

Comparison of the diagnostic yield of rapid versus non-rapid onsite evaluation in endoscopic ultrasound-guided fine-needle aspiration cytology of solid pancreatic lesions

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Abstract

Background The role of rapid on-site evaluation (ROSE) for endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA) of pancreatic lesions is debatable. In this study, we aimed to compare the diagnostic yield of ROSE vs. non-ROSE in solid pancreatic lesions.

Methods This retrospective single-center study included patients undergoing EUS-FNA of solid pancreatic lesions from 2019-2021. Patients with cystic lesions, those undergoing fine-needle core biopsy, those undergoing repeat procedures, and patients with non-diagnostic smears with less than 6-month follow up were excluded. The diagnostic yield, need for repeat procedures and number of passes required with and without ROSE were analyzed in these patients.

Results Of the 111 patients included, 56 underwent ROSE. The majority of lesions were malignant in both groups (79.6% ROSE vs. 75% non-ROSE). The diagnostic yield was 96.4% in the ROSE group and 94.5% in the non-ROSE group. Repeat samples were needed in 1 ROSE and 2 non-ROSE patients. The median number of passes made was significantly fewer in the ROSE group (3.5, interquartile range - 3,4) compared with the non-ROSE group (4, interquartile range - 3,5) $P=0.01$. However, the frequency of procedure-related complications was similar in both groups.

Conclusion The utilization of ROSE during EUS-FNA of solid pancreatic lesions does not affect the diagnostic yield or the need for repeat samples, but reduces the number of passes needed for acquiring samples.

Keywords Endoscopic ultrasound-guided fine-needle aspiration, rapid on-site evaluation, diagnostic yield, cellularity of smears

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Introduction

Pancreatic cancer is the 12th most prevalent cancer worldwide and the 7th leading cause of cancer-related fatalities. Recent data from Globocan 2020 suggests a rising incidence of pancreatic cancer in India, where it ranks as the 24th most frequent cancer and the 19th most frequent cause of cancer-related death [1].

The diagnosis of pancreatic cancer remains challenging, and many patients are diagnosed at an advanced stage. Tissue diagnosis of pancreatic cancer is an important component of the diagnostic workup. Until the advent of endoscopic ultrasound (EUS), obtaining tissue from a pancreatic space-occupying lesion was challenging. It was in 1992 that Vilman *et al* performed the first EUS-guided fine-needle aspiration (FNA) cytology (FNAC) [2]. However, the tissue processing and diagnosis remained challenging and in 1994 rapid onsite evaluation (ROSE) of tissue samples obtained at EUS was introduced [3].

ROSE involves the evaluation of direct smears of tissue by the cytopathologist at the point of care. The advantage of ROSE is that the endosonographer receives immediate feedback regarding the adequacy of the sample and the need for repeat FNA passes [3-7]. A major disadvantage of ROSE is the requirement for an onsite cytopathologist to evaluate the smears, adding to the infrastructure requirements and cost implications for the procedure [8]. We therefore planned this study to compare the diagnostic yield of EUS-guided FNAC of solid pancreatic lesions performed with and without ROSE. The secondary aims were to compare the number of needle passes and the need for repeat procedures, when EUS-FNACs were performed with and without ROSE.

Patients and methods

This was a single-center retrospective study carried out in a tertiary care hospital in South India. Before the COVID-19 pandemic, all EUS-guided FNACs at our center were done with the assistance of ROSE. However, with the advent of the pandemic, ROSE-assisted EUS-FNAC posed logistical issues; therefore, we performed EUS-FNAC without the assistance of ROSE. In this study, we included all patients who underwent EUS-guided FNAC for solid pancreatic lesions between June 2019 and May 2021, and we compared the outcomes of EUS-guided FNAC with and without ROSE. The ROSE group included consecutive patients who underwent EUS-guided FNAC between June 2019 and March 2020. The non-ROSE group included consecutive EUS-guided procedures performed between April 2020 and May 2021.

We excluded tissue obtained using a core biopsy needle, i.e., fine-needle biopsy (FNB), cystic pancreatic lesions and repeat EUS-FNA procedures. Patients with non-diagnostic smears who had a follow-up of less than 6 months were also excluded. The clinical profile, laboratory findings, details of EUS findings and procedure (site and size of lesions, number of passes performed during FNAC, type and size of FNAC needle used), adequacy of the obtained specimen and the final diagnosis were recorded on structured data forms. The prerequisites for FNA were similar to those for any therapeutic endoscopic procedure [9]. The study was approved by the institutional review board at Christian Medical College, Vellore (IRB No.14889).

