Surg Endosc (2016) 30:2431–2441
DOI 10.1007/s00464-015-4494-1

Diagnostic efficacy of endoscopic ultrasound-guided needle sampling for upper gastrointestinal subepithelial lesions: a meta-analysis

Xiao-Cen Zhang[1] · Quan-Lin Li[1] · Yong-Fu Yu[2] · Li-Qing Yao[1] · Mei-Dong Xu[1] · Yi-Qun Zhang[1] · Yun-Shi Zhong[1] · Wei-Feng Chen[1] · Ping-Hong Zhou[1]

Received: 10 April 2015 / Accepted: 3 August 2015 / Published online: 27 August 2015

Abstract

Background An increasing number of studies have been conducted on the use of endoscopic ultrasound (EUS)-guided needle sampling for upper gastrointestinal subepithelial lesions (SEL). However, reported diagnostic efficacy varies greatly.

Objective To summarize up current evidences on the diagnostic efficacy of EUS-guided needle sampling for upper GI SEL.

Method A reproducible strategy was used to search four databases. Search results were evaluated for eligibility, and the quality of eligible studies was assessed by QUADAS-2. Pooled efficacy of EUS-guided needle sampling in upper GI SEL was calculated. Procedure-related complications, diagnostic errors, and independent factors related to a higher success rate were also recorded and analyzed.

Results Seventeen studies, comprising 978 attempts of EUS-guided needle sampling, were included in a meta-analysis. Pooled diagnostic rate of EUS-guided needle sampling was 59.9 %, with a heterogeneity I^2 of 55.2 %. Subgroup analysis showed no difference in diagnostic rate among fine needle aspiration (FNA), trucut needle biopsy (TCB), and fine needle biopsy (FNB), or among 19-, 22-, and 25-G needles. Subgroup analysis and meta-regression suggested that the cell block method might be correlated with a higher diagnostic rate. Few severe complications were reported. Diagnosis errors were rare.

Conclusion EUS-guided needle sampling is a safe, but only moderately effective method for pathology diagnosis of upper GI SEL. Choice of FNA/TCB/FNB, or 19 G/22 G/25 G does not seem to alter the overall diagnostic rate.

Keywords Endosonography · Biopsy, needle · Diagnosis · Subepithelial lesion

Endoscopic ultrasound (EUS) can provide details of gastrointestinal (GI) wall structures, as well as multiple characteristics of subepithelial lesions (SEL). Although EUS is usually sufficient in the diagnosis of lesions such as lipoma, simple cysts, and varices, pathology examination is often required for other lesions, especially for hypoechoic lesions originating from the third and fourth endoscopic layer proven to be gastrointestinal mesenchymal tumors (GIMT) under a lot of circumstances and often challenging to diagnose by EUS alone [1]. With the advent of imatinib mesylate, one particular type of GIMT—gastrointestinal stromal tumor (GIST), is drawing spotlight in the past decade. GIST features gain-of-function of c-kit (CD117) and is now considered to have universal malignant potential, regardless of its size [2]. As a result, differentiation of GIMT from other SEL, and of GIST from other GIMT (mainly leiomyoma and schwannoma), is crucial in the diagnosis and treatment of upper GI SEL.

The efficacy and safety of EUS-guided fine needle aspiration (FNA) have long been proven in pancreatic lesions [3]. However, its ability to reliably diagnose SEL has been challenged in recent years [4]. Although earlier

Dr. Xiao-Cen Zhang and Dr. Quan-Lin Li have contributed equally to this work.

✉ Ping-Hong Zhou
zhou.pinghong@zs-hospital.sh.cn

[1] Endoscopy Center and Endoscopy Research Institute, Zhongshan Hospital, Fudan University, 180 FengLin Road, Shanghai 200032, People's Republic of China

[2] Section for Epidemiology, Department of Public Health, Aarhus University, Aarhus, Denmark

studies showed promising results [5, 6], prospective studies with strict requirement for immunohistochemistry (IHC) tend to give diagnostic rates dismally low [7, 8]. Crude examination revealed a diagnostic rate varying from 34 [7] to 91 % [5]. On the other hand, new methods, such as trucut needle biopsy (TCB) and fine needle biopsy (FNB), which get larger amount of tissues with preserved histological structure, should theoretically lead to more successful diagnosis. Therefore, a meta-analysis was conducted to summarize current evidences on this topic and systemically evaluate the diagnostic rate of EUS-guided needle sampling for upper GI SEL.

Materials and methods

Defining the terms

Subepithelial lesions (SEL) literally denote any pathological intraluminal bulge of the GI wall with intact covering epithelium. We abandoned the commonly used term submucosal tumor (SMT) since: (1) lesions such as neuroendocrine (NET) tumor, lymphoma, and metastatic carcinoma are not submucosal, but simply subepithelial; (2) non-tumorous lesions like ectopic pancreas and inflammatory granulomas should also be included in the discussion.

Diagnostic rate, defined as the percentage of diagnostic results among all sampling attempts, was chosen to be the major measurement of this review. Sensitivity was not used because SEL contains both malignant and benign lesions, leading the term sensitivity ambiguous, if not misleading. A result was considered diagnostic when a clear pathology could be tagged to the target lesion. Many studies used 'suspicious' to describe a cytological diagnosis of spindle cell/mesenchymal tumor without further IHC staining. These results were counted non-diagnostic in the analysis because differentiating GIST from other types of GIMT is one of the major reasons why sampling is done. All 'atypical,' as well as descriptive results were also counted non-diagnostic for their doubtful significance.

Sampling attempt, rather than number of lesions, was used as denominator of the rate. This strategy was adopted because repeated attempts by multiple needles, or the same needle on separate occasions, typically resulted in an increased success rate, drawing in bias when the rate is pooled. What this review presents is diagnostic rate from one attempt. For example, 40 lesions, which were sampled by both FNA and TCB, or 22- and 25-G needles independently, would be counted 80 attempts in calculation. Failed attempts, in which sampling was not actually done due to technical reasons, were also included in the denominator. Of note is that one procedure usually contained multiple punctures of the lesions, and one puncture typically contained many back and forth movement of the needle. These were all considered one attempt as long as no change of needle occurs.

Gold standard

In this review, surgery histology and needle sampling cytology with IHC/immunocytochemistry (ICC) when needed were accepted as the gold standard. If needle sampling finds the lesion benign, a minimum follow-up of 6 months is required.

