

## Editorial

# Endoscopic Ultrasound-Guided Sampling in Gastroenterology: European Society of Gastrointestinal Endoscopy Technical Guidelines

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## Abstract

At present, the European Society of Gastrointestinal Endoscopy (ESGE) guidelines on endoscopic ultrasound-guided sampling are almost complete and express state of the art developments. However, future developments are anticipated. This editorial focuses on a few recently published papers with some additional information and on two important additional techniques, elastography and contrast enhanced ultrasound (CEUS), which are mentioned, but not explained in detail in the current ESGE guidelines. Elastography and CEUS might be of importance in the near future to improve the biopsy techniques.

**Keywords:** guidelines, recommendations, biopsy, complications, pancreas, rectum

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## INTRODUCTION

The European Society of Gastrointestinal Endoscopy (ESGE) recently published recommendations on endoscopic ultrasound (EUS)-guided sampling, including EUS-guided fine needle aspiration (EUS-FNA) and EUS-guided trucut biopsy. The first part (the clinical guidelines) targeted as readers gastroenterologists, oncologists and surgeons and focused on patient management.<sup>1</sup> The second part (the technical guidelines) discussed issues related to learning, techniques and complications of EUS-guided sampling and to processing of specimens.<sup>2</sup> The second part, therefore, is targeting endoscopists who practically perform EUS-guided sampling. The aim of this paper is to maximize the diagnostic yield (e.g., rapid on-site evaluation (ROSE) of cytopathological, needle diameter, microcore isolation for histopathological examination and adequate number of needle passes). Recommendations are made for various settings with a focus on solid and cystic pancreatic lesions, submucosal tumors and lymph nodes. In addition, a summary of evidence statements and recommendations is provided.

At present, the ESGE guidelines are almost complete and express state of the art developments. It is obvious that the ESGE recommendations can only present current knowledge and future developments are anticipated.

In this editorial, we focus on a few recently published papers with some additional information and on two important additional techniques, which are mentioned but not explained in detail in the current ESGE guidelines. Elastography and contrast enhanced ultrasound (CEUS) might be of importance in the near future to improve biopsy techniques.

## MORE RECENTLY PUBLISHED PAPERS

### *Diagnostic accuracy of EUS-guided biopsy in solid pancreatic lesions*

In a systematic review and meta-analysis, a British group recently analyzed the yield of EUS-FNA of solid pancreatic lesions.<sup>3</sup> These meta-analysis pooled data are from 33 studies (21 prospective; 1997-2009;  $n = 4984$  patients). In 30 studies, 22 gauge needles had been used, in 1 study 19 gauge aspiration needles and in 2 studies 25 gauge needles. The results are shown in (Tab. 1). The negative predictive value (NPV) of 64% reflects the important fact, that a negative result of EUS-FNA does not excludes malignancy with absolute certainty.<sup>3</sup>

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**Table 1. Results of two recently published meta-analyses on the diagnostic accuracy of EUS-FNA of solid pancreatic lesions**

Meta-analysis	Studies	Patients	Sensitivity	Specificity
Hewitt <i>et al.</i> <sup>3</sup> 2012	33	4984	85% (91%*)	98% (94%*)
Puli <i>et al.</i> <sup>4</sup> 2013	41	4766	86.8%	95.8%

\*A typical and suspicious results included. EUS-FNA: endoscopic ultrasound-fine needle aspiration.

A second meta-analysis included 41 studies from 1995 to 2011 ( $n = 4766$  patients) and calculated somewhat lower sensitivity and specificity are shown in (Tab. 1).<sup>4</sup> Interestingly, only 14 studies were included in both meta-analyses. The diagnostic accuracy of EUS-FNA was enhanced in large ( $n > 100$ ), prospective, multicenter studies<sup>3</sup> and tended to perform better in more recent studies (2001-2009), compared with studies from the years 1995 to 2000.<sup>4</sup>

