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Comparison between endoscopic ultrasound-guided fine-needle biopsy and bite-on-bite jumbo biopsy for sampling of subepithelial lesions☆

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ABSTRACT

Background and Aims: A direct comparison between endoscopic ultrasound (EUS) fine-needle biopsy (FNB) and current endoscopic biopsy techniques in patients with subepithelial lesions (SELs) is still lacking. Aim of this multicenter study was to compare the diagnostic performance and safety profile between EUS-FNB and bite-on-bite jumbo biopsy.

Methods: Out of 416 patients undergoing endoscopic sampling of SELs between 2017 and 2021, after propensity score matching two groups were compared: 120 undergoing EUS-FNB and 120 sampled with bite-on-bite jumbo biopsy. Primary outcome was sample adequacy. Secondary outcomes were diagnostic accuracy, sensitivity, specificity, and adverse events.

Results: Median age was 61 years and most patients were male in both groups. Final diagnosis was GIST in 65 patients (54.1%) in the EUS-FNB group and 62 patients in the bite-on-bite biopsy group (51.6%; $p = 0.37$). Sample adequacy was significantly higher in the EUS-FNB group as compared to the bite-on-bite biopsy group (94.1% versus 77.5%, $p<0.001$). EUS-FNB outperformed bite-on-bite biopsy also in terms of diagnostic accuracy (89.3% versus 67.1%, $p<0.001$) and sensitivity (89% vs 64.5%; $p<0.001$), whereas specificity was 100% in both groups ($p = 0.89$). These findings were confirmed in subgroup analysis according to SEL location, final diagnosis, and wall layers of the sampled SEL. Adverse event rate was 6.6% in the EUS-FNB group and 30% in the bite-on-bite biopsy group ($p<0.001$).

Conclusion: EUS-FNB outperforms bite-on-bite biopsy both in terms of diagnostic yield and safety profile.

1. Introduction

Subepithelial lesions (SELs) are detected incidentally in 0.8%–2% of patients undergoing upper gastrointestinal endoscopy [1]. Definitive diagnosis based solely on imaging morphology is uncommon, hence the need of an adequate tissue acquisition strategy in these patients.

Bite-on-bite biopsy, in particular with the use of a jumbo forceps, represents often the first-line approach able to determine variable results in terms of diagnostic yield, ranging from 17% to 94% [2–4]. On the other hand, endoscopic ultrasound (EUS) fine-needle aspiration (FNA) proved to be significantly inferior in this

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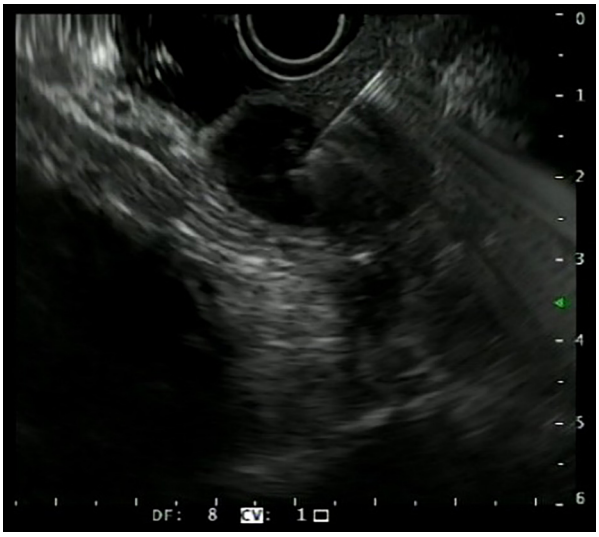

Fig. 1. Endoscopic ultrasound-guided fine-needle biopsy of a subepithelial lesion.

setting as compared to bite-on-bite biopsy in several series [4–6] and a recent meta-analysis of 17 studies found a pooled diagnostic yield of EUS-FNA in patients with SELs below 60% [7].

In fact, cellular acquisition through EUS-FNA does not necessarily retain the stroma or associated architecture of surrounding tissue, which may be necessary to provide a definitive diagnosis and this pitfall in addition to the relatively low diagnostic yield relegated EUS-FNA to a marginal role in the diagnostic management of SELs as suggested by current guidelines [1].

