ORIGINAL ARTICLE

Factors Affecting The Results of Endoscopic Ultrasound-Guided Fine Needle Aspiration In Subepithelial Lesions of The Gastrointestinal Tract

Running title: EUS-guided FNA in subepithelial lesion

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Abstract

Aim: Endoscopic ultrasound-guided fine needle aspiration (EUS-FNA) is a reliable diagnostic method to discriminate gastrointestinal subepithelial lesions (SEL). We aimed to evaluate the factors affecting of EUS-FNA procedure's diagnostic success in SEL.

Method: Between May 2010-March 2020, all patients who underwent EUS-FNA were retrospectively evaluated. Factors effecting success rate (number of passes, needle size, lesion size, lesion localization, endoscopist's experience and presence of on-site cytopathologist) were investigated.

Results:A total of 170 procedures were performed. SEL localization was 36.5% (n=62) esophagus, 55.9% (n=95) stomach. The mean lesion size was 26.5 ± 14.5 mm. Fourty one percent of lesions were ≤20 mm. In 115 (67.6%) of procedures, cytopatology was diagnostic and most common were spindle cell tumors (SCT) (n=42, 24.7%), followed by gastrointestinal stromal tumors (GIST) (n=31, 18.2%) and leiyomyommas (n=21, 12.4%). EUS-FNA success was higher in SEL >20mm (p=0.02) and endoscopist's experience (p = 0.001). Lesion's localization, layer and echogenicity, needle size, number of passes didn't affect success rate. The lesion size >20 mm (P=0.01), endoscopist's experience (P=0.003) and presence of cell block (P=0.02) were independent predictors for diagnostic success.

Conclusions: EUS-FNA procedure is an effective method, lesion size, endoscopist's experience and presence of cell block increases the yield of cytological diagnosis in SEL.

Key words: Endoscopic ultrasonography, subepithelial lesions, Fine needle aspiration

Introduction

Subepepithelial lesion (SEL) are bulges found within the lumen of the gastrointestinal tract, mostly covered by normally appearing mucosa. Although the incidence is not known precisely because of their asymptomatic nature, the prevalence of SEL detection during other endoscopic procedures is 0.36% .1 A lesion detected during endoscopic intervention, suggesting SEL, may be derived from any layer of the gastrointestinal canal wall (intramural), or may be due to an extramural pathology.2

Endoscopic ultrasonography (EUS) is the most important imaging method for diagnosing and evaluating SEL because it allows imaging of the gastrointestinal wall layers; provides data about lesion size, location, sonographic presentation and allows imaging-associated fine needle aspiration.3,4

Endoscopic ultrasound-guided fine needle aspiration (EUS-FNA) is a minimally invasive procedure used to diagnose pathologies such as gastrointestinal tumors, pancreatic tumors, abdominal and mediastinal lymphadenopathies (LAP), mediastinal masses which are related to gastrointestinal tract and neighboring organs. EUS-FNA procedure can be used for cytological and immunohistochemical (IHC) examination.5

When classifying the spindle cell (SCT) like gastrointestinal stromal tumor (GIST), leiomyoma and schwannoma, cell block and IHC examination results have been shown to correlate with the final diagnosis.6 It has also been shown that the localization of the lesion, the experience of the endoscopist, the type of needle used, the number of passes, the FNA technique, the preparation of cytologic specimens, and the presence of a cytopathologist during the procedure are associated with diagnostic success.7 However, the relationship between these factors and diagnostic success has not yet been fully elucidated.

Material- Method

Between May 2010 and April 2020, the results of 438 procedures performed in 388 patients with SEL diagnosis, at Endosonography Unit of the Gastroenterology Department, University of Ankara were retrospectively reviewed. Out of these patients, 170 EUS-FNA procedures from 147 patients were evaluated.