### ***EUS-guided biopsy for staging of lung cancer and extrathoracic malignancy***

On material obtained by EUS-FNA or endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA), a limited panel of immunohistochemical stains allows for subtyping of lung cancer in 80%-90% of cases.<sup>5,6</sup> Moreover, genotyping of adenocarcinoma of the lung (e.g., analysis of epidermal growth factor receptor mutations) has become possible using aspirates obtained by EUS- or EBUS-FNA biopsy.<sup>5,7</sup> A recent prospective randomized controlled multicenter study demonstrated a 94% sensitivity of combined endosonographic staging (EUS-FNA and EBUS-TBNA) for detecting N2/N3-disease in lung cancer patients (compared to 78% sensitivity for surgical staging). Moreover, the endosonographic approach prevented more futile thoracotomies than the surgical one (18% *vs.* 7%).<sup>8</sup> Sensitivity and specificity of EUS-FNA and EBUS-TBNA for the M-staging of extrathoracic cancers in several recent studies was approximately 85% and 100%, respectively. Therefore, in most cases surgical diagnostic techniques (mediastinoscopy and video-assisted thoracoscopy) may be avoided in this particular indication.<sup>9-11</sup>

### ***Technical factors of EUS-guided biopsy***

Several studies in the last years focused on technical aspects of EUS-FNA like optimal needle choice and usefulness of a stylet. Recently, the results of the studies on needle choice have been summarized in a meta-analysis. A total of 25 gauge needles perform somewhat better regarding the number of adequate needle passes in comparison with 22 gauge needles. However, there is no significant advantage with regard to sensitivity (25 gauge: 91%, 22 gauge: 78%), specificity (both needle types: 100%), number of needle passes or complication rates.<sup>12</sup> A single-center randomized prospective study demonstrates equivalency of 25 gauge needles and 22 gauge needles with regard to lymph node biopsies, a non-significant advantage of 25 gauge needles in solid pancreatic lesions and conversely, a non-significant advantage of 22 gauge needles in subepithelial gastrointestinal tumors.<sup>13</sup> Up

to now there are only very limited data on the efficacy of the new histology needles (ProCore). One randomized study compared the new 22 gauge ProCore needle and a new 22 gauge aspiration needle in EUS-guided sampling of solid pancreatic mass lesions. Diagnostic yield or quality of the histologic core did not differ significantly between the two needle types.<sup>14</sup>

### ***ROSE of cytology and other critical factors for success of EUS-guided biopsy***

There is a discussion on the value of ROSE cytology in EUS-FNA. A systematic review and meta-analysis comparing the results of studies with and without ROSE was recently published. ROSE was associated with a statistically significant 10% improvement in the adequacy rate of EUS-FNA only in studies with a low adequacy rate (<90%). On the other hand, ROSE had no impact on diagnostic yield.<sup>15</sup> In a large Japanese study including 996 EUS-FNA of solid pancreatic mass lesions, ROSE and lesion size were found to be the most important factors affecting diagnostic accuracy. The diagnostic performance was significantly higher when both cytological smears and cell-blocks were examined than with only cytological examination.<sup>16</sup>

### ***Results of studies and daily clinical practice***

The potential difference between the results of published studies and daily clinical practice was highlighted in a most interesting survey of 161 participants at the 13<sup>th</sup> international live course of EUS held in Amsterdam. About 57% of the participants answered the questions and 37.7% of the endosonographers reported a sensitivity for the diagnosis of solid mass lesions >80%. Self-reported sensitivity of EUS-FNA was 60%-80% in further 37.7% of respondents and only <60% in 24.6%. Factors independently associated with a high sensitivity were performance of a high number of needle passes (>7) for pancreatic lesions or availability of ROSE (27.9% of endosonographers), a high caseload of the hospital and sampling of small tissue cores for histology in addition to smear cytology.<sup>17</sup> Very similar results were reported in a survey of 142 EUS centers in Germany. The self-reported diagnostic yield of EUS-FNA was assessed to be >75% in only 48% of hospitals and lower than 50% in 15%.<sup>18</sup>