EUS fine-needle biopsy (FNB), which typically uses a core biopsy needle and preserves the cellular architecture, has become an increasingly useful tool in the diagnostic algorithm of other abdominal lesions, such as pancreatic masses [8–10]. In particular, two newer FNB needles were introduced in the endoscopic practice: one with fork-tip design with two leading sharp tips on the opposite side of the lumen (SharkCore®, Medtronic, Minneapolis, USA), and another with three symmetric cutting edges (Acquire®, Boston Scientific Corp, Natick, USA) [11].

A recent meta-analysis showed that EUS-FNB clearly outperformed EUS-FNA for tissue sampling of SELs, thus postulating a fundamental role of FNB in the diagnostic algorithm of these lesions [12].

However, a direct comparison between EUS-FNB and current endoscopic biopsy techniques is still lacking. Therefore, we decided to analyze a multicenter series of patients with SELs to compare the diagnostic performance and safety profile between EUS-FNB and bite-on-bite jumbo biopsy.

2. Materials and methods

2.1. Patients

From an international multicenter retrospective database of consecutive patients undergoing endoscopic sampling of subepithelial lesions of the gastrointestinal tract in 12 high-volume centers between 2017 and 2021, we reviewed data from 867 patients. Institutional Review Board (IRB) approval for this study was obtained.

As per current guidelines, indication to tissue acquisition was considered for SELs ≥20 mm or with high-risk stigmata, such as ulceration or bleeding, or in presence of an atypical EUS appearance with the suspicion of carcinoma, neuroendocrine tumor, lymphoma, or metastasis to the gastrointestinal wall [1].

The following exclusion criteria were used: (1) age < 18 years; (2) clear indication to surgical treatment; (3) coagulopathy (international normalized ratio > 1.5, platelets < 50,000); (4) endoscopic sampling not performed with jumbo forceps; (5) patients who underwent both techniques. All endoscopic procedures were performed by board-certified 10-year-experienced gastroenterologists. Antibiotic prophylaxis was not used routinely before the procedure and patients in antithrombotic treatment suspended the anticoagulant/antiaggregant agent and underwent bridging therapy with enoxaparin according to current guidelines [13].

After excluding patients who did not meet inclusion criteria, we analyzed data of 416 patients who underwent either EUS-FNB or jumbo biopsy.

The flowchart of the patients included in the study was reported in the Supplementary Figure 1.

2.2. Procedures

Bite-on-bite biopsy samples were obtained by using the RJ-4 jumbo biopsy forceps (Boston Scientific, Inc., Natick, MA) with a regular upper endoscope or adult colonoscope. Because of the retrospective and multicenter nature of the study, no intraprocedural standardization was adhered to.

The number of bites was recorded for each lesion, but the final number of biopsy samples was dependent on the endoscopists' discretion. Biopsy specimens were immediately placed in formalin and submitted for histopathologic examination.

A linear array echoendoscope was used for EUS-FNB procedures under deep sedation with propofol administered by an anesthesiologist or under conscious sedation. EUS-FNB was performed using 19 G, 22 G or 25 G Acquire®, SharkCore®, or ProCore® (Cook Medical Inc., Bloomington, IN, USA) needles. Rapid on-site cytologic evaluation (ROSE) was not available in any of the centers involved in the study. No predefined protocol was used in the study and the type of suction or use of stylet was left to the choice of the single operator. In general, a fanning technique was performed and at least 2 passes were performed (Fig. 1). After being grossly checked for adequacy, samples were prepared for histological assessment. Eventual additional passes were performed when macroscopic assessment raised concerns on the adequacy of the sample.

2.3. Outcomes

The primary outcome was sample adequacy, defined as the proportion of samples considered sufficient for diagnosis.

Additional outcomes were diagnostic accuracy, defined as the summary of true positives + true negatives on the total number of patients, diagnostic sensitivity (proportion of positives correctly identified with the test on the prevalence of disease in the study cohort), diagnostic specificity (proportion of negatives correctly identified as such among the patients who were not affected by the disease in the study cohort) [14].

The gold standard for diagnosis was considered surgery and analysis of diagnostic accuracy was restricted only to those patients (75 in the EUS-FNB group and 73 in the bite-on-bite biopsy group) who underwent surgery. None of the patients underwent endoscopic submucosal dissection.