Sample acquisition and processing

EUS-FNAC was performed with a 22-G or 25-G EUS-FNA needle with a removable stylet. EUS-FNA was performed by targeting the lesion in the center of the EUS image, using color Doppler to avoid intervening blood vessels. The size of the needle used was entirely at the endoscopist's discretion. The procedures were performed by one of 5 senior endoscopists, each with more than 10 years of experience, during which they had performed more than 1000 cases each at our center, which deals with a high patient volume.

In the ROSE group the samples were expressed on clean and previously labeled slides, using a stylet and/or air flush; the cytology technician helped prepare the slides. The slides were then stained and examined by the cytopathologist in the endoscopy suite itself. In the non-ROSE group the EUS-FNA material was expressed over slides as described above, and the smears were prepared by the endosonographers themselves.

In both the groups, 2 separate sets of slides were prepared: one set was air-dried and then stained with modified Giemsa stain, while the other set was fixed in alcohol to be stained later with hematoxylin & eosin stain and the Papanicolaou stain. A portion of the material aspirated was also sent in formalin as a cell block in both groups.

The standard protocol followed at our institution was to obtain at least 3 passes while performing the procedure. Additional passes were taken in the ROSE group if the cytopathologist felt the smears were inadequate. In the non-ROSE group, the smears were examined by the endoscopist performing the procedure, and if they were thought to be inadequate, additional passes were taken.

The slides and tissue were reported by pathologists and the reports were recorded. The pathologist reported the cellularity of the smear as acellular if there were no cells noted, scant/mild if <10 cell clusters were noted, moderate if 11-30 cell clusters were noted, and dense if more than 30 clusters were observed. This system of grading cellularity is used by the pathologists at our center and has been adapted from several studies [10,11].

The duration of the procedure was calculated from the monitoring sheets maintained by the nurses assisting with the procedure. The time from oral intubation to the time of withdrawal of the scope was taken as the duration of the procedure.

Outcomes

The primary outcome was the diagnostic yield of EUS-FNAC with ROSE compared to EUS-FNAC without ROSE. A positive diagnostic yield was defined as either a definitively malignant or a definitive benign final cytologic diagnosis. The diagnosis was considered malignant if cancer cells were present, or benign if EUS-FNAC did not reveal evidence of cancer and follow-up at 6 months did not reveal any evidence of cancer. Histopathology reports of patients who underwent surgery were also analyzed. The secondary outcomes were to compare the number of needle passes and the need for repeat procedures, when EUS-FNACs were performed with and without ROSE.

Statistical analysis

Data entry was done using Microsoft Excel. Descriptive and inferential statistical analyses were calculated using SPSS version 23 (IBM Corp. Released 2015. IBM SPSS Statistics for Windows, Version 23.0. Armonk, NY: IBM Corp.) Categorical variables were compared between groups using the chi-square

test. The Mann-Whitney test was used to compare medians and Student's *t*-test was used to compare means. A *P*-value <0.05 was considered statistically significant to refute the null hypothesis.

Results

During the study period, 750 patients underwent EUS (Fig. 1). Of these, 234 underwent EUS-guided FNA from solid lesions, and 119 of the FNACs were for pancreatic lesions. Eight patients with non-diagnostic FNAC and who were lost to follow up were excluded. We therefore included 56 patients who underwent EUS-FNAC with ROSE and 55 patients who underwent EUS-FNAC without ROSE for solid pancreatic lesions (Fig. 1)

The baseline characteristics of the patients are provided in Table 1. Apart from the sex distribution (more males in the non-ROSE group, 45.3% vs. 54.7%), both groups were comparable. The majority of the lesions were malignant in both groups (79.6% vs. 75%). The benign lesions observed were walled-off necrosis/pseudotumors (*n*=13), chronic and acute-on-chronic pancreatitis (*n*=7), groove pancreatitis (*n*=2), and pancreatic tuberculosis (*n*=2). Based on the cytology reports obtained from the reporting pathologist, the cellularity of the smears was classified as acellular, scant/mild, moderate or dense. No difference in cellularity was noted between the groups (Table 2).

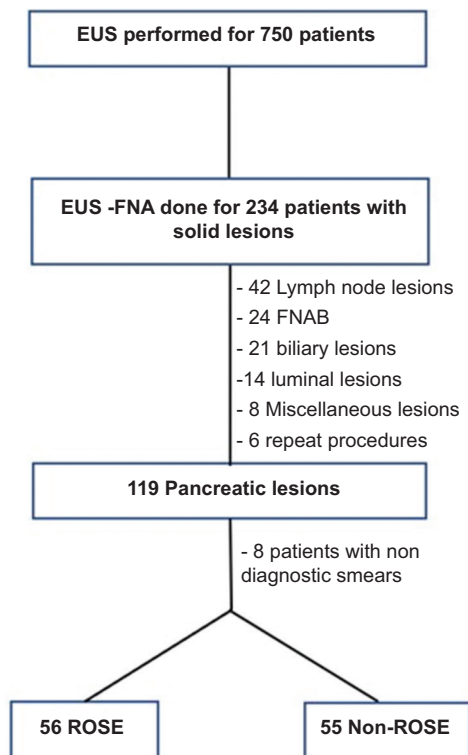


Figure 1 Patient flow diagram
EUS, endoscopic ultrasound; FNA, fine-needle aspiration; FNAB, fine-needle aspiration biopsy; ROSE, rapid onsite evaluation

Cell block was available in 92.2% of patients who underwent EUS-FNAC with a 22-G needle and in 97.3% when a 25-G needle was used, which was not statistically significant (odds ratio 0.33, 95% confidence interval 0.03-2.9; *P*=0.41).

