Endosonography-Guided Fine-Needle Aspiration versus "Key-Hole Biopsy" in the diagnostics of upper gastrointestinal subepithelial tumors. A prospective randomized interventional study

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Background. The management and prognosis of subepithelial tumors (SETs) of the upper gastrointestinal tract depend on the correct preoperative evaluation, including tissue diagnosis in selected cases. Several methods providing deep tissue sampling for cytological and/or histological examinations have been described but their diagnostic yield and precise position in the diagnostic algorithm remain to be established. This prospective randomized study aims to compare the Endosonography-Guided Fine-Needle Aspiration (EUS-FNA) to Key-Hole Biopsy (KHB) in cytological or histological diagnostics of upper gastrointestinal SETs.

Patients and Methods. This study was conducted in a single tertiary endoscopy center in Ostrava, Czech Republic between November 2010 and October 2015. Patients with endoscopically detected SETs of the upper gastrointestinal tract with a diameter ≥ 2 cm, were randomized to either the EUS-FNA with 22G needle, or to the Key Hole biopsy (forceps biopsy through mucosal incision) groups. The main study outcomes were success rate of tissue diagnostics and, in the cases of Gastrointestinal Stromal Tumours (GIST), possibility of determining mitotic activity. A cross-over examination was performed in situations where the first method had failed.

Results. A total of 46 consecutive patients were randomized. Of these, 24 (52%) and 22 (48%) were randomized to EUS-FNA group and KHB arm, respectively. 5 SETs (11%) were detected in the esophagus, 40 (87%) in the stomach and 1 (2%) in the duodenum. The definitive diagnosis was established by the first sampling method in 42 (91%) patients, including 22 (92%) in the EUS-FNA group and 20 (91%) in the KHB group (*P*=0.999), and after a cross-over in another 3 (7%) patients. The most prevalent SET was GIST (70%). Although some mitotic activity could be observed in 11 patients, the mitotic index could be diagnosed in none of them. Of a total of 20 surgically treated patients, preoperative and postoperative tissue diagnosis corresponded in 19/20 (95%) cases, including 100% in FNA group and 91% in KHB group (*P*=0.999). No adverse events of tissue sampling occurred in the study.

Conclusions. Deep tissue sampling by EUS-FNA and KHB are equally effective in the diagnostics of SETs of the upper gastrointestinal tract ≥ 2 cm. However, neither EUS-FNA nor KHB provided adequate tissue sample to determine mitotic index.

Trial Registration: Clinicaltrials.gov (NCT02025244).

Key words: upper gastrointestinal subepithelial tumors, endosonography-guided fine-needle aspiration, key-hole biopsy, gastrointestinal stromal tumors, mitotic activity, mitotic index

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INTRODUCTION

Subepithelial tumors (SETs) of the upper gastrointestinal tract originate from any subepithelial layer of the esophageal, gastric or duodenal wall, mostly from submucosa and muscularis propria[1,2]. SETs are frequently discovered incidentally during upper gastrointestinal endoscopy for other reasons[3]. Nevertheless, some of them may be symptomatic due to their size, localization or bleeding. The estimated prevalence of SETs around 0.33% at routine upper endoscopy has been reported[4]. Recently, an increasing detection rate has been shown that can be

attributed to advanced diagnostic techniques capable of detecting small lesions and higher attention paid to these lesions[2]. Although the endoscopic appearance of SETs is similar, they differ both histologically and biologically. Endoscopic ultrasonography (EUS) proved effective in the differential diagnostics of SETs. EUS may differentiate intra- from extramural lesions and provides information about the layer of origin and its echostructure[5-8]. Despite this advantage, tissue sampling is usually necessary to confirm the diagnosis as shown by previous studies[9-13].

As a rule, standard forceps biopsy of the lesion overlying mucosa is inconclusive. Therefore, deep biopsies are advocated[14,15]. Several methods of deep biopsy including "biopsy on biopsy" and jumbo forceps biopsy are described in the literature. Nevertheless, no consensus about their usage has been achieved until now[12,14,16-18]. Moreover, new sampling strategies, including Key-Hole Biopsy (KHB) which consists of forceps biopsy through mucosal incision with a needle knife, have been reported[8,19].