Safety outcomes, expressed in terms of adverse event rate, were also analyzed.

2.4. Statistical analysis

Categorical variables were reported as the number of cases and percentage, and differences between groups were compared using Chi-square and McNemar analyses before and after matching, respectively.

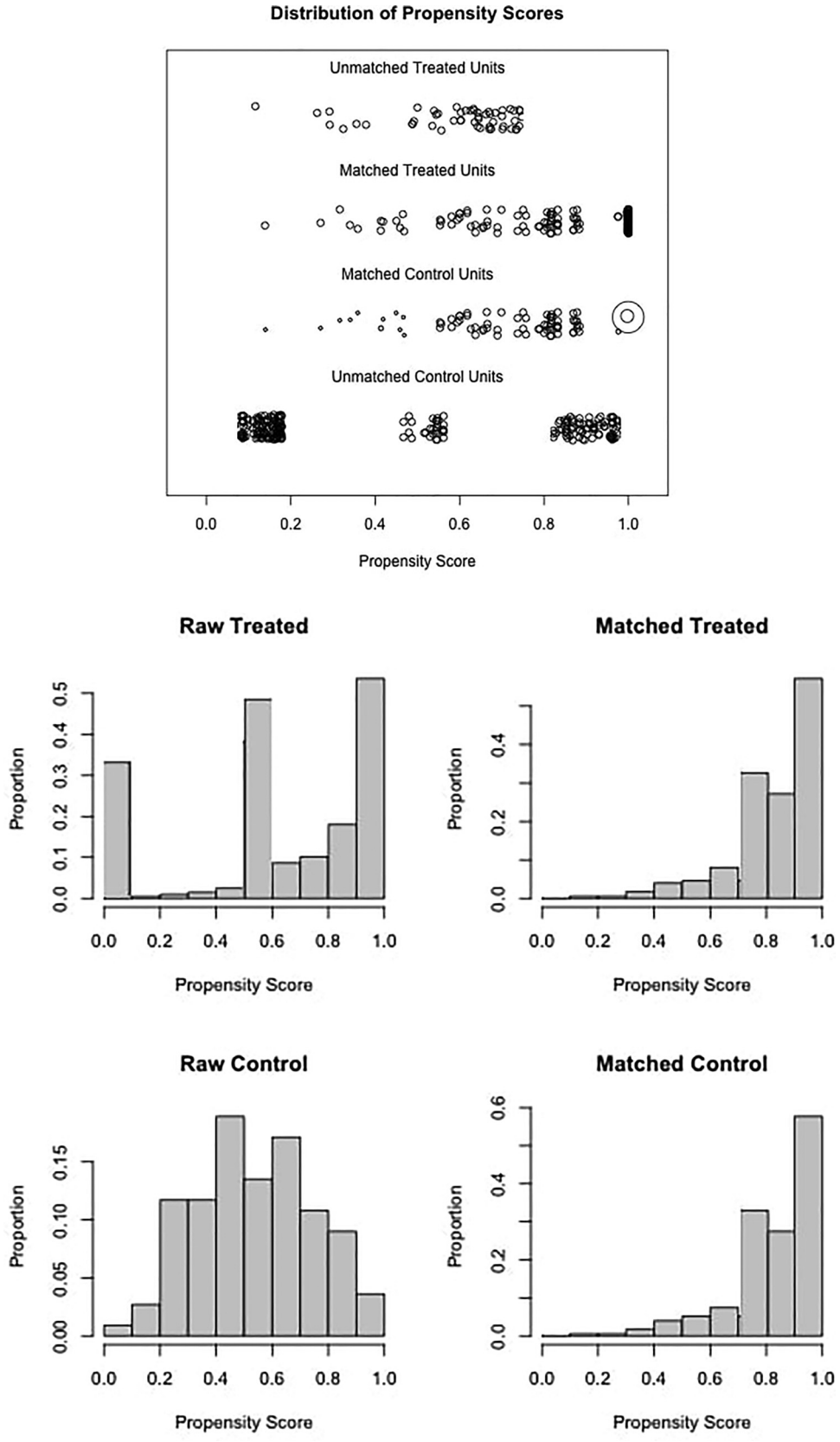

Fig. 2. Propensity score matching. Out of the initial 416 patients, after 1-to-1 propensity score caliper matching 240 patients were selected for comparison: 120 undergoing endoscopic ultrasound-guided fine-needle biopsy and 120 undergoing bite-on-bite biopsy. A. Propensity score matching jitter plot. B. Propensity score matching histogram.

