the lesions are smaller than 2 cm.[4] It also allows for easier tissue retrieval for pathology diagnosis.[5]

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However, there has been a debate over whether pancreatic lesions should be sampled, especially in surgical candidates with resectable lesions. A consensus panel convened by the International Working Group for Pancreatic Surgery (ISGPS) discussed the use of EUS in operative candidates and concluded that staging with EUS before surgical resection of solid resectable pancreatic masses with suspected malignancy would be of limited benefit.[6] However, it is still recommended to attempt tissue diagnosis with EUS-FNA before surgery in suspicious cases to detect conditions that may mimic adenocarcinomas.[7] EUS-FNA may also allow the patient to receive a neoadjuvant chemotherapy protocol if they are considered unresectable.[8] The resulting tissue diagnosis not only diagnoses the benign disease or unusual neoplasia but also reassures elderly patients and their families of malignancy before the surgery. It is still unclear how EUS-FNA affects the subsequent management of pancreatic masses and whether the tissue diagnosis benefits all these patients or not.

In this study, the goal was to determine if EUS-FNA pathology results impact the patient-management with pancreatic solid and cystic lesions.

METHODOLOGY

This study, in compliance with the Declaration of Helsinki, was approved by the Clinical Research Ethics Committee of Cumhuriyet University, Faculty of Medicine, Sivas, Turkiye. A

retrospective evaluation of outpatient follow-up and patient data from the polyclinic between 2018 and 2022 was conducted. A total of 64 patients were included in the study, based on the criteria such as imaging indicating a mass in the pancreas, dilatation in the common bile duct and pancreatic duct, and EUS procedures with biopsy. The size of the pancreatic lesion, its location, and whether there was SMA or CA invasion were evaluated in the patients' CT and EUS scans. Patients with stones in the common bile duct, stones in the pancreatic duct, previous operations on the common bile duct, primary malignancy outside the pancreas, and those who did not attend regular follow-up visits were excluded. Data were collected regarding age, gender, tumour size and region, endoscopic procedures, radiological imaging and pathology follow-up from electronic medical records, and written files.

In all the cases, the EUS-FNA procedure was performed using a 22-gauge needle through the transgastric and transduodenal routes. After the biopsy, smear preparations were created from the aspiration material and fixed with air. The smears were then stained with May Grunwald Giemsa stain kit and alcohol-fixed smears were stained with Papanikola dyes. Smear preparations were obtained from all cases, while biopsy material was obtained from 48 cases which allowed for immunohistochemical staining. The remaining tissue at the needle tip was quickly fixed in formalin and the resulting liquid was centrifuged after they were fixed in the tissue solution. Liquid-based cytology was prepared and cell blocks were obtained from the remaining material in eight cases. Formalin-fixed tissues were blocked after the routine follow-up on the tissue tracking device. Haematoxylin and eosin-stained sections were prepared from both formalin fixation and cell blocks. At least three and 10 simultaneous sections were taken on slides with lysine while preparing the sections allowing for immunohistochemical / histochemical studies. Material could not be obtained from only two of the cases. An average of 6 (1-16) immunohistochemical and/or histochemical studies were performed on the tissues of 46 cases. The cases' clinical information was obtained through the aurthors' centre's system.

The data were analysed using the SPSS software version 22 programme. Categorical variables were presented as numbers and percentages, while continuous numerical parameters were expressed as mean ± standard deviation. The relationship between multiple categorical variables was evaluated using Chi-square analysis. A statistically significant level was considered at $p<0.05$.