The primary aim of this study was to compare success rate of tissue diagnostics using EUS-FNA with 22G needle to KHB of upper gastrointestinal SETs with diameter ≥ 2 cm. Secondary aim was to evaluate the feasibility to use these methods for the determination of mitotic index in the case of GIST.

PATIENTS AND METHODS

This study was conducted in a single tertiary endoscopy center in Ostrava, Czech Republic in the period from November 2010 to October 2015. It was approved by the local ethics committee (Institutional Review Board Number EK27612) and registered at Clinicaltrials.gov (NCT02025244).

All consecutive patients with endoscopically detected SETs of the upper gastrointestinal tract with diameters ≥ 2 cm (Fig. 1) were enrolled and considered for randomization according to the trial´s criteria. All enrolled patients signed informed consent.

Exclusion criteria were age <18 years, tumor size < 20 mm, pregnancy and significant coagulopathy.

All enrolled patients underwent radial EUS examination (GF – UE 160, Olympus Medical systems, Hamburg, Germany and Aloka Pro Sound Alpha 10 ultrasound system). In cases of stomach or duodenal lesions, EUS water immersion method was used while, in the case of oesophageal lesions, balloon method was employed. The lesion size, layer of origin and EUS characteristics were examined. Following radial EUS, the randomization to either EUS-FNA group or KHB group was performed using random sequences generated by a computer software program.

Both EUS-FNA and KHB were performed in a standardized manner with the patients under conscious sedation using midazolam (2-5 mg), butylscopolamine (20-40 mg) and fentanyl (50-100 μg).

EUS- FNA (Fig. 2) was performed with a linear array echoendoscope (GF- UCT 180 or GF – UCT 140, Olympus Medical System, Hamburg, Germany and Aloka ProSound Alpha 10) using a standard 22- gauge fine needle (Expect TM, Boston scientific, Natick, Massachusetts or EZ Shot NA-220H-8019/8022, Olympus Medical system, Hamburg, Germany). Before puncturing, the lesion was visualised in B- mode, in order to confirm the absence of intervening blood vessels by means of color Doppler. After lesion puncture the stylet was withdrawn and the needle was moved back and forth 5–8 times within the lesion in a fan-like manner. Four to five series of punctures in different regions of the tumors were performed (1–2× with suction 5–10 Torr with an empty syringe). Punctures through the peritoneum was avoided. After the needle withdrawal, the specimen was pushed out from the needle on the microscope slide and vial with 10% formalin solution by stylet re-insertion. Rapid On-Site Evaluation (ROSE) of the samples was not available.

KHB (Fig. 3, Fig 4a. – 4g.) was performed using standard gastroscopes (GIF- HQ 190, GIF- 180 or GIF180J, Olympus, Hamburg, Germany). A 5 mm incision ("keyhole") of the mucosa overlying SET was made using a needle knife – length 5 mm (V-System Single-Use Triple-Lumen Needle-Knives, Olympus, Hamburg Germany). Deep forceps biopsy (single- use forceps Jaw 4, Boston Scientific, Natick, Massachusetts, USA) through the hole was then performed. Five to seven samples were taken from different parts of the tumor. After the sampling, the mucosal incision was closed using endoscopic clips.

Following the procedures, patients were kept under observation for 24 h. Both CRP level and blood count were checked 4 h after the procedure.

Specimen obtained via EUS-FNA were processed in the form of cytological smears stained by the method of May – Gruenwald – Giemsy (MGG QUICK STAIN 04 – 090805 – Bio – optical) and the Periodic Acid Schiff (PAS). Part of the material was processed as a routine cell block, whereby a fixed pellet of material from a fine needle was sealed in a paraffin block, and processed using the method of biopsy, including attempt of performing an immunohistochemical analysis (Table 1).

The material of the KHB was fixed in 10% neutral- buffered formalin and sealed in paraffin blocks. Subsequently, tissue sections were stained with hematoxylin and eosin and used for routing histological and immunohistochemical analysis (Table 1).