Table 1
Baseline patients' characteristics before and after propensity score matching.

Before Propensity score matching				
Variable	Total (n = 416)	EUS-FNB (n = 164)	Bite-on-bite biopsy (n = 252)	p value
Age (years)	61 (54–72)	58 (53–72)	63 (55–71)	**0.05**
Gender Male	269 (64.6%)	101 (61.5%)	168 (66.6%)	0.28
Female	147 (35.4%)	63 (38.5%)	84 (33.4%)	
Lesion size (mm)	22 (17–31)	25 (18–33)	20 (17–30)	**0.03**
Location				**0.05**
Esophagus	58 (13.9%)	20 (12.1%)	38 (15%)	
Stomach	291 (69.9%)	124 (75.6%)	167 (66.2%)	
Duodenum	25 (6%)	4 (2.4%)	21 (8.3%)	
Rectum	42 (10.2%)	16 (9.9%)	26 (10.5%)	
FNB needle	–		–	–
20 G Procore		25 (15.2%)		
22 G Procore		11 (6.7%)		
22 G Acquire		65 (39.6%)		
25 G Acquire		8 (4.8%)		
22 G SharkCore		55 (33.7%)		
Number of passes/bites	–	3 (2–3)	8 (4–10)	**0.01**
FNB technique slow pull	–	132 (80.4%)	–	–
Patients on antithrombotic therapy	100 (24%)	36 (22%)	64 (25.5%)	0.43
After Propensity score matching				
Variable	Total (n = 240)	EUS-FNB (n = 120)	Bite-on-bite biopsy (n = 120)	p value
Age (years)	61 (53–70)	59 (53–72)	61 (55–70)	0.28
Gender Male	147 (61.2%)	72 (60%)	75 (62.5%)	0.48
Female	93 (38.8%)	48 (40%)	45 (37.5%)	
Lesion size (mm)	21 (18–30)	22 (19–31)	21 (18–30)	0.61
Location				0.93
Esophagus	30 (12.5%)	14 (11.6%)	16 (13.3%)	
Stomach	180 (75%)	92 (76.6%)	88 (73.4%)	
Duodenum	8 (3.3%)	4 (3.3%)	4 (3.3%)	
Rectum	22 (9.2%)	10 (8.5%)	12 (10%)	
FNB needle	–		–	–
20 G Procore		20 (16.6%)		
22 G Procore		9 (7.5%)		
22 G Acquire		48 (40%)		
25 G Acquire		2 (1.6%)		
22 G SharkCore		41 (34.3%)		
Number of passes/bites	–	3 (2–3)	6 (3–8)	**0.03**
FNB technique slow pull	–	98 (81.6%)	–	–
Patients on antithrombotic therapy	48 (20%)	24 (20.1%)	24 (20.1%)	1.0

Continuous variables were reported as median values and interquartile range. Comparisons were performed with Mann-Whitney U test for continuous variables and Fisher exact test for categorical ones before propensity score matching and with McNemar test for continuous variables and Fisher exact test for categorical ones after propensity score matching.
The following demographic and lesion-related variables were selected for propensity score calculation:.
age, gender, lesion size, location, patients on antithrombotic therapy.
Abbreviations: EUS, Endoscopic Ultrasound; FNB, Fine-Needle Biopsy.
Significances were reported in bold.

Continuous variables were expressed as the median and interquartile range (IQR) and differences between groups were explored by the Mann–Whitney and Wilkoxon-rank test before and after matching, respectively. All analyses were 2-tailed, and the threshold of significance was assessed at $\leq$0.05.

To overcome biases owing to the different distribution of covariates among patients who were submitted to jumbo biopsy or EUS-FNB, a 1-to-1 match was created using propensity score analysis.

The propensity score represents the probability of each individual patient being assigned to a particular condition in a study given a set of known covariates [15].