Sampling methods

Only EUS-guided needle samplings, more specifically FNA, TCB, and FNB, were analyzed in this review. Although methods such as bite-on-bite biopsy [9], unroofing biopsy [10], single-incision needle-knife biopsy (SINK) [11], mucosal incision with a fixed flexible snare (MIF) biopsy [12], retract-ligate-unroof biopsy [13], or endoscopic submucosal resection (EMR) [14] for mucosa muscularis lesions seem to give promising results, these methods are generally used by single centers and thus do not provide enough data for analysis. Choosing only needle sampling also enhances the homogeneity of studies included.

Search strategy

We searched PubMed, EMBASE (through Ovid), Cochrane Library, and ClinicalTrial.gov systematically. The search term used for EMBASE was: [(FNA or FNB or TCB or TNB or needle aspiration or biopsy or sampling).ti. or exp needle biopsy/or exp aspiration biopsy/] and [(EUS or endosonography or endoscopic ultrasonography or EUS).ti. or exp endoscopic echography/] and [(submucosa* or subepithelial or mesenchyma* or spindle or stroma* or GIST or leiomyoma or mural or intramural).mp. or GIST/or gastrointestinal tumor/or leiomyoma/or stomach tumor/or submucosa/or esophagus tumor/] and (diagnos* or sensitivity or accura* or adequa* or yield).mp. and (article or conference paper).pt. not (varices or lung or pancrea* or node* or nodal or liver or spleen or cancer* or carcinoma* or adenocarcinoma* or celiac ganglia or a case).ti. (search done on December 31, 2014). A similar strategy was used for other databases. Only studies published after 2000 were analyzed. No language restriction was used. A recursive search of study references was also done (Fig. 1).

Study quality assessment

Included studies were assessed for their risk of bias and applicability using revised Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) [15]. This was done

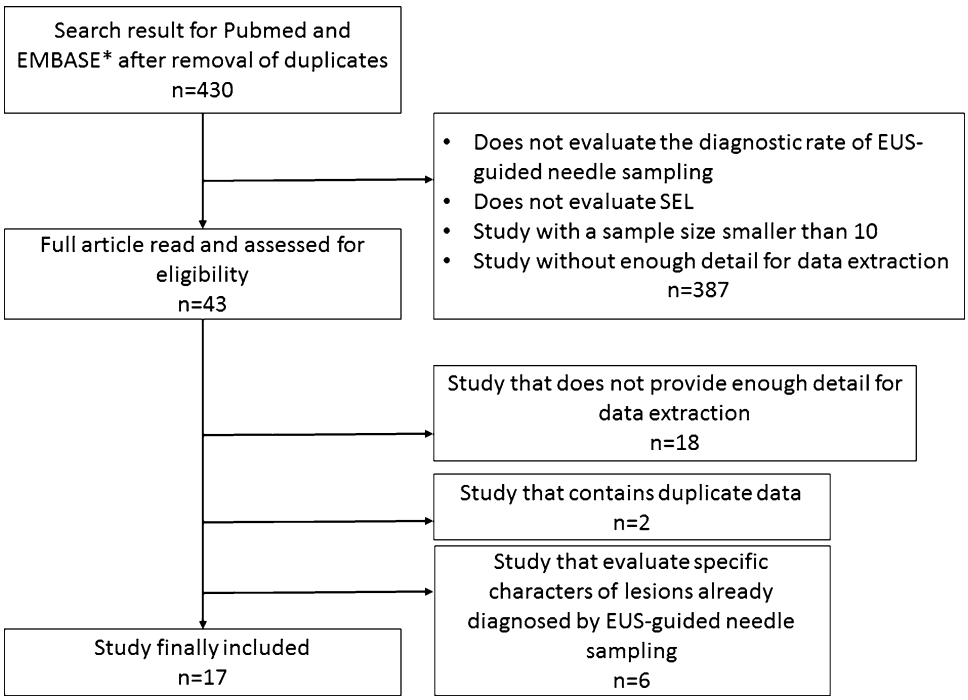

Fig. 1 Flowchart of study screening. *Search results from Cochrane Library and ClinicalTrial.gov were processed separately. No relevant study was identified after removal of duplicate

by two reviewers independently, and disagreement was solved by discussion with a senior reviewer (Table 1).

Data extraction

Study details, including bibliographic data, number of diagnostic sampling and total attempts of sampling, details of method/device, and study design, were extracted. Diagnostic errors and serious complications were recorded as well. Data extraction was done by two reviewers independently (Table 2).

Outcome measurements

The major outcome measurement was the pooled diagnostic rate of EUS-guided needle sampling in GI SEL. I^2 was used to quantify study heterogeneity. Secondary outcomes were procedure-related complications, diagnostic errors, and independent factors related to a higher success rate.

Statistical analysis

Diagnostic rate with corresponding 95 % confidence interval was used as effect size, and all analyses were based on the logit-transformed rate to stabilize the variance. Heterogeneity among studies was assessed by Cochrane's Q test and Higgins' I^2, which reflect the percentage of variation between studies that is due to heterogeneity rather than chance. Values of 25, 50, and 75 % show low, moderate, and high degrees of heterogeneity, respectively [16]. If no obvious heterogeneity among studies was detected, fixed-effect model was used; otherwise, the DerSimonian and Laird random-effect model was used to estimate the pooled diagnostic rate [17]. To account for heterogeneity, subgroup analysis and meta-regression were performed to assess the influence of study design, technical details, and lesion features. Publication bias was assessed by the funnel plot, the Egger's test, and the nonparametric trim and fill method [18]. Rate pooling and subgroup analysis were done in R3.1.2 (R Foundation for Statistical Computing, Vienna, Austria) with metaprop, a command designed specifically for meta-analysis of single proportions. Meta-regression was done in STATA/SE 12.0 (Stata Corporation, College Station, TX, USA) with the metareg command.

Result

Study inclusion and assessment

As shown in Fig. 1, our research yielded 43 studies in total for eligibility assessment. Two studies were excluded because they contained overlapping samples with other included studies, 6 studies were excluded because they evaluated only lesions already diagnosed by EUS-guided needle sampling, and 18 studies were excluded for a lack of detail which precluded reliable data extraction. Seventeen studies [7, 8, 19–33] were included in the final analysis. QUADAS-2 of included studies shows an overall high quality in terms of risk of bias and applicability.