The procedure was considered successful when tissue sample sufficient to make a histological diagnosis was obtained. In the case of failure of the initial method, the alternative method was performed.

Mitotic activity defined as a number of mitoses in 50 high-power-fields, was examined in the case of GIST.

Statistical analysis

R Programming and NCSS 2007 (Kaysville, Utah, USA) were used for statistical analyses. Differences between independent proportions of SETs diagnosed by EUS-FNA and KHB, respectively, were compared using the binomial exact test. Proportions of SETs across sites and types of diagnosis were calculated. Differences between subcategories were compared using the chi-square statistic while Fisher's exact test was used, if the expected

Table 1. Immunohistochemical markers used to confirm the diagnosis of subepithelial tumors.

Typ of used immunohistochemical marker	Typ of detected subepithelial tumors
CD 117, DOG-1	GIST
CD 34, S100 proteins,PDGFRA	GIST
SMA	Leiomyoma
Desmin	Leiomyoma
CD20, CD25	Lymphoma(MALT)
CK 20	Adenocarcinoma
CDX2	adenocarcinma
CD56, Chromogranin A, Synaptofyzin	NET

CD (Cluster of differentiation), PDGFRA (platelet-derived growth factor receptor-alpha), DOG - 1 (Discovered On GIST-1), SMA (smooth muscle actin), desmin, S100 proteins, CK (CytoKeratin), CDX2 (Homeobox protein), GIST (Gastrointestinal Stromal tumors), NET (Neuroendocrine tumor)

Table 2. Baseline Characteristics of the study.

Number	Gender	Age (year)	Site (Organ)	Type of deep biopsy	Cyto / Histological diagnosis	Management / postoperative diagnosis
1	Female	54	Stomach	KHB	Lipoma	Follow up
2(X)	Male	64	Stomach	KHB X FNA	Susp. GIST X Fusif. GIST	Follow up
3	Male	37	Stomach	KHB	Leiomyoma	Resection => Leiomyoma
4	Female	64	Stomach	KHB	Leiomyoma	Follow up
5	Male	47	Stomach	FNA	Epith. GIST, MA – yes	Resection => Epith. GIST
6	Female	47	Stomach	KHB	Leiomyoma	Resection => GIST
7	Male	66	Stomach	FNA and KHB	Malt Lymphoma, Malt lymphoma	Radio and chemotherapy
8	Female	57	Stomach	FNA X (planned) Resignation	Autolysis, Necrosis => no diagnosis	–
9(X)	Female	68	Stomach	FNA X KHB	Susp. GIST Fusif. GIST MA: yes	Resection => Fusif. GIST
10	Male	57	Stomach	KHB	Fusif. GIST	Resection => Fusif. GIST
11	Male	68	Stomach	FNA	Adeno Ca	Resection => Adeno Ca
12	Female	73	Stomach	FNA	Fusif. GIST	Follow up
13(X)	Male	73	Stomach	KHB X FNA	Insuf. Sampling X Fusif. GIST MA: yes	Resection
14	Female	67	Stomach	KHB	Leiomyoma	Follow up
15	Female	81	Stomach	FNA	Vret.GIST MA : yes	Resection
16	Female	64	Stomach	FNA	Fusif. GIST	Resection => Fusif. GIST
17	Male	76	Oesophage	KHB	Epith. GIST	Follow up
18	Female	81	Stomach	KHB	Epith. GIST MA: yes	Resection => Epith. GIST
19	Male	63	Stomach	FNA	Fusif. GIST	Resection => Fusif. GIST
20	Female	73	Stomach	FNA	Fusif. GIST	Follow up
21	Female	76	Stomach	KHB	Fusif. GIST MA: yes	Resection => Fusif. GIST
22	Female	90	Stomach	KHB	Lipoma	Follow up
23	Male	70	Stomach	KHB	Epith. GIST MA yes	Resection => Epith. GIST
24	Female	68	Stomach	FNA	Mixed GIST	Follow up
25	Female	79	Stomach	FNA	Fusif. GIST MA yes	Resection
26	Male	83	Stomach	FNA	Fusif. GIST	Follow up