Patients' demographic data, number of procedures, endoscopic lesion localization, endosonographic lesion characteristics (size, echogenicity, origin layer, presence of ulcer-bleeding, serosal invasion, edge irregularity) were noted. EUS-FNA procedure data (needle type and size, pass count, onsite pathologist attendance), pathology results (cytology and immunhistochemical examination when it is done) and when surgical resection is done pathology results of the resected material were collected.

Endoscopic ultrasonography:EUS procedure was performed after one night fasting. Before EUS procedure sedation with midazolam or midazolam-propofol-fentanyl is used and procedure is done with Fujinon 4400 SU-7000-EG-530 UR radial and/or Lineer EUS (Fujinon 4400 SU-7000-EG-530 UT) and Pentax+Hitachi previous echoendoscopes. All procedures were performed with radial echoendoscopy first.

Endoscopic ultrasound guided cystic lesion aspiration procedure: Linear EUS (Fujinon 4400 SU-7000-EG-530 UT) device was used for aspiration. Platelet levels, active partial thromboplastin time, and prothrombin time were measured before the procedure. EUS-FNA procedures were performed by a single endoscopist. During the procedure, one of the standard 19Gy, 22Gy, and 25Gy needles (Olympus, Boston, Cook) was used according to the localization, size and status of the lesion.

Cytopathological evaluation: Cytopathological evaluation is done by only one experienced cytopathologist from the Department of Pathology, Ankara University of Medical School. Material was spreaded on microscope slide, dried with air or fixated with alcohol and stained with May-Grunwald Giemsa or Papanicolaou (PAP) dyes. Due to the inability to differentiate SCT cytologically, tissue pieces were sent in physiological saline solution for cell block and IHC staining if adequate tissue was obtained. Cytological and IHC examination results were evaluated separately.

Preparations that contain enough cells and suggest a cytopathologic diagnosis were considered as "diagnostic"; preparations that contain normal tissue elements, hemorrhagic, insufficient cells, and do not give diagnosis were considered as "non-diagnostic". The diagnostic cytology results were classified as SCT, lipoma, aberrant pancreatic tissue, abcess, cyst. Preperations which can be classified by IHC considered as diagnostic, when cell block can not be obtained or cell block was IHC negative considered as non-diagnostic.

The first EUS-FNA procedure was carried out in 2010 at the University of Ankara Endosonography Unit. In order to assess the endoscopist's experience over the success of the procedure; years 2010-2014 and 2015-2020 evaluated within itself and success rates compared. When it is possible to reach follow-up data of the patients, pathologic results of surgical resections were compared with the results of EUS-FNA guided cytology and IHC.

SPSS statistics program version 21.0 for Windows program was used for patient records and statistical analyzes. Descriptive statistical methods were applied for all features of subepithelial lesions. Continuous data were summarized as mean ± standard deviation and median (minimum-maximum), categorical data as frequency and percentage. Non-parametric test was used for continuous variables without normal distribution and $p < 0.05$ was considered significant. Univariate and multivariate logistic regression analysis were performed to assess the predictors for the diagnostic success. The study was approved by Ankara University School of Medicine Ethics Committee (Ethics Committee Date: 14.04.2014, Decision No: 06-258-14).

RESULTS

Between May 2010 and March 2020, a total of 170 EUS-FNA procedures were performed in 147 patients with SEL. EUS-FNA procedures were performed more than once in 17 patients (four times in 2 patient, thrice in 2 patients, twice in 13 patients). Mean patient age was 54.2 ± 13.5; 40.6% (n=69) were male. Ninetyfive (55.9%) of lesions were in stomach, 62 (36.5%) in esophagus, 12 (7.1%) in duodenum and 1 (0.6%) in rectum (Table-1). Mean lesion size was 26.5 ± 14.5 mm; 42.7% (n=70) of the lesions were <20mm, 57.3% (n=94) were >20 mm in size (6 lesions' size data were unavaliable). During EUS procedure, there were hypoechoic lesions in 68.2% (n=116), heterogen lesions in 34.1% (n=58), hyperechoic lesions in 2.4% (n=4) and anechoic lesions in 1.8% (n=3). In EUS procedure, 12 patients had lymphadenopathy, 26 lesions had border irregularity, 12 lesions had cysts, 15 lesions had calcification. Ulcer was observed in the middle of the lesion during endoscopy at 16 patients. Endosonographic characteristics of the patients are summarized in (Table 1).