Table 1 QUADAS-2 for included studies

Study		Risk of bias				Applicability		
		Patient selection	Index test	Reference standard	Flow and timing	Patient selection	Index test	Reference standard
2014	Akahoshi, K.	L	L	L	H	H	L	L
2014	Kim, G. H.	L	H	L	H	L	L	L
2012	Eckardt, A. J.	L	L	L	H	L	L	L
2011	Watson, R. R.	L	L	L	L	L	L	L
2011	Camellini, L.	L	H	L	L	L	L	UC
2011	Julio Iglesias-Garcia	L	L	L	L	L	L	UC
2011	Lee, J. H.	L	H	L	L	L	L	L
2011	Suzuki, T.	L	L	L	L	L	L	L
2011	DeWitt, J.	H	L	L	H	L	L	L
2010	Fernandez-Esparrach, G.	L	L	L	L	L	H	L
2010	Philipper, M.	H	L	L	L	L	L	L
2010	Mekky, M. A.	L	L	H	L	L	L	L
2009	Polkowski, M.	L	L	L	L	L	L	L
2009	Imazu, H.	L	L	L	L	L	L	L
2009	Hoda, K. M.	L	H	L	L	L	L	L
2009	Yoshida, S.	L	L	L	H	L	H	L
2004	Arantes, V.	L	L	H	H	L	L	L

Unclear was reserved for studies that evaluated both subepithelial lesions and other lesions, which typically provided less information pertinent to this review

Signaling questions: (1) Risk of bias-patient selection: Could the selection of patients have introduced bias? Low risk, consecutive patients undergoing EUS-guided needle sampling. High risk, patients who fulfilled certain additive criteria, e.g., patients whose diagnosis is confirmed by surgery histology. (2) Risk of bias-index test: Could the conduct or interpretation of the index test have introduced bias? This item was tailored specifically for studies which include subgroups. When multiple needle types/sizes, etc., were used in the same study, variable crossover from the usage of one device to another was judged high risk of bias, while no crossover or fixed crossover in which multiple devices were used constantly for all lesions were considered low risk of bias. (3) Risk of bias-reference standard: Could the reference standard, its conduct, or its interpretation have introduced bias? Low risk, study used gold standard included in the introduction section of this review. High risk, unclear or different standard. (4) Risk of bias-flow and timing: Could the patient flow have introduced bias? Low risk, all patients included in the final analysis; patient flow described clearly; enough information given for data extraction; no ambiguity or inconsistency of figures exists. High risk, otherwise. (5) Applicability-patient selection: Are there concerns that the included patients and setting do not match the review question? Low risk, only upper gastrointestinal subepithelial lesions included, or data specific for subepithelial lesions could be extracted. Selection criteria of patients compatible with the common practice. High risk, rectal, epithelial, or extraluminal lesions included as well. Selection criteria of patients significantly different from the common practice. (6) Applicability-index test: Were there concerns that the index test, its conduct, or its interpretation differs from the review question? High risk, methods/devices used deviate significantly from the common practice. Low risk, otherwise. (7) Applicability-reference standard: Were there concerns that the target condition as defined by the reference standard did not match the question? High risk, classification of GIMT on cytology alone. Low risk, diagnosis of GIMT based on IHC

H high risk of bias, *L* low risk of bias, *UC* unclear

Pooled diagnostic rate

A total of 978 sampling attempts were included in this meta-analysis. The pooled diagnostic rate of EUS-guided needle sampling for upper GI SEL was 59.9 % (54.8–64.7 %). For inter-study heterogeneity, Cochrane's Q was 35.73 and I^2 was 55.2 % (22.7–74.1 %) (Fig. 2).

Publication bias

Visual inspection of the funnel plots did not indicate apparent publication bias (Fig. 3). It was confirmed by Egger's test ($p = 0.59$). After trim and fill method was performed, the adjusted pooled diagnostic rate was 59.4 % (54.3–64.5 %), which was very close to the previous 59.9 % (54.8–64.7 %). Therefore, there is no evidence that our study was affected by publication bias.

Heterogeneity among studies

The pooled diagnostic rate had an I^2 of 55.2 %, suggesting heterogeneity among studies. Thus, we further investigated potential source of heterogeneity by subgroup analysis and meta-regression.

Subgroup analysis showed no evidence that different needle types (FNA, TCB, FNB), or needle sizes (19, 22,

Table 2 Details of included studies

Year	Origin	Author	Evaluate SEL only	Needle type	Needle size	ROSE	Cell block used	Diagnostic sampling	Total sampling	Diagnostic rate	Stomach lesions only	Lesion size	Lesion depth	Mean needle pass
2014	Asia	Akahoshi, K.	Yes	FNA	22, 25	Yes	Yes	56	90	0.622	Yes	<2 cm	3, 4	3.2
2014	Asia	Kim, G. H.	Yes	FNA	22	No	No	2	12	0.167	No	>2 cm	2, 3,4	3.2
				FNB	22	No	No	14	19	0.737				1.8
2012	Europe	Eckardt, A. J.	Yes	FNA	19	No	No	24	46	0.522	Yes	>1 cm	2, 3, 4	2[a]
2011	USA	Watson, R. R.	Yes	FNA	19, 22	Yes	Yes	31	42	0.738	No	Any	2, 3, 4	2.3
				FNA	19, 23	No	Yes	14	24	0.583				
2011	Europe	Camellini, L.	No	FNA	22	Yes	Yes	8	13	0.615	NA			NA
				FNA	25	Yes	Yes	2	7	0.286				
2011	Europe	Iglesias-Garcia, J.	No	FNB	19	No	Yes	9	11	0.818	NA			NA
2011	Asia	Lee, J. H.	Yes	FNA	UC	No	No	6	22	0.273	Yes	>2 cm	3, 4	NA
				TCB	19	NA	NA	37	65	0.569				3.2
2011	Asia	Suzuki, T.	Yes	FNA	22	No	Yes	35	47	0.745	Yes	>1 cm	4	NA
2011	USA	DeWitt, J.	Yes	TCB	19	NA	NA	29	37	0.784	No	>2 cm	4	3[a]
2010	Europe	Fernandez-Esparrach, G.	Yes	FNA	22	Yes	Yes	21	40	0.525	Yes	>2 cm	2, 3, 4	1.9
				TCB	19	NA	NA	22	40	0.550				2.1
2010	Europe	Philipper, M.	Yes	FNA	19, 22	No	No	16	47	0.340	No	Any	2, 3, 4	NA
2010	Asia	Mekky, M. A.	Yes	FNA	22	Yes	Yes	88	141	0.624	Yes	Any	3, 4, 5	2.5
2009	Europe	Polkowski, M.	Yes	TCB	19	NA	NA	31	49	0.633	Yes	>2 cm	2, 3, 4	3.9
2009	Asia	Imazu, H.	No	FNA	22	No	No	16	20	0.800	NA			1
				FNA	25	No	No	12	20	0.600				1
2009	USA	Hoda, K. M.	Yes	FNA	22	Yes	Yes	69	112	0.616	No	Any	4	5.3
				TCB	19	NA	NA	7	15	0.467				2.1
2009	Asia	Yoshida, S.	Yes	FNA	22	No	No	31	49	0.633	Yes	UC	UC	NA
2004	USA	Arantes, V.	Yes	FNA	22	Yes	Yes	5	10	0.500	No	>2 cm	2, 3, 4	2.7