Three patients underwent repeat FNAC (1 in the ROSE group and 2 in the non-ROSE group) because of a high suspicion of malignancy. The repeat FNAC report of the ROSE patient was benign, whereas both patients in the non-ROSE group had evidence of malignancy on repeat FNAC. ROSE was not used for any of the repeat procedures. The median number of passes required was significantly lower in the ROSE group when compared with the non-ROSE group (3.5, interquartile range (IQR) - 3,4) vs. (4, IQR - 3,5), *P*-value - 0.01 (Table 2).

The number of patients who underwent surgery was similar in both groups (9 vs. 13). Consistency with the surgical diagnosis was noted to be similar in both groups (100% vs. 92%).

Discussion

The present study aimed to compare the diagnostic yields of EUS-FNAC with and without ROSE in patients with solid pancreatic lesions. The percentage of malignant lesions was 76.8% and 70.9% in the ROSE and non-ROSE groups, respectively. A smaller number of lesions in the ROSE (23.2%) and non-ROSE groups (29.1%) were labelled as benign, based on histology and follow up at six months. The overall diagnostic yield of EUS-FNAC for solid pancreatic lesions in our study was 95.9%.

There was no significant difference in the diagnostic yield between the ROSE and non-ROSE groups. The findings of our study are consistent with those of a randomized trial that did not reveal any significant difference in the diagnostic yield with the use of ROSE [12]. A systematic review and meta analysis also showed that ROSE does not improve diagnostic yield and adequacy in solid pancreatic lesions [13]. Another recent study demonstrated a diagnostic yield of more than 80% if ROSE was not used in solid pancreatic lesions, when the procedure was performed by experienced endoscopists [14]. A small subset of patients (1 ROSE and 2 non-ROSE) with a high suspicion of a neoplasm required repeat EUS-FNAC: the repeat FNA reports were benign in the ROSE group and malignant in both non-ROSE patients. All the repeat procedures were done without ROSE.

Satisfaction with the smears and the need for repeat procedures have been concerns regarding EUS-FNAC procedures without ROSE [15]. Our study did not show any difference between the groups in the cellularity or in the need for repeat procedures. This was probably due to the rapid in-room processing of the samples in the endoscopy suite itself. All the smears in the non-ROSE group were prepared by the endosonographer in the endoscopy suite. Our study suggests that if endosonographers or endoscopy technicians can be trained to prepare the smears, then the need for cytology technicians can be reduced. This finding has been demonstrated in 2 recent randomized trials, which showed that the evaluation of smears by the endoscopist improved diagnostic accuracy in FNA of solid pancreatic lesions and could lead to shorter procedure times [16,17].

Table 1 Baseline characteristics

Parameters	Patients who underwent EUS-FNA (n=111)	ROSE (n=56)	Non-ROSE (n=55)	P-value
Mean age (SD)	53.3 (13.4)	53.4 (14.5)	53.1 (12.4)	0.87
Mean size of mass in mm (SD)	30.8 (13.8)	30.5 (13.1)	31.2 (14.7)	0.82
Location of lesion (%)				
Head	76 (68.5)	35 (62.5)	41 (74.5)	0.40
Uncinate process	12 (10.8)	8 (14.2)	4 (7.4)	
Neck	4 (3.6)	3 (5.4)	1 (1.8)	
Body	18 (16.2)	10 (17.9)	8 (14.5)	
Tail	1 (0.9)	0	1 (1.8)	
Indication for FNA* (%)				
Mass lesion in pancreas	107 (96.4)	54 (94.7)	53 (96.3)	0.54
Obstructive jaundice	4 (3.6)	2 (3.5)	2 (3.7)	
Pain	1 (0.9)	1 (1.8)	0	
Sex (%)				
Male	85 (76.6)	49 (57.6)	36 (42.4)	0.007
Female	26 (23.4)	7 (26.9)	19 (73.1)	
Needle gauge (%)#				
22	64 (57.7)	29 (58)	35 (68.6)	0.31
25	37 (33.3)	21 (42)	16 (31.4)	
Median number of passes (IQR)	4 (3.4)	3.5 (3,4)	4 (3,5)	0.01
Number of patients who underwent surgery (%)	22 (19.8)	9 (16.1)	13 (23.6)	0.32
Mean duration of procedure, min (SD)^	61.8 (21.3)	58 (18.4)	66 (23.4)	0.09