RESULTS

The study included a total of 64 cases, with 24 (37.5%) women and 40 (62.5%) men. The patients had an average age of 64.88 ± 1.618 years. Among the cases, 27 (42.2%) were from the gastroenterology clinic, 9 (14.1%) from internal medicine, 9 (14.1%) from general surgery, 16 (25.0%) from the emergency department, and 3 (4.7%) from the oncology. All the patients underwent abdominal CT imaging, EUS imaging, and FNA procedures with 16 (25.0%) requiring surgery. Of those who did not undergo surgery, five were considered inoperable or negative for malignancy due to SMA and CA invasion, two had lymphoma, and four were diagnosed with IPMN and were followed up. The remaining 37 patients did not undergo surgery due to their unwillingness to accept surgical risks. Table I displays the descriptive statistics of the cases.

Table II presents a comparison of the size and vascular invasion of the masses found in patients through imaging methods. Based on the data in Table II, CT did not detect any masses in 17 (26.6%) patients. Of these patients, 12 (18.8%) had a mass that was smaller than 20 mm, while 5 (7.8%) had a mass that ranged between 21-40 mm, as detected by EUS. Moreover, 5 (7.8%) patients showed SMA and CA invasion on CT, whereas 14 (21.9%) patients showed the same on the EUS. The crosstable Chi-Square analysis revealed a significant difference between CT and EUS ($p<0.001$), with EUS being superior in detecting masses smaller than 20 mm and vascular invasion.

In this study, the FNA biopsy results and features of pancreatic masses were compared using CT and EUS. The findings are presented in Table III. Out of the seven patients who were negative for malignancy, 2 (28.6%) were not visible on CT, while 5 (71.4%) were observed on both imaging methods. Among the 46 adenocarcinoma cases, 11 (23.9%) did not show a mass on CT, but seven were present between 0-20 mm on EUS, and four had masses between 21-40 mm. In the remaining 17 cases where no mass was visible on CT, EUS revealed IPMN low-grade dysplasia in one case, Neuroendocrine tumour in one case, SPN in one case, and high-grade B-cell lymphoma in one case. FNA biopsy confirmed adenocarcinoma in five cases with SMA or CA invasion on both EUS and CT, and in nine cases with no invasion on CT but identified as invasion on EUS.

Out of 16 cases, 11 were diagnosed with adenocarcinoma, one with IPMN low-grade dysplasia, one with IPMN high-grade dysplasia, one with neuroendocrine tumour, and two with SPN after FNA biopsy report evaluation (Figure 1).

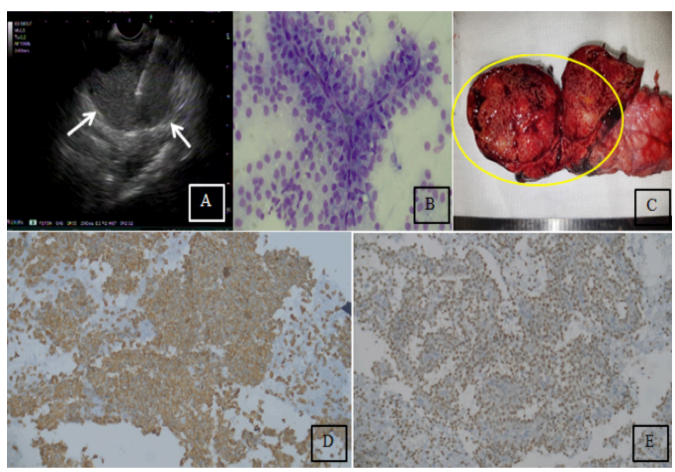

Figure 1: Solid pseudopapillary tumour of the pancreas: (A) The tumour was located in the corpus pancreas and its size was 45x45 mm on the EUS imaging. (B) With cytoplasm arranged around the capillaries, with unclear borders and cytoplasmic vacuoles in places, uniform appearance, neoplastic cells (MGGx 400). (C) 40 mm sized tumoural lesion with clearly distinguishable borders, encapsulated with occasionally haemorrhagic areas on the cut surface (the yellow circle). (D) Neoplastic cells that stain positively with vimentin (x200). (E) Neoplastic cells showing nuclear positivity by PR (x200). MGG: May Grunwald-Giemsa, PR: Progesterone receptor.