Lesion depth, the origin of lesions from the five ultrasonographic gastrointestinal wall layers. Stomach lesions only, lesion size, lesion depth, and mean needle pass were only recorded in studies which evaluated SEL only, since these data were generally missing in studies that evaluated SEL together with other types of lesions

NA not applicable, *UC* unclear

[a] Median, not mean, was recorded

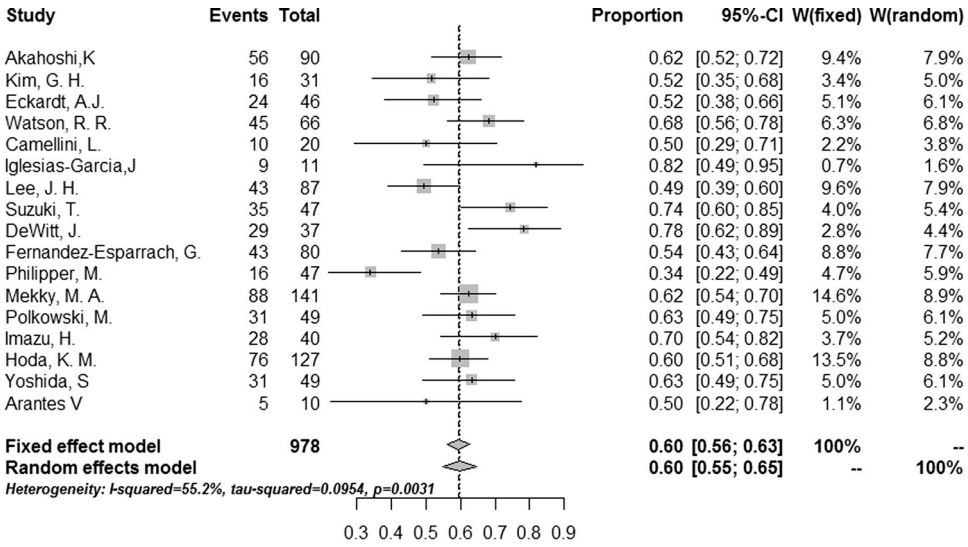

Fig. 2 Forest plot for pooled diagnostic rate. *n* diagnostic sampling, *N* total sampling attempts, *Proportion* diagnostic rate, *W* (*fixed*) weight by fixed-effect model, *W* (*random*) weight by random-effect model

25 G) have different diagnostic rate. Nor was difference detected when the data were grouped by the following criteria: whether only SEL were included, sample size, geographical location of the study center, whether rapid on-site pathological evaluation (ROSE) was used, and whether only stomach lesions were included, the lesion size and depth. It also showed that using the cell block method might lead to a higher diagnostic rate ($p = 0.08$). However, this finding was not supported by the overlapping 95 % CI between subgroups (Table 3).

To further elucidate the role of the cell block method, meta-regression was done. Both univariate and multivariate with ROSE were performed, as the cell block method and ROSE are both pathology processing methods, and interaction between them might exist. However, results are still equivocal (univariate coefficient = 0.48, $p = 0.086$; multivariate coefficient = 0.82, $p = 0.061$) (Table 4).

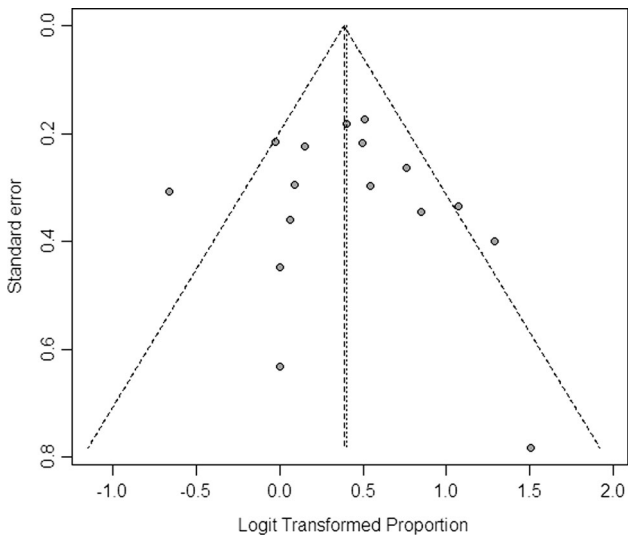

Fig. 3 Funnel plot of included studies

Meta-regression was also done to investigate the relation between mean needle pass and diagnostic rate, with no significant relation found (FNA, coefficient = −0.30, $p = 0.772$; TCB, coefficient = 0.23, $p = 0.406$) (Table 4).

Complications

Among the 17 studies included in this review, only three severe complications were reported. Polkowski et al. [30] reported two septic complications: one on an ulcerated tumor that eventually turned out to be a left liver lobe hepatoma invading the stomach (mistaken for an SMT on EUS) and the other on a 45-mm-large GIST. Eckardt et al. [21] reported one death resulted from multi-organ failure developed after complications caused by FNA of a large centrally necrotic GIST. Notably, all three complications occurred in large and/or ulcerated tumors and were all caused by 19-G needles (TCB by Polkowski, FNA by Eckardt).

Bleeding after needle sampling was frequently reported. Nevertheless, minor bleeding was usually manageable conservatively or endoscopically. Compared to sepsis, bleeding as a complication is harder to define. Current data do not allow us to calculate a well-based complication rate due to the low incidence and variability in interpretation.