A multivariate logistic regression was built to predict the probability of each individual patient being submitted to the two groups on the basis of several demographic and lesion-related covariates, namely age, gender, lesion size, location and patients on antithrombotic therapy.

The predictive values were then used to obtain a 1-to-1 match by using the nearest neighbor matching within a specified caliper distance. Nearest neighbor matching within a specified caliper distance selects for matching an untreated subject whose propensity score is closest to that of the treated subject ("nearest neighbor matching" approach) with the further restriction that the absolute difference in the propensity scores of matched subjects must be below some pre-specified threshold (the caliper distance) [16,17]. Thus, patients for whom the propensity score could not be matched because of a greater caliper distance were excluded from further analysis. As suggested by Austin, a caliper of width equal to 0.2 of the standard deviation of the logit of the propensity score was used, as this value has been found to minimize the mean squared error of the estimated treatment effect [16].

Subgroup analysis according to lesion location, wall layer of the lesion and final diagnosis was also performed.

An univariate/multivariate logistic regression analysis assessing the correlation between baseline parameters and diagnostic yield was also performed and results were expressed in terms of odds ratio (OR) and 95% confidence interval (CI). Significant factors in univariate analysis were then entered into the multivariate model. Also, a logistic regression analysis was performed for the correlation between baseline parameters and diagnostic accuracy separately in the two study groups.

Table 2
Outcomes.

	EUS-FNB (120 pts)	Bite-on-bite biopsy (120 pts)	p value
Sample adequacy			**<0.001**
	113 (94.1%)	93 (77.5%)	
Diagnostic accuracy*			**<0.001**
	67/75 (89.3%)	49/73 (67.1%)	
Adverse event rate			**<0.001**
	8 (6.6%)	36 (30%)	
Type of adverse event			–
Bleeding	8 (6.6%)	35 (29.1%)	
Perforation	0 (0%)	1 (0.9%)	
Severity adverse event			**<0.001**
Mild	8 (6.6%)	10 (8.4%)	
Moderate	0 (0%)	26 (21.6%)	
Severe	0 (0%)	0 (0%)	
Fatal	0 (0%)	0 (0%)	
Diagnostic sensitivity			**<0.001**
	89% (81.7%–94.2%)	64.5% (54.8%–73.4%)	
Diagnostic specificity	100% (69.1%–100%)	100% (67%–100%)	0.89
Final diagnosis			0.37
GIST	65 (54.1%)	62 (51.6%)	
Leiomyoma	28 (23.3%)	31 (25.8%)	
NET	8 (6.6%)	3 (2.5%)	
Other	19 (16%)	24 (20.1%)	

* Analysis restricted to 75 patients in the EUS-FNB group and 73 patients in the bite-on-bite biopsy group who underwent surgery.

The statistical analysis was run using the *MatchIt* package in R Statistical Software 3.0.2 (Foundation for Statistical Computing, Vienna, Austria).

3. Results

3.1. Patients

The baseline characteristics of the whole study population of 416 patients, 164 undergoing EUS-FNB and 252 bite-on-bite biopsy, initially enrolled in the study were reported in Table 1.

Median age was 58 (IQR 53–72) years in EUS-FNB group and 63 (55–71) years in bite-on-bite biopsy group ($p = 0.05$). Male patients represented the majority of subjects in both groups ($p = 0.28$) and the most common location of SELs was the stomach (75.6% and 66.2% of patients in the two groups, respectively; $p = 0.05$). Median size of the sampled lesion was 25 mm (18–33) in the EUS-FNB and 20 mm (17–30) in the bite-on-bite biopsy group ($p = 0.03$).

After 1-to-1 propensity score match, 240 patients were selected for comparison: 120 EUS-FNB and 120 bite-on-bite biopsy patients. Details of propensity score matching are shown in Fig. 2A and B.

The characteristics of the 240 propensity score-matched patients were reported in Table 1.

Median age was 61 years (53–70) with no difference between the two groups ($p = 0.28$), with 72 (60%) and 75 (62.5%) male patients in the EUS-FNB and bite-on-bite biopsy group, respectively ($p = 0.48$).

Again, stomach was the most common location of sampled SELs (76.6% and 73.4% in the two groups, respectively; $p = 0.93$) and no difference in terms of mean lesion size was observed (22 mm in the EUS-FNB group and 21 mm in the bite-on-bite biopsy group, $p = 0.61$).