Table I: Descriptive characteristics of cases.

		N	%
Gender	Males	40	62.5
	Females	24	37.5
The first polyclinic	Gastroenterology	27	42.2
	Internal medicine	9	14.1
	General surgery	9	14.1
	Emergency	16	25.0
	Oncology	3	4.7
EUS-FNA	Pancreas	59	92.2
	Intrapancreatic common bile duct	5	7.8
Pathology result	Malignite negative**	7	10.9
	Adenocarcinoma	46	71.9
	IPMN low-grade dysplasia	2	3.1
	IPMN high-grade dysplasia	2	3.1
	NET	3	4.7
	High-grade B lymphoma	2	3.1
	Solid pseudopapillary neoplasia	2	3.1
Surgical operation	Operated	16	25.0
	Unoperated	48	75.0
Chemotherapy (CTx)	CTx (+)	39	60.9
	CTx (-)	25	39.1
Radiotherapy (RT)	RT (+) (operated patients)	16	25.0
	RT (-)	48	75.0

FNA: Fine needle aspiration; IPMN: Intraductal papillary mucinous neoplasia; NET: Neuroendocrine tumour; (+) Applied, (-) Not applied.
*** It is insufficient for diagnosis, but there are no findings suggestive of malignancy.*

Table II: Characteristics of the data obtained from imaging methods.

Tumour size	CT		EUS		p*
	N	%	N	%	
Mass not observed	17	26.6	4	6.25	
0-20 mm	4	6.3	16	25.0	<0.001
21-40 mm	26	40.6	26	40.6	
≥41 mm	12	18.8	8	12.5	
Mass + SMA or CA invasion	5	7.8	14	21.9	

** Pearson's Chi-square test; CT: Computerised tomography; EUS: Endoscopic ultrasound; SMA: Superior mesenteric artery; CA: Celiac artery.*

Table III: Comparison of mass features observed in imaging methods according to FNA biopsy results.

FNA biopsy results	CT features (n): patient	EUS features n: patient (%)			
		0-20mm	21-40mm	≥41mm	SMA and CA invasion
Malignancy negative (n:7)	No mass (2)	2 (28.6%)	-	-	-
	0-20mm (1)	1 (14.3%)	-	-	-
	21-40mm (4)	1 (14.3%)	3 (42.9%)	-	-
Adenocarcinoma (n:46)	No mass (11)	7 (15.2%)	4 (8.7%)	-	-
	0-20mm (3)	-	3 (6.5%)	-	-
	21-40mm (17)	1 (12.5%)	7 (15.2%)	3 (6.5%)	6 (13.0%)
	≥41mm (10)	-	5 (10.9%)	2 (4.3%)	3 (6.5%)
	SMA and CA invasion (5)	-	-	-	14 (21.9%)
IPMN –LGD (n:2)	No mass (1)	1 (50.0%)	-	-	-
	21-40mm (1)	1 (50.0%)	-	-	-
IPMN-HGD (n:2)	21-40mm (2)	-	1 (50.0%)	1 (50.0%)	
NET (n:3)	No mass (1)	1 (33.3%)	-	-	
	21-40mm (1)	-	1 (33.3%)	-	
	≥41mm (1)	-	-	1 (33.3%)	
HGBL (n:2)	No mass (1)	1 (50.0%)	-		
	21-40mm (1)	-	1 (50.0%)		
SPPN (n:2)	No mass (1)	-	1 (50.0%)	-	
	≥41mm (1)	-	-	1 (50.0%)	

FNA: Fine needle aspiration; CT: Computerised tomography; EUS: Endoscopic ultrasound; SMA: Superior mesenteric artery; CA: Celiac artery; IPMN: Intraductal papillary mucinous neoplasia; LGD: Low-grade dysplasia; HGD: High-grade dysplasia; NET: Neuroendocrine tumour; HGBL: High-grade B lymphoma; SPN: Solid pseudopapillary neoplasia.