Diagnostic error

A diagnostic result does not by nature mean that the diagnosis is correct, although a diagnosis of malignancy or a particular type of GIMT after IHC confirmation is generally considered final by most studies, and by this review. Misdiagnosis of malignancy, or misclassification of GIMT after IHC staining does exist, but these cases are quite rare. Polkowski et al. [30] reported one schwannoma and one

Table 3 Investigation of heterogeneity by subgroup analysis

Grouping criteria	Subgroup	*k*	Pooled rate	95 % CI	I^2 (%)	*p*
Evaluate SEL only	Yes	14	0.59	0.54–0.64	58.2	0.47
	No	3	0.66	0.48–0.80	44.9	
Sample size >40	Yes	12	0.59	0.54–0.65	58.7	0.71
	No	5	0.62	0.47–0.76	54.9	
Sample size >60	Yes	6	0.59	0.54–0.64	33.5	0.78
	No	11	0.61	0.52–0.69	64.5	
Geographical location	Asia	7	0.62	0.55–0.68	45.6	0.20
	Europe	6	0.53	0.43–0.63	57.2	
	USA	4	0.66	0.56–0.74	45.0	
Needle type	FNA	14	0.56	0.49–0.63	66.2	0.12
	FNB	2	0.76	0.58–0.88	0.0	
	TCB	5	0.60	0.51–0.70	41.5	
Needle size	19	7	0.60	0.52–0.68	39.9	0.49
	22	9	0.62	0.57–0.67	12.6	
	25	2	0.48	0.21–0.76	48.0	
	Mixed/unknown	4	0.49	0.31–0.67	85.2	
ROSE	Yes	7	0.61	0.57–0.66	0	0.43
	No	9	0.57	0.45–9.67	72	
The cell block method used	Yes	9	0.63	0.58–0.67	11	0.08
	No	6	0.50	0.38–0.63	72.4	
Stomach lesions only	Yes	8	0.60	0.54–0.65	37.9	0.80
	No	6	0.58	0.45–0.70	74.7	
Lesion size	<2 cm/any/UC	6	0.59	0.51–0.66	65.7	0.88
	>1 cm	2	0.64	0.40–0.82	79.4	
	>2 cm	6	0.58	0.49–0.66	49.9	
Lesion depth	2, 3, 4/UC	8	0.55	0.47–0.63	54.5	0.18
	3, 4/3, 4, 5	3	0.58	0.50–0.66	53.6	
	4	3	0.70	0.56–0.81	67	

k number of studies/subgroups. Evaluation of SEL only, sample size, and geographical location were assessed on the study level (thus add-up $k = 17$). Since TCB gives core samples, most studies did not process TCB material cytologically (although this can be done with flushed 'leftover' materials). As a result, we did not regard TCB as a candidate for the cell block method or ROSE, which are both cytological processing approaches. And results from TCB were not used for the subgroup analysis of these two covariates. For needle type, size, ROSE, and the cell block method, subgroups within the same study were treated as separate studies in calculation (thus add-up $k = 21$ 22, 16, 15, respectively). For reason given in Table 2, subgroup analysis for stomach lesion only, lesion size, and lesion depth used studies which only evaluated SEL

Table 4 Investigation of heterogeneity by meta-regression

Covariate		Univariate regression		Multivariate regression	
		Coef	*p*	Coef	*p*
Pathology processing method	Cell block used	0.48	0.086	0.82	0.061
	ROSE used	0.17	0.570	−0.43	0.291
Mean needle pass[a]	FNA	−0.30	0.772		
	TCB	0.23	0.406		

Coef meta-regression coefficient factor

[a] Two studies that reported only median needle pass were not included in the analysis

malignant lymphoma misinterpreted as CD117-negative GIST. Akahoshi et al. [20] reported one leiomyoma misdiagnosed as GIST.

A diagnosis of benignancy is more prone to error, due to the possibility that material we get does not come from the target lesion, or from the 'bad part' of the target lesion. Mekky et al. [28] reported one GIST misdiagnosed as benign inflammatory granuloma. Interestingly, report of misdiagnosis of benignancy was not very common, presumably because many such results were not recognized during follow-up. In this review, a diagnosis of ectopic pancreas, lipoma, inflammatory granuloma, fibroma, or hematoma, etc. was considered successful diagnosis. However, there are few ways to confirm these findings, especially for inflammatory type of lesions.

Discussion

Up to now, there has been no consensus on the diagnosis and management of GI SEL. With the rapid accumulation of evidence on biological behavior of GIST, and developments of less traumatic methods such as needle sampling, EMR, and endoscopic submucosal dissection (ESD), practitioners tend to take a more aggressive attitude toward SEL than before [34, 35]. Although EUS can give important information regarding certain features of SEL, its ability to differentiate non-tumorous lesions from subepithelial tumors is less than satisfactory [1, 36]. And when it comes to hypoechoic lesions originating from the fourth echo layer, EUS alone is almost of no value in differentiating GIST from other GIMT if high risk features, such as heterogeneity, irregular border, and rapid growth, are not present. In face of this, tissue diagnosis is recommended by many guidelines for certain SEL [2, 37, 38].

Many studies have been done in order to evaluate the diagnostic efficacy of EUS-guided needle sampling for GI SEL. However, success rate reported varies greatly. Further examination shows that relevant studies often use varying terms, such as sensitivity, diagnostic rate, yield, success rate, and have a different definition for a sampling attempt being 'successful.' Patient selection criteria are also not the same and further exacerbate heterogeneity between studies. The lack of global standard poses challenge when readers want to decide how effective EUS-guided needle sampling really is, and furthermore, to formulate a diagnostic algorithm. In addition, although only incidentally reported, severe complications after EUS-guided needle sampling do exist [21, 30], leading this procedure potentially costly more than financially.

As a result, it might be valuable to systemically analyze current evidence on this topic. Since significant heterogeneity exists between studies, direct pooling is meaningless. Maximizing comparability of individual studies was the key issue here, and we tried to solve the problem on three levels: (1) We chose diagnostic rate, with clear definition, as the major measurement for pooling and extracted raw data from studies rather than using the reported efficacy measurements directly. (2) Possible source of heterogeneity were investigated by subgroup analysis and meta-regression.

The pooled diagnostic rate of 978 sampling attempts from 17 studies was 59.9 %, (54.8–64.7 %), not surprisingly somewhat midway between the extremes. To call this figure high or low is pointless without a prior expectations, or assessment of the particular clinical scenario. Diagnostic efficacy has to be weighted with the potential impact of sampling result on patient management. For example, a fourth-layer hypoechoic lesion that measures 0.8 cm in length probably will not undergo surgery even if proven to be GIST, yet still requires periodical follow-up when proven to be leiomyoma. Here, tissue sampling has little impact on the management plan. In contrast, tissue sampling can be extremely useful under certain circumstances, e.g., before initiating imatinib mesylate in unresectable GIST, deciding on or against the performance of surgery [38], or lowering follow-up frequency in confirmed lipoma/ectopic pancreas.