Table 2. *(Continued)*

Number	Gender	Age (year)	Site (Organ)	Type of deep biopsy	Cyto / Histological diagnosis	Management / postoperative diagnosis
27	Female	68	Stomach	KHB	GIST	Follow up
28	Male	57	Stomach	KHB	Mixed GIST MA yes	Prefered Follow up
29	Female	77	Stomach	FNA	Fusif. GIST	Follow up
30	Male	68	Oesophage	FNA	Leiomyoma	Follow up
31	Female	67	Oesophage	FNA	Leiomyoma	Follow up
32	Female	66	Stomach	KHB	Mixed GIST	Follow up
33	Male	76	Oesophage	FNA	Fusif. GIST	Follow up
34	Male	70	Stomach	FNA	Fusif. GIST	Follow up
35	Female	30	Stomach	KHB	Mixed GIST MA yes	Resection
36	Female	61	Stomach	FNA	Fusif. GIST	* Neoadj.th + resection => Fusif. GIST
37	Female	71	Oesophage	FNA	Leiomyoma	Follow up
38	Male	41	Stomach	KHB	Fusif. GIST	Resection => Fusif. GIST
39	Female	71	Stomach	FNA	Fusif. GIST	Follow up
40	Female	64	Stomach	KHB	NET-G1	Resection
41	Male	50	Stomach	FNA	Fusif. GIST	Follow up
42	Female	69	Stomach	FNA	Fusif. GIST	Follow up
43	Male	86	Stomach	KHB	GIST MA yes	Resection => Fusif GIST
44	Male	74	Stomach	FNA	Mixed GIST	Resection => Mixed GIST
45	Male	73	Duodenum	KHB	inflammatory fibroid polyp	Follow up
46	Male	56	Stomach	KHB	GIST	Follow up

X = cross-over, FNA = Endosonography-Guided Fine-Needle Aspiration, KHB = Key-Hole biopsy, MA = Mitotic Activity, GIST = Gastrointestinal Stromal Tumor, Fusif. = Fusiform, Epith. = Epitheloid, NET = Neuroendocrine Tumor, Adeno Ca = Adenocarcinoma

Table 3. Area and type of diagnosed subepithelial tumors (SETs).

Area and Type of SETs	Tissue			Exact Fisher	
	n	Diagnosed n (%)	Not diagnosed n (%)	Chi-Square	*P*
Area of primary diagnosed SETs				90.07	<0.001
Esophagus	46	5 (11)	41(89)		
Stomach	46	40 (87)	6 (13)		
Duodenum	46	1 (2)	45 (98)		
Type of SETs				75.82	<0.001
GIST	46	32(70)	14(30)		
Leiomyoma	46	7(15)	39 (85)		
Lipoma	46	2(4)	44(96)		
Malt Lymphoma	46	1(2)	45(98)		
Adenocarcinoma	46	1(2)	45(98)		
Infl. Fibroid polyp	46	1(2)	45(98)		
Neuroendocrine tumor	46	1(2)	45(98)		
No dg	46	1(2)	45(98)		

value of a cell was less than 5. Pairwise comparisons were adjusted using Marascuilo's multiple comparison test[20]. For all analyses, $P<0.05$ was defined as statistically significant.

RESULTS

During a study period a total of 52 patients with upper gastrointestinal SETs were enrolled in the study. Of them 46 were randomized (Table 2, study Flow diagram). The location of SETs were as follows n (%): Esophagus of 5 (11) stomach of 40 (87) and duodenum of 1(2) pa-

Table 4. Comparison of EUS-FNA and KHB in preoperative and postoperative diagnostics of upper gastrointestinal SETs (EUS-FNA vs KHB).

Analyses	Diagnostic Method			Exact Binomial		
	n	EUS-FNA *P*% (n/total)	KHB *P*% (n/total)	Difference ± SE	95%CI (Miettinen)	*P*
Primary dg SETs	46	92(22/24)	91(20/22)	0.01 ± 0.08	[-0.19; 0.21]	0.999
Dg after cross-Over	47	92(24/26)	91(21/23)	0.01 ± 0.08	[-0.17; 0.20]	0.999
POTIDIC	19	100(9/9)	91(9/10)	0.10 ± 0.98	[-0.23; 0.41]	0.999
Supposed MA	32	21(4/19)	54(7/13)	-0.32 ± 0.17	[-0.61; 0.01]	0.042

SE= Standard Error estimated of the difference, 95% CI= 95% Confidence Intervals, MA = Mitotic Activity, POTIDIC= Postoperative Tissue Diagnosis Correspondence.