In the EUS-FNB group, 20 G ProCore® was used in 20 patients (16.6%), 22 G SharkCore® in 41 patients (34.3%) and 22 G Acquire® in 48 (40%) subjects. Slow pull technique for FNB sampling was used in 98 patients (81.6%).

Median number of passes with the FNB needle was 3 (2–3) whereas median number of bites with jumbo forceps was 6 (3–8; $p = 0.03$).

As reported in the Supplementary Table 1, the number of patients enrolled at each center was homogeneous.

3.2. Outcomes

A detailed list of study outcomes is reported in Table 2.

Sample adequacy was significantly higher with EUS-FNB (94.1%) as compared to bite-on-bite biopsy (77.5%; $p < 0.001$). A similar finding was observed in the initial sample before propensity score matching (Supplementary Table 2).

As reported in Table 3, sampling technique (OR 4.68, 95% CI 1.95–11.2; $p<0.001$) and lesions size (OR 1.41, 1.03–2.22; $p = 0.05$) resulted as significantly correlated to higher sample adequacy rates in univariate logistic regression analysis. Both of these variables were confirmed as significant predictors of higher adequacy rates also in the multivariate model (OR 5.21, 2.12–14.3 and OR 2.23, 1.18–3.21, respectively).

Diagnostic accuracy rate was also significantly higher in the EUS-FNB group as compared to bite-on-bite biopsy (89.3% vs 67.1%, $p<0.001$). Likewise, EUS-FNB outperformed bite-on-bite biopsy also in terms of diagnostic sensitivity (89% vs 64.5%; $p<0.001$), whereas specificity was 100% in both groups ($p = 0.89$).

The same significant difference concerning these diagnostic outcomes was observed in the whole sample size before propensity score matching (Supplementary Table 2).

As reported in the Supplementary Tables 3 and 4, lesion size was the only significant predictor for diagnostic accuracy in both study groups (OR 1.56, 1.11–2.28 in the EUS-FNB group and OR 1.68, 1.15–2.32 in the bite-on-bite group).

No difference in terms of diagnostic performance among the different FNB needles was observed (data not shown).

Final diagnosis was GIST in 65 patients (54.1%) in the EUS-FNB group and 62 patients in the bite-on-bite biopsy group (51.6%), while leiomyoma was detected in 28 (23.3%) and 31 (25.8%) patients, respectively ($p = 0.37$).

Adverse event rate was 8/120 (6.6%) in the EUS-FNB group and 36/120 (30%) in the bite-on-bite biopsy group ($p < 0.001$). EUS-FNB patients experienced mild bleeding in 8 cases whereas 10 cases of mild bleeding, 25 of moderate bleeding and 1 case of perforation were observed in the control group.

Table 3
Univariate/Multivariate logistic regression analysis for diagnostic yield.

Variables	Univariate Analysis Odds Ratio (CI 95%)	p-value	Multivariate Analysis Odds Ratio (CI 95%)	p-value
Age	1.41 (0.89–1.82)	0.23		
Gender (reference Female)	1.04 (0.75–1.52)	0.71		
Location (reference stomach)	0.92 (0.71–2.2)	0.43		
Lesion size (reference <20 mm)	1.41 (1.03–2.22)	**0.05**	2.23 (1.18–3.21)	**0.05**
Sampling strategy (reference bite-on-bite)	4.68 (1.95–11.2)	**<0.001**	5.21 (2.12–14.3)	**<0.001**
Needle size (reference 22 G)*	1.12 (0.68–1.88)	0.62		
Number of needle passes*	1.14 (0.71–1.93)	0.39		
Type of needle (reference Acquire)*	1.18 (0.78–2.21)	0.36		
Biopsy technique (reference slow-pull)*	1.15 (0.65–2.34)	0.63		

CI 95%, confidence interval 95%;.
*Analysis restricted to the Fine-needle biopsy cohort
Significancies were reported in bold.

Table 4
Subgroup analysis according to lesion location, wall layer of the lesion and final diagnosis.