Furthermore, potential ways to increase diagnostic rate of EUS-guided needle sampling were investigated by subgroup analysis and meta-regression. Needle type has been investigated by multiple studies as potential influencing factors for the efficacy of EUS-guided sampling. Our meta-analysis did not show evidence that the choice of different types of needle (FNA, FNB, TCB) has impact on the final diagnostic rate ($p = 0.12$). Some writers attribute this finding to the fact that TCB gives larger sample for histology examination but are technically more demanding [8], while the opposite goes true for FNA. A new device, FNB, attempts to combine merits of both TCB and FNA and seemed to give higher diagnostic rate (pooled rate = 0.76). Since only two studies [19, 25], involving 30 lesions, evaluated this new method, power to detect difference is low. Further studies might shed more light on its effectiveness compared with the traditional FNA and TCB. Similar to needle type, different needle size [19, 22, 25] also did not show any detectable disparity in their diagnostic rate ($p = 0.49$). And the same logic may apply here: Larger needle is harder to use, while smaller needle gets too little material. In addition, meta-regression failed to detect relation between mean needle pass and diagnostic rate (FNA, $p = 0.772$; TCB, $p = 0.406$). However, this figure was missing for multiple studies and individual approach might bring significant heterogeneity, so current data can hardly lead to the conclusion that increasing needle pass cannot increase the diagnostic rate.

Subgroup analysis and meta-regression of two cytological processing approaches, ROSE and the cell block method, detected no correlation of the former and suggested possible correlation of the latter. Previous studies on ROSE led to positive results, with most studies focusing on pancreatic, lung, and thyroid lesions [39–41]. Unlike these lesions, SEL commonly require a large amount of tissue and intact histological structure for diagnosis. Thus, simply making sure adequacy of cytological specimen might not be enough. In addition, majority of studies without ROSE involved macroscopic assessment of the sampled material by endoscopists. Nevertheless, it might be too early to conclude that in the case of SEL, macroscopic evaluation of specimen by endoscopists is as effective as microscopic evaluation done by pathologists. We look forward to future studies done on this topic. In comparison, the cell block method involves collection and centrifugation of 'leftover' material in fluid, which is later processed as a histological specimen. According to our knowledge, no previous study has been designated for assessment of this method in SEL.

Certain characteristics of the lesions are also analyzed. While there is study showing diagnostic rate higher for gastric lesions than those in the esophagus or duodenum [22], this did not lead to overall difference in studies that evaluate gastric lesions only and those that evaluate the full upper GI tract ($p = 0.80$). Nor was larger lesion size ($p = 0.88$) or deeper lesion depth ($p = 0.18$) found to be related to a higher rate of sampling success.

Study design (SEL only or not), sample size (threshold of 40 or 60), and geographical location of institution (Asia, Europe, and USA) were grouping criteria commonly used in meta-analysis. No difference between subgroups was found here.

Other factors may also have contributed to the heterogeneity between studies. The instinct is that endoscopists' experience influences success rate of the procedure. However, this is not supported by previous studies [30, 42]. Pathologists' experience in GIMT diagnosis or local epidemiology might play a role as well.

Putting conservatively, no significant influencing factor on the diagnostic rate of EUS-guided sampling for upper GI SEL has been identified by this review, probably because of the small total sample size and limited power of subgroup analysis. Meanwhile, we believe role of the cell block method in cytological evaluation for SEL might be interesting areas to investigate in future studies.

To see it in another way, diagnostic rate of different subgroups seems fairly close. Whether this indicates the existence of some inherent limitations of needle sampling in SEL as a whole cannot be judged from current data. Our conjecture is that some lesion characteristics, such as particular location, elasticity, or histological heterogeneity of tissue within a tumor, naturally render the lesion resistant to tissue acquirement, and these limitations cannot be solved by altering technical details.

Except for the diagnostic rate, severe complications were also recorded. Only 3 occurred in the 17 studies included in this review, all being sepsis. In addition, all occurred in large and/or ulcerated lesions sampled by a 19-G needle. Based on these, antibiotic prophylaxis before sampling of large/necrotic lesions may be considered. However, to say that large/necrotic lesions are the major risky zone for large bore needle sampling might be a bit too hasty. After all, severe complications have also been reported in tumors without these features. For instance, Liu et al. reported one case of tumor rupture caused by 22-G FNA of a homogeneous, hypoechoic, and approximately 36 mm × 35 mm GIST without detectable internal blood flow [43]. Inoue et al. reported one case of life threatening delayed bleeding 9 days after TCB of a 30 × 26 mm GIST [44]. Overall, EUS-guided needle sampling is safe. Nevertheless, it seems we cannot reliably predict and prevent the occasional life-threatening complications, except for antibiotic prophylaxis for large/necrotic lesions.

In conclusion, EUS-guided needle sampling is a safe, but only moderately effective method of tissue diagnosis for upper GI SEL. Altering sampling device or pathology processing method does not markedly improve the diagnostic efficacy, but the utility of the cell block method and macroscopic assessment of specimens might be interesting areas to explore. Heterogeneity between studies still exists after subgroup analysis, suggesting that under-recognized factors might have influenced the rate. Furthermore, except for asking 'does it work,' we may also want to ask the question 'are there better ways.' Taking the diagnostic uncertainties into consideration, this method may further lose points when compared to other modalities, such as direct EMR/ESD. Unlike needle sampling, which leaves the wounded lesion in situ, EMR/ESD enables complete histology examination while bringing definite resolution of the lesion. Nevertheless, safety of these approaches is still under debate, and the potential risk of over-diagnosis/over-treatment should not be ignored. In short, decision on whether to perform EUS-guided needle sampling should only be made after full assessment of necessity, risk, and potential clinical impact of the procedure, with local experience of its success rate and possible alternatives taken into account.

Acknowledgments This study was supported by the grants from the Major Project of Shanghai Municipal Science and Technology Committee (11411950502 and 13411950801), Academic Leader Training Project of Shanghai Municipal+ Commission of Health and Family Planning (13B038), National Natural Science Foundation of China (81302098, 81201902, 81470811, and 81401930), and Natural Science Foundation of Shanghai (13ZR1452300). No other financial relationships relevant to this publication were disclosed. We

appreciate the effort of statistician Hui-Xun Jia, from Clinical Statistics Center, Fudan University Shanghai Cancer Center, in reviewing statistical methods used in this paper.

Compliance with ethical standards

Disclosures Xiao-Cen Zhang, Quan-Lin Li, Yong-Fu Yu, Li-Qing Yao, Mei-Dong Xu, Yi-Qun Zhang, Yun-Shi Zhong, Wei-Feng Chen, and Ping-Hong Zhou have no conflicts of interest or financial ties to disclose.