### ***Complications***

A systematic review of 51 studies ( $n = 10,941$  patients) reported on a pooled morbidity of EUS-FNA of 0.98%. A more realistic number is a frequency of complications of 1.71%, which was calculated from the data of 31 prospective studies.<sup>19</sup> A very similar risk assessment is derived from the data of the prospective German EUS registry with a 2.1% complication risk of EUS-FNA.<sup>20</sup> The most frequent complications are pain (34%), acute pancreatitis (34%), fever and infection (16%) and extra- or intraluminal hemorrhage (13%). Perforation and biliary leakage are rare (3%). Lethal complications are very rare events. EUS-FNA is exceptionally

**Table 2. Seven cases of needle tract seeding related to EUS-FNA (published until January 2013)**

Reference	Target	Details of EUS-FNA	Complication	Outcome
Hirooka <i>et al.</i> <sup>24</sup>	Malignant IPMN T1N0M0	Transgastric, number of needle passes not given, 22 gauge	Peritoneal carcinosis, diagnosis 20 months following EUS-FNA	Death 5 months following diagnosis
Shah <i>et al.</i> <sup>25</sup>	Perigastric lymph node metastasis (malignant melanoma)	Transgastric, 1 needle pass, 22 gauge	Gastric wall metastasis 6 months following EUS-FNA	Surgery, no outcome information
Paquin <i>et al.</i> <sup>26</sup>	Pancreatic tail cancer T1N0M0	Transgastric, 5 needle passes, 22 gauge	Gastric wall metastasis 21 months following EUS-FNA	Palliative chemotherapy, death 12 months following diagnosis
Doi <i>et al.</i> <sup>27</sup>	Mediastinal lymph node metastasis (gastric cancer)	Transesophageal, 1 needle pass, 19 gauge	Esophageal wall metastasis 22 months following EUS-FNA	Effective radiotherapy
Ahmed <i>et al.</i> <sup>21</sup>	Cystic pancreatic body cancer T2N0M0	Transgastric, multiple needle passes, no information given on needle diameter	Gastric wall metastasis nearly 4 years following EUS-FNA	Death resulting from another malignancy
Chong <i>et al.</i> <sup>22</sup>	Cystic pancreatic tail cancer T2N0M0	Transgastric, 2 needle passes, 22 gauge	Gastric wall metastasis 26 months following EUS-FNA	Non-resectable, no information on outcome is given
Katanuma <i>et al.</i> <sup>23</sup>	Solid pancreatic cancer T2N0M0	Transgastric, 4 needle passes, 22 gauge	Gastric wall metastasis 22 months following EUS-FNA	No information on outcome is given

EUS-FNA: endoscopic ultrasound-fine needle aspiration.

safe in mediastinal lesions (complication rate: 0.38%), abdominal mass lesions (0.26%) and in left adrenal gland (0%). Morbidity of pancreatic EUS-FNA is 1.03% (prospective studies: 2.64%). A somewhat higher morbidity is reported for EUS-FNA of perirectal lesions (2.07%), liver lesions (2.33%) and ascites (3.53%). There is a striking risk difference between solid and cystic pancreatic lesions (solid: 0.82%, prospective studies: 2.44% *vs.* cystic: 2.75%, prospective studies: 5.07%).<sup>19</sup>

In 2011 and 2012, three new cases of metastatic needle track implantation in consequence of EUS-FNA have been reported.<sup>21-23</sup> The total number of case studies reporting EUS-FNA related tumor seeding now is seven (Tab. 2). In six of seven cases, a long latency between performance of EUS-FNA and diagnosis of FNA-related metastasis is apparent. In all five cases of tumor seeding following EUS-FNA of pancreatic mass lesions according to the tumor node metastasis stage there had been a realistic chance of curation, which was dashed in consequence of EUS-FNA. In three cases, a cystic pancreatic mass lesion had been the target of EUS-FNA (Tab. 2).