There were 4 cases with adenocarcinoma diagnosis and one NET case that underwent surgical operation. However, one of the two cases with SPN diagnosis was initially considered to have chronic pancreatitis after CT and only EUS showed a mass. The patient was operated on after the FNA biopsy report confirmed the diagnosis but the postsurgical pathology report revealed serous cystadenoma (SCA) instead. Out of all the cases, only one showed inconsistency between FNA biopsy and biopsy material after the surgery.

Out of the 48 cases that were not operated on but were diagnosed through FNA biopsy, 2 (4.1%) showed high-grade B-cell lymphoma. The patients were promptly given chemotherapy. Among the diagnosed cases of adenocarcinoma, 12 (25.0%) received chemotherapy and radiotherapy while 11 (22.9%)

cases received only chemotherapy. Additionally, 1 (2.08%) case each of IPMN and NET received chemotherapy.

In the 2-year follow-up of seven patients (10.9%), who did not have malignancy detected in EUS-FNA, no clinical, laboratory or imaging findings supporting pancreatic malignancy, or distant metastasis were found.

DISCUSSION

Pancreatic lesions can be categorised as cystic or solid, with solid lesions further divided into non-neoplastic and neoplastic types. Non-neoplastic solid lesions, such as focal pancreatitis and chronic pancreatitis can lead to masses in the pancreas, and account for roughly 5-10% of pancreatectomy patients initially suspected of having malignancies.[9,10] On the other hand, solid neoplastic lesions include pancreatic adenocarcinoma (pancreatic cancer), NET, SPN, and metastatic lesions. Pancreatic cysts may present as pseudocysts, mucinous cyst neoplasm (MCN), IPMN, or SCN.

In this study, 72% of 64 patients who underwent EUS-FNA biopsy had results compatible with adenocarcinoma, while 6% had IPMN, 5% had NET, and 3% had SPN. In 11% patients, findings were consistent with pancreatitis, and no signs of malignancy were observed in some cases. High-grade B lymphoma was in 3% of patients. This study's findings for patients with no malignancy were consistent with the rates reported in the literature (5-10%) for the patients who underwent pancreatectomy with suspicion of malignancy but whose surgical pathology results did not confirm malignancy.[10]

EUS is a highly sensitive imaging technique for detecting pancreatic lesions, with an average sensitivity of 94%.[11] Compared to computed tomography, EUS has been shown to have superior sensitivity (98% *vs.* 74%) in detecting pancreatic lesions.[12] EUS can also detect lesions that may not be visible using the other imaging methods.[13] In this study, 17 out of 64 patients did not have a mass detected on CT, but EUS revealed the presence of a mass. These patients were evaluated with EUS due to pancreatic atrophy and dilatation of the pancreatic or common bile duct. The authors found that EUS was superior to CT in detecting masses with 27% of the patients having a mass detected only on EUS ($p < 0.001$). EUS-FNA biopsy confirmed adenocarcinoma in 11 of the 17 patients without a mass detected on CT. This highlights the benefits of EUS-FNA not just for detecting masses, but also for managing treatment and follow-up by providing the opportunity for the biopsy.

When pancreatic tumours are metastatic, borderline, or locally advanced biopsy is usually recommended. However, when dealing with resectable masses, the decision to confirm malignancy in the tissue before performing surgery can be controversial. The benefits and risks of biopsy must be carefully evaluated for each patient. According to a systematic review by Hartwig *et al*.,[14] EUS-FNA has a better negative predictive value (NPV) for pancreatic masses than biopsies using other imaging techniques, but it is still not reliable enough to exclude malignancy completely. The American Society for Gastrointestinal Endoscopy (ASGE) recommends taking tissue biopsies from the patients using the most appropriate method for managing suspected resectable or unresectable pancreatic solid masses.[15] If a mass is considered resectable, surgery should be done as soon as possible before a biopsy is taken from the lesion. However, if the patient wants to know the diagnosis, the surgeon will discuss biopsy options with them. If neoadjuvant chemotherapy (NAC) is planned, a sample should be taken using EUS.[16] In this study, all the patients were sampled using EUS-FNA, regardless of whether they were resectable or unresectable.