*Multiple indications for 111 patients, #Data unavailable for 10 patients, ^ Data not available for 31 patients
EUS, endoscopic ultrasound; FNA, fine-needle aspiration; ROSE, rapid onsite evaluation; SD, standard deviation

Table 2 Primary and secondary outcomes

Outcomes	ROSE (n=56)	Non-ROSE (n=55)	P-value	Odds ratio (95%CI)
Diagnostic smears (%)	54 (96.4)	52 (94.5)	0.68	1.55 (0.25-9.7)
Repeat FNAC (%)	1 (1.8)	2 (3.6)	0.62	0.48 (0.04-5.47)
Diagnostic smears in repeat procedures (%)	0	3 (100)		
Nature of diagnosis (%)			0.48	1.35 (0.58-3.17)
Malignant	43 (76.8)	39 (70.9)		
Benign	13 (23.2)	16 (29.1)		
Cellularity (%)			0.29	0.67 (0.31-1.43)
Scant/mild	21 (37.5)	26 (47.3)		
Moderate/dense	35 (62.5)	29 (52.7)		
Consistency with surgical diagnosis (%)	9/9 (100)	12/13 (92.3)	0.62	2.23 (0.08-62.43)

FNAC, fine-needle aspiration cytology; ROSE, rapid onsite evaluation; CI, confidence interval

EUS-FNAC has been in vogue for a long time. The initial reports that showed lower diagnostic accuracy in EUS-FNAC could be the result of pathologists' misinterpretation and misdiagnosis [18]. Since the procedure has been around for a long time, the experience of cytopathologists has also improved, resulting in better diagnostic yields.

We did not note any significant difference between the ROSE and non-ROSE groups in the need for repeat EUS-guided FNAC. This finding is at variance with the report by Collins *et al*, who found twice the number of repeat procedures in the non-ROSE group compared with the ROSE group [4].

In our study, we noticed that there were more needle passes in the non-ROSE group as compared to the ROSE group, and the difference was statistically significant. In a study by Le Blanc *et al*, the number of needle passes was ≥ 7 when EUS-FNAC was performed without the assistance of ROSE [19]. Erickson *et al* also observed an increase in the number of needle passes in procedures where an onsite cytopathologist was not available [20]. The higher number of needle passes during EUS-FNAC without ROSE is probably due to the lack of real-time feedback of sample adequacy and diagnosis. Recent studies suggest that the number of needle passes has no bearing on the incidence

of complications or procedure time [12]. Lee *et al* demonstrated similar diagnostic accuracy in patients randomized to undergo either ROSE or 7 passes during the EUS-FNAC procedure. They also demonstrated that the procedure cost was 2.8 times greater when ROSE was used [21]. In a previous observational study by Iglesias *et al* there was a report of complications in the non-ROSE arm [22]. In the present study, we did not note any increase in complications with a higher number of passes.

The retrospective nature of the study is a major limitation. We excluded patients undergoing FNB; therefore, our results may not be generalizable. Studies comparing FNAC vs. FNB have not shown a significant advantage with FNB, especially for the evaluation of pancreatic solid lesions [23-26]. Considering the cost constraints of single-use FNB at our center, we prefer to use single-use FNAC needles for EUS-guided tissue access. The relatively small sample size would be another limitation of the study. Our findings are in concordance with recent studies [12,13,21] suggesting that ROSE is probably not necessary for solid pancreatic lesions, as it does not improve the diagnostic yield or diagnostic adequacy.

Summary Box

What is already known:

- There is conflicting evidence regarding the diagnostic yield of endoscopic ultrasound (EUS)-guided fine-needle aspiration cytology (FNAC) of solid pancreatic lesions, with or without rapid onsite evaluation (ROSE)
- There is contradictory evidence regarding the effectiveness of ROSE in decreasing the need for repeat EUS-FNAC procedures to enhance diagnostic accuracy
- The number of passes needed for tissue acquisition during EUS-FNAC is higher when ROSE is not used
- There are limited data on the diagnostic accuracy when assessment of smears is performed by the endoscopist/endoscopy technician

What the new findings are:

- The diagnostic yield of EUS-FNAC of solid pancreatic lesions was similar whether ROSE is performed or not, as was also the need for repeat FNAC
- The cellularity of smears obtained during EUS-guided FNAC was similar with or without ROSE
- Though the number of passes required to obtain tissue was higher when ROSE was not used, there was no associated increase in complications
- Assessment of the smears by a trained endoscopist had a similar diagnostic accuracy when compared to ROSE by a pathologist

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