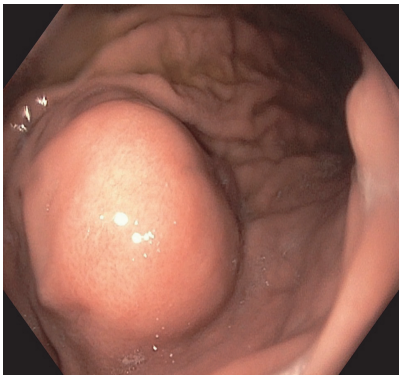

Fig. 1. Gastric subepithelial tumor- gastroscopy.

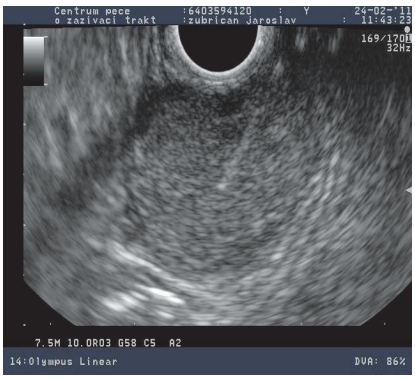

Fig. 2. Endosonography-guided aspiration.

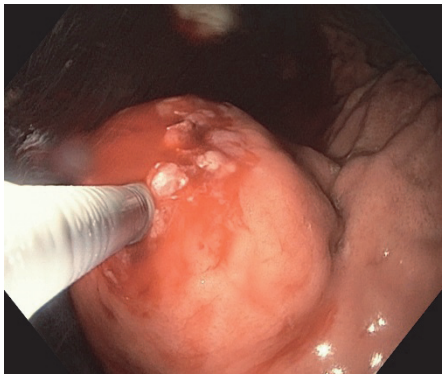

Fig. 3. Key Hole Biopsy.

tients (Table 3). The final diagnosis was established by the initial sampling method in 42 (91%) patients, including 22 (92%) in the EUS-FNA group and 20 (91%) in the KHB group (*P*=0.999). A cross over examination was performed in 3 (7%) of patients while one other patient refused cross-over. Final diagnosis after cross-over was established in 45 (98%) (Table 4).

The final tissue diagnosis in the whole randomized population is shown in Table 3. GIST (70%) and leiomyoma (15%) were the most frequent SETs.

The mitotic activity was approximately specified only in 11 (34%) of patients with preoperative diagnosis of GIST, including 7 (54%) in the KHB group and 4 (21%) in the EUS-FNA group. (*P*=0.042) (Table 4).

A total of 20 patients including 14 with GIST underwent surgical treatment. Postoperative tissue diagnosis corresponded to preoperative tissue diagnosis in 10 (91%) patients in the KHB group and 9 (100%) in the FNA group (*P*=0.999) (Table 4). In one case, the preoperative tissue diagnosis by KHB showed leiomyoma, whereas the definitive postoperative diagnosis was a GIST.

DISCUSSION

SET can be regarded as an umbrella term that encompasses lesions of the GI tract growing under the epithelial layer, regardless of their histology[1,2]. The clinical management and prognosis of SETs depend on correct preoperative diagnosis which is mostly based on imaging methods, including EUS (ref.[8,21]).

Based on EUS finding, The American Gastroenterological Association (AGA) recommends surgical resection of SETs > 3 cm, originating from the muscularis propria layer, with hypoechoic or heterogeneous echostructure. On the other hand, SETs < 3 cm in size without EUS malignant signs can be periodically followed up, preferably by EUS (ref.[21]).