When it comes to resectable pancreatic lesions, one reason doctors may not perform a preoperative biopsy is due to the potential for pancreatitis developing after the biopsy, which could cause the previously resectable mass to become unresectable.[17] While the complication rate with EUS-FNA can vary depending on the endoscopist's experience, it typically averages around 0.08%.[18] However, in this study, none of the patients experienced pancreatitis or any other complications following an EUS-FNA biopsy. Another reason preoperative biopsy may not be recommended for resectable pancreatic lesions is the risk of insemination. In a study by Micames *et al*., involving percutaneous FNA and EUS-FNA-guided pancreatic solid lesion biopsies,[19] peritoneal carcinomatosis was detected in seven patients in the percutaneous FNA group, while none were found in the EUS-FNA group.[19] The present study also found adenocarcinoma in 46 patients due to EUS-FNA biopsy, but there have been no findings suggesting insemination in the follow-ups of these patients so far.

Based on the literature, it was suggested that collecting samples from resectable pancreatic masses would not yield much benefit.[6,14] However, a study conducted by Ngamruengphong *et al.*, indicated that preoperative EUS-FNA in the patients with resectable pancreatic mass did not increase the cancer-specific risk or overall mortality in patients with resectable pancreatic mass resected pancreatic cancer patients,[20] and there were no severe side effects of EUS-FNA. Upon analysis, seven of these patients had findings compatible with the chronic pancreatitis, and the authors did not detect any findings in the favour of malignancy. While it is stated in the literature that the negative predictive value of EUS-FNA biopsy taken from pancreatic lesions is low,[14] these patients with chronic pancreatitis were followed up for an average of two years and did not detect any findings in favour of malignancy in imaging and clinical examinations. As a result, these patients did not have to undergo unnecessary operations. Two patients were found to have high-grade lymphoma and were referred for chemotherapy before the operation. In total, 16 patients underwent surgery at the

authors' centre because 12 were non-resectable, some did not want the operation, and some went to another centre. The pathology results from the surgical material obtained after the operation and the EUS-FNA biopsy results obtained from these lesions before the operation were compatible with each other, except for one patient. Based on these results, EUS-FNA was found to contribute positively in order to manage the patients with resectable or unresectable pancreatic masses, as it prevents unnecessary operations and has no side effects in any of these patients. This study had some limitations, including its retrospective design, the low number of patients, and the fact that it was conducted in a single centre. Lastly, pancreatic masses were not surgically resected because some patients had poor general conditions or some patients did not want the operation to be done.

CONCLUSION

To avoid unnecessary surgeries and ease patient anxiety, a biopsy can be conducted using EUS-FNA for preoperative diagnosis of pancreatic lesions. The decision to perform preoperative tissue sampling depends on whether the lesion is resectable or non-resectable. Tissue sampling with EUS-FNA is deemed valuable and has minimal side effects for managing resectable or suspicious pancreatic masses.

ETHICAL APPROVAL:

Before starting the research, a permission was obtained from the Ethical Committee of Cumhuriyet University Hospital, Sivas, Turkiye (Dated: 08.07.2020, Approval number: 2020-07/30).

PATIENTS' CONSENT:

At the beginning of this study, all the patients were informed and an informed consent form was obtained from the patients for the publication of their data in the study.

COMPETING INTEREST:

The authors declared no conflict of interest.

AUTHORS' CONTRIBUTION:

EA, EC: Formation of the main idea, hypothesis of the research, and examination of endoscopic data.
EA, AK: Examining pathology data and making statistics.
All authors approved the final version of the manuscript to be published.

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