Table 1. Endosonographic characteristics of subepithelial lesions

		N	%
Gender	Female	101	59.4
	Male	69	40.6
Age	54.2±13.5		
Localisation	Esophagus	62	36.5
	Stomach	95	55.9
	Duodenum	12	7.1
	Rectum	1	0.6
Origin	Muscularis mucosa	18	10.6
	Submucosa	18	10.6
	Muscularis propria	134	78.8
Lesion size	≤20mm	70	42.7
	>20mm	94	57.3
Echogenity	Hypoechoic	116	68.2
	Heterogeneous	58	34.1
	Hyperechoic	4	2.4
	Anecoic	3	1.8
Other findings	Lymphadenopathy existance	12	7.1
	Edge Irregularity	26	15.3
	Cyst in the lesion	12	7.1
	Hyperechogenic areas in the lesion	15	8.8

Of 170 EUS-FNA procedures, 115 (%67.6) were cytopathologically diagnosed; 55 (32.4%) were not diagnostic. Forty two (24.7%) of cytologically diagnosed patients had SCT, 21 (12.4%) had leiyomyomas, 31 (18.2%) had GIST, 6 (3.5%) had ectopic pancreas, 5 (2.9%) had lipoma, 3 (1.8%) had schwannoma and 7 (4.1%) had other diagnosis (abcess, adenocarcinoma, metastasis of over ca, bronchogenic cyst and neuroendocrine tumor) (Table-2). In 81 patients who we were able to obtain cell block, 36 (44%) got definitive diagnosis through IHC. In 45 (56%) cases no diagnostic staining pattern was detected. Patients with positive IHC staining; 17 were diagnosed as GIST, 14 were leiomyoma, 2 were ectopic pancreas, 1 was neuroendocrine tumour (NET), 1 was adeno carcinoma and 1 was schwannoma.

Size of the needle that was used were 19Gy, 22Gy and 25Gy in 17.6% (n=30), 59.4% (n=101) and 20.6% (n=35) of the procedures respectively. Four of patient's needle information were not found. The diagnostic success rates for needle type were 66.7%, 70.3%, 60% for 19Gy, 22Gy and 25Gy needles, respectively (p=0.53). The results of IHC examination success of 19Gy, 22Gy and 25Gy needles were 30%, 21.8% and 14.3% respectively (p = 0.31). The mean number of passes were 2.18 ± 0.77 (min/max=1/5), 2.21 ± 0.77 in diagnostic group and 2.13 ± 0.77 in non-diagnostic group (p=0.5).

Onsite cytopathologist was present during 15.3% (n=26) of the procedures while rest were done 84.7% (n=144) without onsite cytopathologist. None of the patients had complications due to the procedure (Table 2).

Table 2: Evaluation of EUS-FNA results and parameters related to the procedure

		N	%
Cytology result	Diagnostic	115	67.6
	Nondiagnostic	55	32.4
Cytopathological diagnosis	Spindle cell tumor	42	24.7
	GIST	31	18.2
	Leiyomyomma	21	12.4
	Ectopic pancreas	6	3.5
	Lipoma	5	2.9
	Schwannoma	3	1.8
	Others	7	4.1
Immunohistochemical examination	Done	81	47.6
Immunohistochemical examination	Diagnostic	36	21.2
	Non diagnostic	45	26.5

Diagnosis according to immunohistochemical examination	GIST Leiomyoma Ectopic pancreas Schwannoma NET Adeno carcinoma	17 14 2 1 1 1	10 8.2 1.2 0.6 0.6 0.6
Neddle size	19Gy 22Gy 25Gy	30 101 35	17.6 59.4 20.6
Mean number of passes (1-5)	Diagnostic Non diagnostic	2.21±0.77 2.13±0.77	
Pass number	<3 ≥3	119 49	70 28.8
Onsite cytopathologist	Yes No	26 144	15.3 84.7
Procedure related complications	No		