	EUS-FNB	Bite-on-bite biopsy	p value
Stomach			
Sensitivity	88% (80.4%%–92.4%)	64.2% (53.8%–72.5%)	**<0.001**
Sample adequacy	85/92 (92.3%)	68/88 (77.2%)	**<0.001**
Esophagus			
Sensitivity	90.8% (82.3%–94.7%)	65% (56.9%–76.3%)	**<0.001**
Sample adequacy	13/14 (92.8%)	12/16 (75%)	**<0.001**
Rectum			
Sensitivity	89.3% (80.9%–93.8%)	65.4% (56.9%–71.6%)	**<0.001**
Sample adequacy	9/10 (90%)	8/12 (66.6%)	**<0.001**
GIST			
Sensitivity	89.7% (82.1%–95.3%)	65.6% (52.5%–74.4%)	**<0.001**
Sample adequacy	62/65 (95.3%)	48/62 (77.4%)	**<0.001**
Leiomyoma			
Sensitivity	88.2% (83.5%–96.5%)	63.8% (55.1%–75.8%)	**<0.001**
Diagnostic adequacy	26/28 (93%)	23/31 (74.1%)	**<0.001**
Third layer (submucosa)			
Sensitivity	90.7% (82.1%–96.3%)	69.6% (62.5%–81.4%)	**<0.001**
Diagnostic adequacy	70/74 (94.5%)	60/72 (83.3%)	**<0.001**
Fourth layer (muscularis propria)			
Sensitivity	88.7% (80.4%–92.8%)	61.2% (52.3%–74.4%)	**<0.001**
Diagnostic adequacy	43/46 (93.4%)	33/48 (68.7%)	**<0.001**

3.3. Subgroup analysis

As described in Table 4, results of the main analysis were confirmed in the subgroup analysis performed according to SEL location (stomach versus esophagus versus rectum). In fact, sample adequacy rates with EUS-FNB were 92.3% in gastric SELs, 92.8% in esophageal lesions and 90% in rectal SELs, whereas adequacy rates after bite-on-bite biopsy were 77.2%, 75%, and 66.6% in the three subgroups, respectively ($p < 0.001$). Likewise, diagnostic sensitivity was significantly superior with EUS-FNB as compared to bite-on-bite biopsy in all the subsets of patients ($p < 0.001$).

Similar results were observed also in subgroup analysis according to the final diagnosis of the sampled lesion (GIST versus leiomyoma) and GI wall layer where the SEL was located (third-submucosa versus fourth layer-muscularis propria). Of note, sample adequacy rates were significantly lower in SELs of the fourth layers after bite-on-bite biopsy whereas similar results were observed in both cases after EUS-FNB.

4. Discussion

Based on the poor performance of EUS-FNA reported in previous studies, endoscopic ultrasound has still a marginal role in the diagnostic algorithm of SELs. In fact, the current guidelines suggest performing bite-on-bite biopsy as the first diagnostic procedure in these patients, thus restricting recommendations to EUS-guided sampling only in the case of inadequate endoscopic sampling and in certain subgroups of patients [1].

However, bite-on-bite biopsy yields highly variable and commonly disappointing results in patients with SELs, as shown in a meta-analysis reporting a diagnostic yield ranging from 17% to 94% (pooled estimate 62%) [3].

Jumbo biopsy forceps enables to obtain a wider and deeper sample as compared to standard forceps [2,18] and biopsy sampling with jumbo forceps is technically easier to perform than more advanced techniques such as complete or partial endoscopic submucosal dissection [19].

On the other hand, the recent development and introduction in the clinical practice of newer EUS-FNB needles with end-cutting design of the tip allowed to significantly improve the diagnostic yield of several abdominal lesions [8-11,20], including SELs as demonstrated in a recent meta-analysis reporting optimal rates of adequate samples (94.9%) and diagnostic accuracy (87.9%) [12].

However, a direct head-to-head comparison between EUS-FNB and the current gold-standard for diagnosis of SEL, namely endoscopic bite-on-bite biopsy is still lacking.

To the best of our knowledge, our multicenter series represents the first attempt to compare the two techniques in this setting. In order to overcome the potential biases related to the retrospective nature of the study and to take into account properly all confounding variables, we performed a propensity score matching analysis on the basis of several demographic and lesion-related covariates, thus two perfectly balanced treatment groups were obtained.