References

1. Hwang JH, Saunders MD, Rulyak SJ, Shaw S, Nietsch H, Kimmey MB (2005) A prospective study comparing endoscopy and EUS in the evaluation of GI subepithelial masses. Gastrointest Endosc 62(2):202–208 **(Epub 2005/07/28)**
2. Demetri GD, von Mehren M, Antonescu CR, DeMatteo RP, Ganjoo KN, Maki RG et al (2010) NCCN Task Force report: update on the management of patients with gastrointestinal stromal tumors. J Natl Compr Canc Netw JNCCN 8(Suppl 2):S1–S41 **(quiz S2-4. Epub 2010/05/18)**
3. Yoshinaga S, Suzuki H, Oda I, Saito Y (2011) Role of endoscopic ultrasound-guided fine needle aspiration (EUS-FNA) for diagnosis of solid pancreatic masses. Dig Endosc 23:29–33
4. Polkowski M, Bergman JJ (2010) Endoscopic ultrasonography-guided biopsy for submucosal tumors: Needless needling? Endoscopy 42(4):324–326 **(Epub 2010/04/01)**
5. Ando N, Goto H, Niwa Y, Hirooka Y, Ohmiya N, Nagasaka T et al (2002) The diagnosis of GI stromal tumors with EUS-guided fine needle aspiration with immunohistochemical analysis. Gastrointest Endosc 55(1):37–43 **(Epub 2002/01/05)**
6. Vander Noot MR, Eloubeidi MA, Chen VK, Eltoum I, Jhala D, Jhala N et al (2004) Diagnosis of gastrointestinal tract lesions by endoscopic ultrasound-guided fine-needle aspiration biopsy. Cancer 102(3):157–163 **(Epub 2004/06/24)**
7. Philipper M, Hollerbach S, Gabbert HE, Heikaus S, Bocking A, Pomjanski N et al (2010) Prospective comparison of endoscopic ultrasound-guided fine-needle aspiration and surgical histology in upper gastrointestinal submucosal tumors. Endoscopy 42(4): 300–305 **(Epub 2010/03/23)**
8. Fernandez-Esparrach G, Sendino O, Sole M, Pellise M, Colomo L, Pardo A et al (2010) Endoscopic ultrasound-guided fine-needle aspiration and trucut biopsy in the diagnosis of gastric stromal tumors: a randomized crossover study. Endoscopy 42(4):292–299 **(Epub 2010/04/01)**
9. Ji JS, Lee BI, Choi KY, Kim BW, Choi H, Huh M et al (2009) Diagnostic yield of tissue sampling using a bite-on-bite technique for incidental subepithelial lesions. Korean J Intern Med 24(2): 101–105
10. Lee CK, Chung IK, Lee SH, Lee TH, Park SH, Kim HS et al (2010) Endoscopic partial resection with the unroofing technique for reliable tissue diagnosis of upper GI subepithelial tumors originating from the muscularis propria on EUS (with video). Gastrointest Endosc 71(1):188–194 **(Epub 2009/11/03)**
11. de la Serna-Higuera C, Perez-Miranda M, Diez-Redondo P, Gil-Simon P, Herranz T, Perez-Martin E et al (2011) EUS-guided single-incision needle-knife biopsy: description and results of a new method for tissue sampling of subepithelial GI tumors (with video). Gastrointest Endosc 74(3):672–676 **(Epub 2011/08/30)**
12. Kim JH, Chung JW, Ha M, Rim MY, Lee JJ, An J et al (2013) A feasible modified biopsy method for tissue diagnosis of gastric subepithelial tumors. World J Gastroenterol WJG 19(29): 4752–4757 **(Epub 2013/08/08)**
13. Binmoeller KF, Shah JN, Bhat YM, Kane SD (2013) Retract-ligate-unroof-biopsy: a novel approach to the diagnosis and therapy of large nonpedunculated stromal tumors (with video). Gastrointest Endosc 77(5):803–808 **(Epub 2013/02/02)**
14. Cantor MJ, Davila RE, Faigel DO (2006) Yield of tissue sampling for subepithelial lesions evaluated by EUS: a comparison between forceps biopsies and endoscopic submucosal resection. Gastrointest Endosc 64(1):29–34 **(Epub 2006/07/04)**
15. Whiting PF, Rutjes AW, Westwood ME, Mallett S, Deeks JJ, Reitsma JB et al (2011) QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. Ann Intern Med 155(8):529–536 **(Epub 2011/10/19)**
16. Higgins JP, Thompson SG (2002) Quantifying heterogeneity in a meta-analysis. Stat Med 21(11):1539–1558 **(Epub 2002/07/12)**
17. Fleiss JL (1993) The statistical basis of meta-analysis. Stat Methods Med Res 2(2):121–145 **(Epub 1993/01/01)**
18. Mavridis D, Salanti G (2014) How to assess publication bias: funnel plot, trim-and-fill method and selection models. Evid Based Ment Health 17(1):30 **(Epub 2014/01/31)**
19. Kim GH, Cho YK, Kim EY, Kim HK, Cho JW, Lee TH et al (2014) Comparison of 22-gauge aspiration needle with 22-gauge biopsy needle in endoscopic ultrasonography-guided subepithelial tumor sampling. Scand J Gastroenterol 49(3):347–354 **(Epub 2013/12/12)**
20. Akahoshi K, Oya M, Koga T, Koga H, Motomura Y, Kubokawa M et al (2014) Clinical usefulness of endoscopic ultrasound-guided fine needle aspiration for gastric subepithelial lesions smaller than 2 cm. J Gastrointestin Liver Dis JGLD 23(4): 405–412 **(Epub 2014/12/23)**
21. Eckardt AJ, Adler A, Gomes EM, Jenssen C, Siebert C, Gottschalk U et al (2012) Endosonographic large-bore biopsy of gastric subepithelial tumors: a prospective multicenter study. Eur J Gastroenterol Hepatol 24(10):1135–1144 **(Epub 2012/07/17)**
22. Watson RR, Binmoeller KF, Hamerski CM, Shergill AK, Shaw RE, Jaffee IM et al (2011) Yield and performance characteristics of endoscopic ultrasound-guided fine needle aspiration for diagnosing upper GI tract stromal tumors. Dig Dis Sci 56(6): 1757–1762 **(Epub 2011/03/02)**
23. Suzuki T, Arai M, Matsumura T, Arai E, Hata S, Maruoka D et al (2011) Factors associated with inadequate tissue yield in EUS-FNA for gastric SMT. ISRN Gastroenterol 2011:619128 **(Epub 2011/10/13)**
24. Lee JH, Choi KD, Kim MY, Choi KS, Kim DH, Park YS et al (2011) Clinical impact of EUS-guided Trucut biopsy results on decision making for patients with gastric subepithelial tumors >/ = 2 cm in diameter. Gastrointest Endosc 74(5):1010–1018 **(Epub 2011/09/06)**
25. Iglesias-Garcia J, Poley JW, Larghi A, Giovannini M, Petrone MC, Abdulkader I et al (2011) Feasibility and yield of a new EUS histology needle: results from a multicenter, pooled, cohort study. Gastrointest Endosc 73(6):1189–1196 **(Epub 2011/03/23)**
26. DeWitt J, Emerson RE, Sherman S, Al-Haddad M, McHenry L, Cote GA et al (2011) Endoscopic ultrasound-guided Trucut biopsy of gastrointestinal mesenchymal tumor. Surg Endosc 25(7):2192–2202 **(Epub 2010/12/25)**
27. Camellini L, Carlinfante G, Azzolini F, Iori V, Cavina M, Sereni G et al (2011) A randomized clinical trial comparing 22 G and 25 G needles in endoscopic ultrasound-guided fine-needle aspiration of solid lesions. Endoscopy 43(8):709–715 **(Epub 2011/05/26)**
28. Mekky MA, Yamao K, Sawaki A, Mizuno N, Hara K, Nafeh MA et al (2010) Diagnostic utility of EUS-guided FNA in patients with gastric submucosal tumors. Gastrointest Endosc 71(6): 913–919 **(Epub 2010/03/17)**
29. Yoshida S, Yamashita K, Yokozawa M, Kida M, Takezawa M, Mikami T et al (2009) Diagnostic findings of ultrasound-guided