Although the contribution of EUS in the diagnosis of SETs is evident, low accuracy of EUS in the diagnosis of gastric SETs in the range of 46% -68% have been reported[9,22]. For instance, Tae et al. reported that 43% of patients, who underwent surgical resection without preoperative pathological diagnosis, were confirmed to have benign lesions[11]. This and other trials showed that EUS alone may not be sufficient for making a diagnosis and that, in many cases, histological examination is necessary[12,14,15,22]. Such an examination requires deep biopsy techniques capable of reaching the layer of the upper GI wall beyond intact epithelium.

This study shows that both EUS-FNA and KHB have an equal potential to contribute to the diagnosis of upper gastrointestinal SETs (Table 4). As for EUS- FNA, it provided tissue sample sufficient for diagnosis of upper gastrointestinal SETs in 92% of cases. This finding is in agreement with Mekky´ s study showing that EUS-FNA could obtain representative material for cytological assessment in 70-84% of SETs[15]. In another study, Gleeson

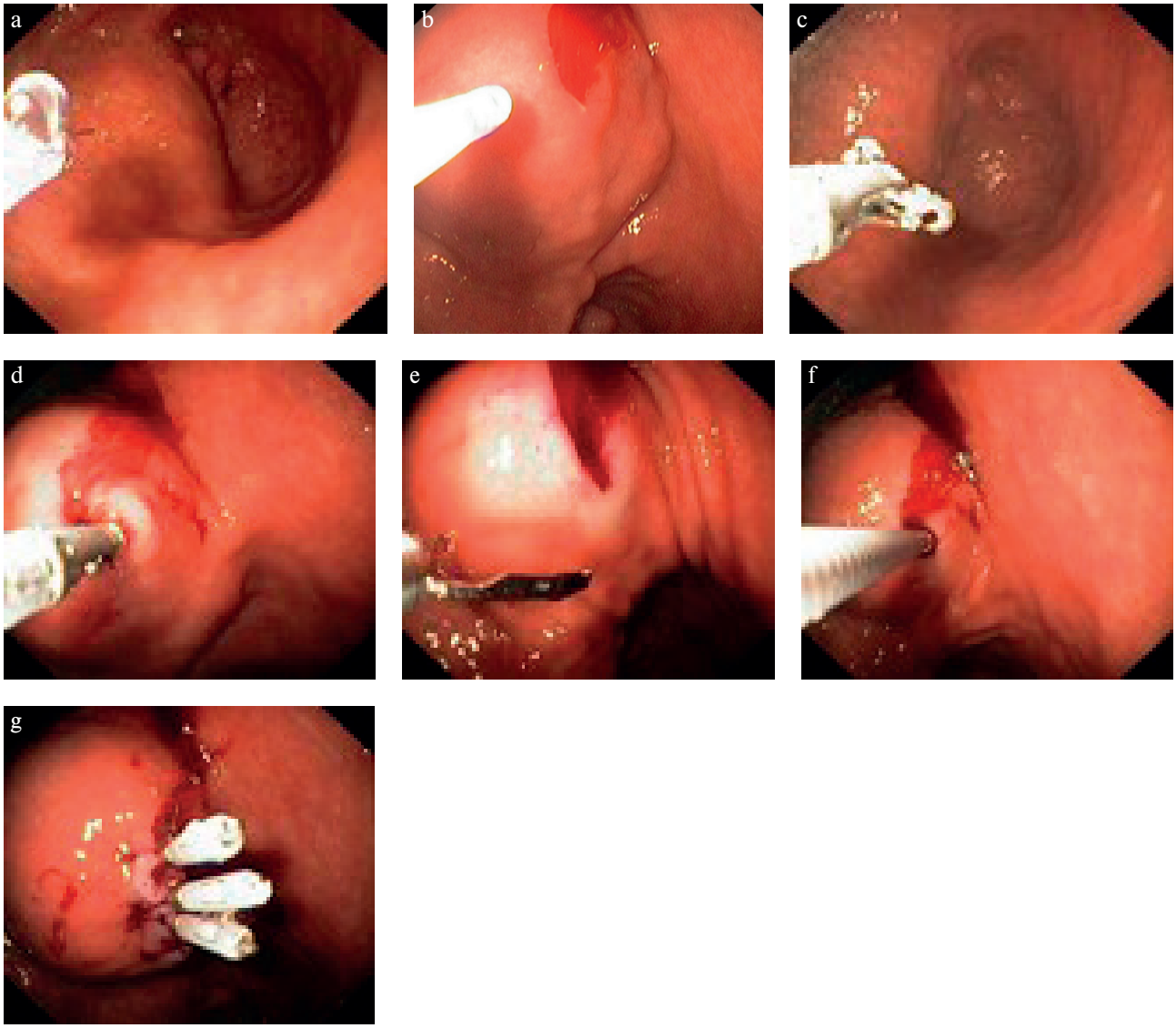

Fig. 4. Differents steps of Key Hole Biopsy. 4a. Pre-cutting knife before incision, 4b. Incision (KeyHole) maked by pre cutting knife, 4c. Opened forceps before biopsy, 4d. and 4e. Deep biopsy using forceps- samples are taken deeply, from different parts of the tumor, 4f. Opened endoscopic clips before closing the mucosal incision "Keyhole", 4g. The closed "Keyhole" by endoscopic clips.

et al. showed concordance in between invasive biopsy (EUS-FNA) results with corresponded surgical specimens in 96% (ref.[14,23]). Their finding is supported by the current study, which proved concordance in 100% cases.