According to EUS-FNA outcome, the diagnostic success rates were according to site of the lesion; esophagus 75.8%, stomach 65.3%, duodenum 41.7%, rectosigmoid 100% (p = 0.08). When success rates of esophagus and stomach lesions are compared, there is a statistically insignificant superiority in esophageal lesions (%75.8 vs. 65.3%, p = 0.16). EUS-FNA success rate was significantly higher in SEL patients with long axis > 20 mm than in those with <20 mm (%74.5 vs 57.1%, p = 0.02). The diagnostic success of the EUS-FNA procedures performed between 2015 and 2020 compared with the procedures between 2010 and 2014 to determine whether the success of EUS-FNA procedure is effected by the endoscopist's experience. Procedure success rates in last five years were significantly higher than first five years (%75.6 vs 49%, p = 0.001). The diagnostic success rate was significantly higher without onsite cytopathologists (%71.5 vs 46.2%, p = 0.01) than those with onsite cytopathologists (Table 3).

Table 3. Factors affecting EUS-FNA results in cytopathological diagnosis of SEL

		Non diagnostic n(%)	Diagnostic n (%)	P value
Organ	Esophagus Stomach Duodenum Rectum	15(24.2) 33(34.7) 7(58.3) 0(0)	47(75.8) 62(65.3) 5(41.7) 1(100)	0.08
Lesion long size	<20mm >20mm	30(42.9) 24(25.5)	40(57.1) 70(74.5)	0.02
Needle type	19Gy 22Gy 25Gy	10(33.3) 30(29.7) 14(40)	20(66.7) 71(70.3) 21(60)	0.53
Pass number	<3 ≥3	42(35.3) 13(26.5)	77(64.7) 36(73.5)	0.27
Onsite cytopathologist	Yes No	14(53.8) 41(28.5)	12(46.2) 103(71.5)	0.01
Experience of endoscopist	2010-2014 2015-2020	26(51) 29(24.4)	25(49) 90(75.6)	0.001

According to logistic regression analysis, the lesion which was larger than 20 mm (OR 2.52; 95% CI, 1.22-5.21; P=0.01), experience of the endoscopist (OR 3.21; 95% CI, 1.50-6.86; P=0.003) and presence of a cell block (OR 2.40; 95% CI, 1.16-4.97; P=0.02) were independent predictors for diagnosis.

When our hospitals archives investigated, it is found that twenty five (17 %) of 147 patients who underwent EUS-FNA for SEL underwent surgical resection. Pathological diagnoses of resected lesions were; 10 reported as leiomyoma, 12 as GIST, 2 as aberrant pancreatic tissue, and 1 as schwannoma, which were similar to EUS-FNA finding. In 10 of 25 patients (40%) who underwent surgical resection, the cytopathology reports were diagnostic. All ten immunohistochemically examined patients were diagnosed with the same histopathological diagnosis after surgery (Table 4).

Table 4. Pathology, cytology and IHC results of surgically resected patients

Patient	Pathology after surgery	Cytological diagnosis	IHC diagnosis
1.	**Aberrant pancreas**	Non diagnostic	*
2.	**Leiomyoma**	Non diagnostic	Not diagnostic
3.	**Leiomyoma**	**Spindle cell tumor**	**Leiomyoma**