Sample adequacy was significantly higher with EUS-FNB (94.1%) and confirmed the results of the above cited meta-analysis [12]; on the other hand, results with bite-on-bite biopsy (77.5% adequacy and 67.1% accuracy), although superior to those reported in previous studies [4], were poorer ($p<0.001$).

As a consequence, sampling technique and lesions size resulted as significantly correlated to higher sample adequacy rates both in univariate and multivariate regression analysis (OR 5.21, 2.12–14.3 and OR 2.23, 1.18–3.21, respectively).

As reported in other series [4], there appeared to be a trend toward lower diagnostic yield with the jumbo forceps when lesions originating from the deeper muscularis propria (fourth) layer were targeted, whereas results remained stable with EUS-FNB regardless of the location of the SEL in the mucosal wall. This seems to suggest a lower accuracy with the jumbo forceps that has to tunnel through the overlying mucosal and submucosal layers to reach the underlying pathologic lesion, a problem that is not faced with EUS-FNB that can target directly the lesion.

It might be argued that EUS-FNB represents a more time-consuming and resource-intensive procedure in comparison to bite-on-bite biopsy that can be performed during standard endoscopic exams. However, EUS characterization of a SEL is usually needed to define the eventual infiltration of the GI wall or eventual loco-regional lymph node involvement and the optimal diagnostic performance of EUS-FNB seems to obviate to the need of additional repeated procedures [21,22].

As already reported with other abdominal lesions, diagnostic specificity is very high with both these procedures given the uncommon occurrence of false positive findings.

No difference in terms of diagnostic performance among the different FNB needles was observed, a finding in keeping with the results of newer FNB needles for sampling of pancreatic or lymph-node masses [11,23].

Bite-on-bite biopsy was already known to determine high rates of adverse events, particularly bleeding [4]. In fact, one case of perforation and 25 cases of moderate bleeding requiring endoscopic hemostasis were observed in the bite-on-bite biopsy group whereas only 8 cases of mild bleeding were registered in the EUS-FNB group ($p < 0.001$). This suggests that bleeding in these patients was more likely with bite-on-bite biopsy because of the endoscopist's attempt to tunnel deeper with the forceps for more tissue.

There are some limitations to our study. Its main limitation is the retrospective nature of the study which could have led to selection biases. However, a propensity score matching analysis based on the baseline covariates known to influence diagnostic outcomes was performed in order to obviate to the aforementioned bias. Thus, the study groups were perfectly balanced without statistically different baseline parameters. Other limitation is the fact that cost considerations were beyond the scope of the present study and could not be addressed. Furthermore, the multicenter design of our series determined a non-standardized endoscopic technique bearing some negative effect on the interpretable results. For example, the decision to obtain additional bites with the jumbo forceps, or perform additional passes with the FNB needle, or management of bleeding events, depended on the discretion of the attending endoscopist and varied from patient to patient. Finally, a real blinding of the pathologists assessing the specimens was not feasible because the quality of the samples obtained with the two techniques is usually different.

In conclusion, despite these weaknesses, our study represents the first series aiming to directly compare EUS-guided FNB and bite-on-bite jumbo biopsy in patients with SELs. Our results speak clearly in favor of EUS-FNB, which was found to outperform bite-on-bite biopsy both in terms of diagnostic yield and safety profile.

Given the high impact of an adequate tissue sampling on the quality of the procedure, we are confident our results will inform forthcoming guidelines concerning the diagnostic management of patients with SELs.

Conflict of Interest

None declared.

Specific author contributions

Antonio Facciorusso designed the study and performed the statistical analysis; Stefano Francesco Crinò, Daryl Ramai, Andrew Ofosu, Nicola Muscatiello, Benedetto Mangiavillano, Andrea Lisotti, Pietro Fusaroli, Paraskevas Gkolfakis, Laura Lamonaca, Elisa Stasi, Christian Cotsoglou, Juliana Londoño Castillo, Filippo Antonini, Jayanta Samanta, Jahnvi Dhar collected the data and performed the procedures; Antonio Facciorusso and Filippo Antonini revised the manuscript. All the authors approved the final draft submitted.

Disclosures

None of the authors have any relevant financial disclosures.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.dld.2022.01.134.

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