fine-needle aspiration cytology for gastrointestinal stromal tumors: proposal of a combined cytology with newly defined features and histology diagnosis. Pathol Int 59(10):712–719 **(Epub 2009/10/01)**

30. Polkowski M, Gerke W, Jarosz D, Nasierowska-Guttmejer A, Rutkowski P, Nowecki ZI et al (2009) Diagnostic yield and safety of endoscopic ultrasound-guided trucut [corrected] biopsy in patients with gastric submucosal tumors: a prospective study. Endoscopy 41(4):329–334 **(Epub 2009/04/03)**
31. Imazu H, Uchiyama Y, Kakutani H, Ikeda K, Sumiyama K, Kaise M et al (2009) A prospective comparison of EUS-guided FNA using 25-gauge and 22-gauge needles. Gastroenterol Res Pract 2009:546390 **(Epub 2009/12/10)**
32. Hoda KM, Rodriguez SA, Faigel DO (2009) EUS-guided sampling of suspected GI stromal tumors. Gastrointest Endosc 69(7):1218–1223 **(Epub 2009/04/28)**
33. Arantes V, Logrono R, Faruqi S, Ahmed I, Waxman I, Bhutani MS (2004) Endoscopic sonographically guided fine-needle aspiration yield in submucosal tumors of the gastrointestinal tract. J Ultrasound Med 23(9):1141–1150 **(Epub 2004/08/26)**
34. Park YS, Park SW, Kim TI, Song SY, Choi EH, Chung JB et al (2004) Endoscopic enucleation of upper-GI submucosal tumors by using an insulated-tip electrosurgical knife. Gastrointest Endosc 59(3):409–415 **(Epub 2004/03/05)**
35. Lee IL, Lin PY, Tung SY, Shen CH, Wei KL, Wu CS (2006) Endoscopic submucosal dissection for the treatment of intraluminal gastric subepithelial tumors originating from the muscularis propria layer. Endoscopy 38(10):1024–1028 **(Epub 2006/10/24)**
36. Karaca C, Turner BG, Cizginer S, Forcione D, Brugge W (2010) Accuracy of EUS in the evaluation of small gastric subepithelial lesions. Gastrointest Endosc 71(4):722–727 **(Epub 2010/02/23)**
37. Nishida T, Kawai N, Yamaguchi S, Nishida Y (2013) Submucosal tumors: comprehensive guide for the diagnosis and therapy of gastrointestinal submucosal tumors. Dig Endosc 25(5):479–489 **(Epub 2013/08/02)**
38. Dumonceau JM, Polkowski M, Larghi A, Vilmann P, Giovannini M, Frossard JL et al (2011) Indications, results, and clinical impact of endoscopic ultrasound (EUS)-guided sampling in gastroenterology: European Society of Gastrointestinal Endoscopy (ESGE) Clinical Guideline. Endoscopy 43(10):897–912 **(Epub 2011/08/16)**
39. Iglesias-Garcia J, Dominguez-Munoz JE, Abdulkader I, Larino-Noia J, Eugenyeva E, Lozano-Leon A et al (2011) Influence of on-site cytopathology evaluation on the diagnostic accuracy of endoscopic ultrasound-guided fine needle aspiration (EUS-FNA) of solid pancreatic masses. Am J Gastroenterol 106(9):1705–1710
40. Mondoni M, Carlucci P, Di Marco F, Rossi S, Santus P, D'Adda A et al (2013) Rapid on-site evaluation improves needle aspiration sensitivity in the diagnosis of central lung cancers: a randomized trial. Respiration 86(1):52–58 **(Epub 2013/04/19)**
41. Witt BL, Schmidt RL (2013) Rapid onsite evaluation improves the adequacy of fine-needle aspiration for thyroid lesions: a systematic review and meta-analysis. Thyroid 23(4):428–435 **(Epub 2012/10/10)**
42. Eloubeidi MA, Tamhane A (2008) Prospective assessment of diagnostic utility and complications of endoscopic ultrasound-guided fine needle aspiration. Results from a newly developed academic endoscopic ultrasound program. Dig Dis 26(4): 356–363 **(Epub 2009/02/04)**
43. Liu W, Sun S, Ge N, Wang S, Liu X, Wang G et al (2012) Rupture of a duodenal stromal tumor during EUS-FNA: a case report. Endosc Ultrasound 1(1):53–55 **(Epub 2012/04/01)**
44. Inoue H, Mizuno N, Sawaki A, Takahashi K, Aoki M, Bhatia V et al (2006) Life-threatening delayed-onset bleeding after endoscopic ultrasound-guided 19-gauge Trucut needle biopsy of a gastric stromal tumor. Endoscopy 38(Suppl 2):E38 **(Epub 2007/03/17)**