4.	**Leiomyoma**	**Spindle cell tumor**	*
5.	**Leiomyoma**	Non diagnostic	*
6.	**Leiomyoma**	Non diagnostic	*
7.	**Leiomyoma**	**Spindle cell tumor**	Not diagnostic
8.	**Leiomyoma**	**Spindle cell tumor**	**Leiomyoma**
9.	**GIST**	**Spindle cell tumor**	**GIST**
10.	**GIST**	Non diagnostic	*
11.	**GIST**	**Spindle cell tumor**	**GIST**
12.	**GIST**	**Spindle cell tumor**	**GIST**
13.	**GIST**	**Spindle cell tumor**	**GIST**
14.	**Leiomyoma**	**Spindle cell tumor**	*
15.	**Leiomyoma**	**Spindle cell tumor**	*
16.	**GIST**	**Spindle cell tumor**	*
17.	**Leiomyoma**	**Spindle cell tumor**	*
18.	**Aberrant pancreas**	Non diagnostic	*
19	**GIST**	**Spindle cell tumor**	*
20.	**GIST**	**Spindle cell tumor**	**GIST**
21.	**GIST**	**Spindle cell tumor**	**GIST**
22.	**GIST**	**GIST**	*
23.	**GIST**	**Spindle cell tumor**	*
24.	**GIST**	**Spindle cell tumor**	**GIST**
25.	**Schwannoma**	**Spindle cell tumor**	**Schwannoma**
*** Patients without cell block**			

Discussion :

In our study, 67.6% of gastrointestinal SEL were diagnosed cytopathologically by EUS-FNA. Success rates in previous studies ranged from 52 to 88%.6,8-14 In a study made by Rong et al, 46 of the 170 EUS FNA procedures were performed on SEL, diagnostic success rate was 80.4%, cell block was obtained in 57.1% of the procedures and IHC examination was performed.15

In another study, thirty seven c-kit (+) GIST which were surgically resected, EUS-FNA was cytologically diagnostic in 78.4% of them. Cell block was obtained in 35.1% of them; also in 16,2% of cases, c-kit (+) was found by IHC staining.16 Study by De Moura et al compared FNA and FNB, the rate of IHC examination in the group with FNA was found to be 40%.17 In our study, cell block was obtained from 47.6% of the EUS-FNA procedures and 21.2% were IHC.

The present of on-site cytopathologists in EUS-FNA procedure increaes diagnostic yield by up to 20%.18 Jhala et al. reported that the success of the EUS-FNA procedure in SEL was due to the presence of on-site cytopathologists and the number of passages performed.19 In another study reported by Alsohaibani et al, 60 EUS-FNA procedures performed in the presence of onsite cytopathologist and 49 EUS-FNA procedures performed without onsite cytopathologist were compared. The success rate of onsite cytopathologic procedures was found to be significantly higher (77% vs. 53%, p = 0.01).20 In our study, 26 procedures performed in the presence of an on-site cytopathologist before 2014. In later tears we did not have an on-site cytopathologist during 144 procedures performed. The diagnostic success of without onsite cytopathologist procedures was found to be significantly higher than with onsite cytopathologist procedures (%69.4 vs.% 46.2, p = 0.04), as contradictory to previous studies. The lack of success in the initial period may be due to the inexperience of the cytopathologist to evaluate EUS-FNA results. Because EUS and EUS-FNA procedures started in 2010 in our hospital. Furthermore it may also be related to an increase in the endoscopist's experience in that the diagnostic success of procedures performed between 2015 and 2020 is significantly higher than the procedures performed between 2010 and 2014.

Another factor affecting the success of the EUS-FNA procedure is the number of passes.15,21 In a study made by Rong et al. the success of EUS-FNA procedures performed in the absence of an on-site cytopathologist with a pass count of ≥3 was significantly higher than that of <3.15 In our study, there was no difference in success between pass numbers ≥3 and <3. In a randomized controlled trial of 142 patients with pancreatic mass, EUS-FNA procedures were done with onsite cytopathologists or without onsite cytopathologists with 7 passes, success rates were similar.22 In the light of this current data, it is controversial how many ideal pass numbers should be made; it is recommended that more passes can be made for procedures without an on-site facility of cytopathologist.23,24

In our study, EUS FNA success in subepithelial lesions was found to be higher in those of >20 mm in long axis dimension than <20 mm (%74.5 vs 57.1%, p = 0.02). Similarly; The diagnostic success of IHC examination was also higher in lesions with >20 mm but there was no statistical difference