Several other methods of EUS guided sampling are reported. Of these, trucut biopsy could improve results due to larger tissue sample. However, in a study by Fernández-Esparrach G. et al EUS-trucut biopsy was no more accurate than EUS-FNA (ref.[16]). In order to increase the sample size, suction or a needle with a larger size could be used[15,24].

There were no complications of EUS-FNA in our study. This result is consistent with the literature[24,25]. Despite the safety of EUS-FNA, it remains an expert-dependent method[24].

As for the KHB, it enables the preoperative diagnosis of upper GI-SETs in 91% of cases. The correlation between preoperative tissue diagnosis using KHB and the postoperative histological diagnosis of SETs was 91%, *P*=0.999. So far, we have found no other studies using KHB in the diagnosis of upper gastrointestinal SETs that would allow us to compare the results with the results in this study. As predicted by Grubel P in Endoscopy in 2010 (ref.[19]), the current trial confirmed that Keyhole biopsy is an alternative to fine-needle aspiration in the diagnostic of upper gastrointestinal subepithelial tumors (Table 4).

Mitotic index (MI) is an established prognostic criterion of GIST. In our study, mitotic activity (MA) could be estimated only in 21% and 54% in EUS FNA and KHB group, respectively. Moreover, the difference is not statistically significant (Fisher´s Exact level = 0.295), As a result, none of the study methods can be recommended for MA or MI evaluation.

The overall high correlation between preoperative and postoperative tissue diagnosis by either EUS-FNA or KHB method confirms the position of both studied

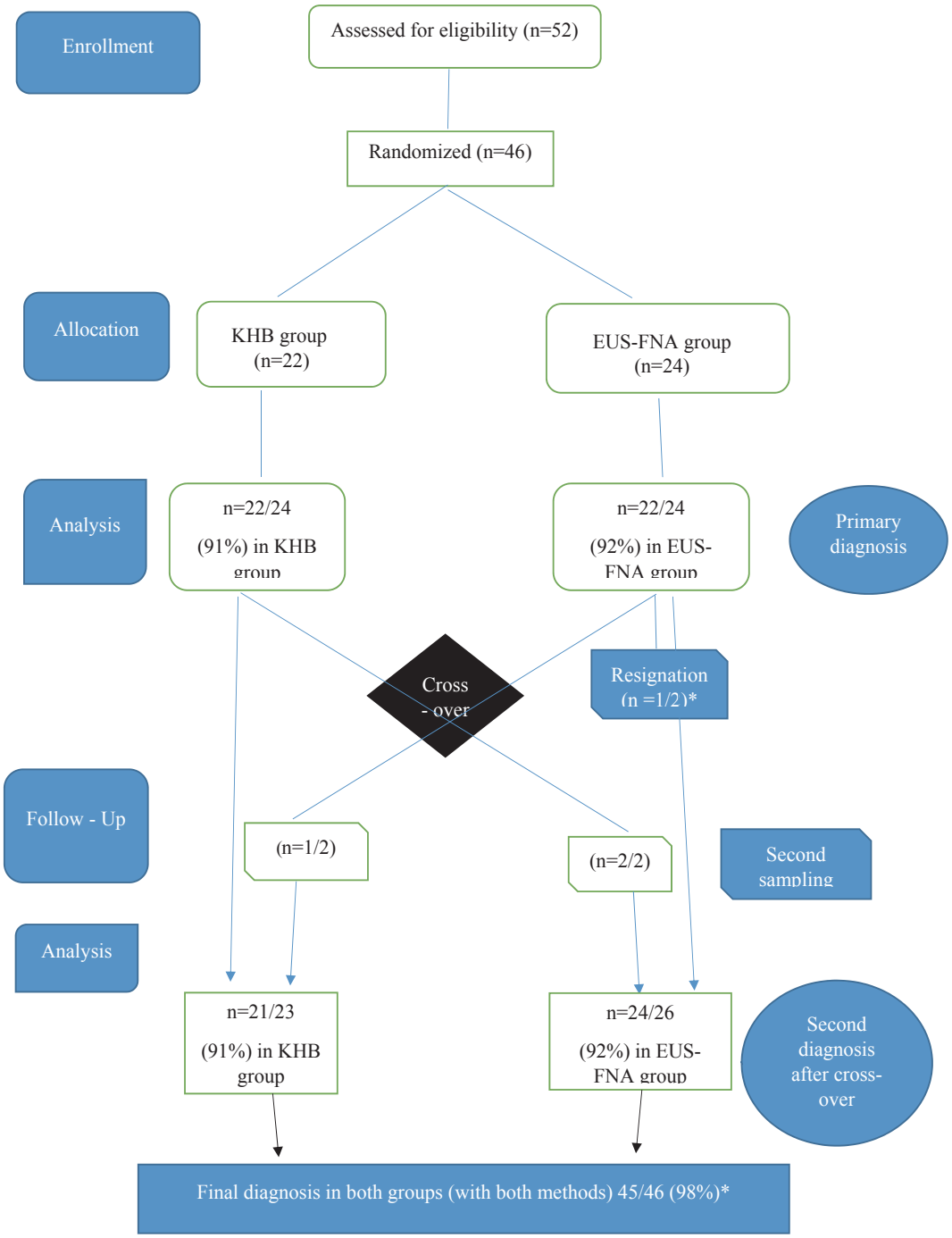

Fig. 5. Study flow diagram.

methods in the diagnostic algorithm of upper gastrointestinal SETs >2 cm (Table 3 and 4). KHB is preferred in a clinical scenario with low availability of EUS-FNA.

For small (<2 cm) incidentally upper GI SETs a follow-up is probably a safe strategy, as shown by Hyun et al.[3], although other studies have reported cases of small GIST (1 cm) with malignant potential and metastasis to distant organs[22,26,27].

Our study has several limitations. The size of study sample is moderate. Rapid On-Site Evaluation (ROSE) of the samples was not available. However, based on the literature, ROSE can be advocated due to its potential for reducing the number of punctures[24]. Peritoneal seeding of malignant cells during deep tissue sampling is an issue. Although it was not the subject of our study, no signs of seeding was find in surgically treated patients.

CONCLUSIONS

Deep tissue sampling by EUS-FNA and KHB are equally effective in diagnostics of SETs of the upper gastrointestinal tract ≥ 2 cm. Neither EUS-FNA nor KHB provide adequate tissue sample to determine mitotic index.

Author contributions: VZ: manuscript writing, designed the study, main coordinator and biopsy performing; PFa: biopsy performing, approved final manuscript; PF, OM: contributed to the acquisition of data; EK, MH: assisted in analysis; KR: histological/cytological examination; DZ: histological/cytological examination, verification; MB: surgion- resection; AT: statistical analysis; MK: data acquisition, assisted in analysis; OU: planed study, biopsy performing, final approval.

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