(%24.5 vs %15.7; p=0.17). However previous studies also show that lesion size is related to diagnostic success.8,16,25

In EUS-FNA procedures, needles with 3 different calibrations were used; 19Gy, 22Gy, 25Gy. While 19Gy and 22Gy needles are bigger and have an advantage of sampling more tissue, 25 Gy needles are more flexible and more suitable for manipulation. Contradictory results are present in previous studies comparing needle diameters. In a meta-analysis involving 17 studies, there was no correlation between needle diameters and diagnostic success.26 There were no significant differences between needle selection and cytological diagnostic success in two different studies using 22Gy and 25Gy needles.15,27 Our study results are also in line with the above mentioned studies as there was no correlation between needle diameters and diagnostic success, similar to these studies.

However, in some publications; 25Gy needles are reported to be more successful in technically difficult procedures such as peripancreatic lesions, small and mobile SEL.28-30 On the contrary, there are also publications that show that 19Gy and 22Gy needles are more successful in lesions that require cell block / IHC because they are at higher calibrations and allow for more tissue sampling.31 In our study; there was no difference between the results of IHC examination of 19Gy, 22Gy and 25Gy needles (%30, %21.8 and %14.3; p = 0.31) respectively.

Another thing that affects the success of EUS-FNA in SEL is the location of the lesion. In two previous studies, the diagnostic success of the EUS-FNA procedure was shown to be higher in gastric localized lesions.10,16 On the other hand, there are publications showing that lesion localization does not affect diagnostic success.8,32 In our study, diagnostic success rates were 75.8% in esophageal lesions, 65.3% in gastric lesions and 41.7% in duodenum lesions (p = 0.08). Although not statistically significant, the success rate was higher in esophageal lesions contrary to the literature.

It is emphasized that the presence of a cytopathologist during the procedure, cell block and IHC examination, lesion localization, endoscopist's experience, type of needle used, number of passages made, FNA technique, the preparation of cytologic specimens are associated with the diagnostic success of SCT.10,7 However, the relationship between these factors and diagnostic success has not yet been fully elucidated. In our study, presence of cell block, experience of endoscopist and lesion diameter (>20 mm) were independent predictors for diagnosis.

To increase diagnostic success rates, FNB, Tru-Cut and ProCore biopsy needles have been developed to be used in the EUS guidance. In a meta-analysis comparing FNA, FNB, and Tru-Cut biopsy needles, no significant difference was found between diagnostic success rates.26 Similar result was found in a prospective multicenter study with 135 FNA and 139 FNB patients with pancreatic or another organ's mass, SEL and lymph nodes were compered. There was no difference in FNA and FNB groups in terms of diagnostic efficiency (FNA 91.1%, FNB 88.5% P = 0.48).33 Conversely, in another study comparing with FNA and FNB for subepithelial lesions (115 FNA versus 114 FNB), it was reported that the sensitivity and accuracy of FNB was higher than FNA and that a lower number of passes was required for the cell block in FNB group.17 In recent studies, there is different results which is stated that FNB is more successful or there is no difference between FNB and FNA.34,35 Since the FNB needles are more expensive in our country, only standard needles are used for EUS-FNA procedure in this study.

Weak aspects of our study are: small number of patients, inadequate number of duodenum and rectum localised cases, low number of IHC examination patients, not having onsite cytopathologist in all cases. The number of patients undergoing surgical resection is low; because of the retrospective nature of the study, it is not possible to access the data completely and our endoscopy laboratory is a reference center; patients sent from other clinics are sent only for EUS-FNA procedure.

In conclusion; EUS-FNA is a reliable, minimally invasive method for differential diagnosis of SELs. The diagnostic success is in two third of patients. We also demonstrated that the success of the diagnosis is related to lesion size, presence of cell block and endoscopist's experience. On the other hand, number of passes, presence of on-site cytopathologist, needle size, and location of the lesion were not related with the diagnostic success.

CONFLICT OF INTERTEST

The authors declared no conflict of interest.

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