The problem of metastatic needle tract implantation was addressed in a retrospective comparative study of 230 patients with malignant pancreatic tumors with and without pre-operative EUS-FNA undergoing distal pancreatectomy.<sup>28</sup> The authors did not find any significant differences in overall or recurrence-free survival between cancer patients with and without EUS-FNA prior to surgery. However, due to suspicion of malignant infiltration of the stomach wall in 7 of 57 patients with pre-operative EUS-FNA of pancreatic tail cancer partial gastric resection was performed. This was not indicated in any patient of the group without pre-operative EUS-FNA.<sup>28</sup>

These findings as well as the five case reports on tumor

seeding following transgastric EUS-FNA of pancreatic tail and body cancers strongly argue against performing EUS-FNA of suspected pancreatic adenocarcinoma on a regular basis before surgery as advocated by some authors.<sup>29,30</sup> Therefore, in patients with resectable mass lesions and fit for surgery, EUS-FNA should be restricted to patients with a suspicion of pancreatic mass lesions other than ductal adenocarcinoma.

## ELASTOGRAPHY

Currently the availability and application of elastographic technology is rapidly expanding.<sup>31</sup> With strain imaging techniques, the tissue is compressed and the resulting strain is measured from the degree to which the tissue distorts. These are referred to as “static” or “quasi-static” methods. Usually, the ultrasound probe is used to palpate the tissue. Alternatively physiological movements such as a vessel or heart pulsations are used as the source of the displacement. Strain imaging techniques applied by EUS are based on the fact that stiffer tissues have very low strains and are the methods used in real time elastography (RTE).<sup>32-34</sup>

RTE has the potential to further improve the accuracy of EUS-FNA by targeting lymph nodes for needle sampling. A recent meta-analysis calculated a pooled sensitivity of 88% and a pooled specificity of 85%, respectively, with EUS elastography for differentiating between benign and malignant lymph nodes.<sup>35</sup> RTE-EUS has also been used to guide biopsy of subepithelial lesions.

We believe that elastography will play a stronger role in future guidelines and recommendations regarding EUS biopsy techniques. This might be reflected by the fact that the European Federation of Societies for Ultrasound in Medicine

and Biology (EFSUMB) has prepared two sets of guidelines regarding the use of elastographic techniques including the current value in EUS.<sup>36,37</sup>

## CE-EUS

CE-EUS is a newly established method, which combines the advantage of high-resolution EUS of internal organs with the administration of ultrasound contrast agents. CE-EUS has been recently addressed in detail in EUS<sup>38</sup> and other reviews including therapeutic options.<sup>39,40</sup>

The technique has been described using two different technical subtypes with similar results: contrast-enhanced endoscopic Doppler ultrasound with high-mechanical index (MI), which does not require specific software and contrast-enhanced low-MI EUS using the contrast-specific mode.<sup>41,42</sup>

The use of CE-EUS improves the diagnostic accuracy of ultrasound in the study of the pancreatic pathologies<sup>43,44</sup> and lymph node evaluation.<sup>43,45</sup>

EFSUMB introduced guidelines on the use of CE-EUS.<sup>45</sup> The recommended uses and indications are mainly as described for the pancreas and additionally for the discrimination of mass-forming chronic pancreatitis from ductal adenocarcinoma in patients with the chronic pancreatitis.

## APPLICATION OF ADVANCED EUS TECHNOLOGIES FOR GUIDANCE OF EUS-FNA

### *Pancreatic mass lesions*

The ESGE clinical guideline on EUS-guided sampling states that due to a relatively low NPV for the diagnosis of pancreatic cancer, pre-operative sampling of potentially resectable pancreatic tumors in operable patients is generally not advised.<sup>1</sup> However, in some highly specialized referral centers one-third of patients with focal pancreatic lesions the final diagnosis is not ductal adenocarcinoma. For instance, among 2413 FNAs of focal pancreatic lesions at the University of Alabama (Birmingham) cytologic diagnosis in 504 cases (21%) was benign. Among 1730 neoplasias, 77% were diagnosed to be ductal adenocarcinoma. However, 11.2% were cystic neoplasias, 6.8% neuroendocrine tumors, 3% metastases, 0.75% mesenchymal tumors, 0.5% lymphoma and 0.5% solid pseudopapillary neoplasia.<sup>46</sup> In most cases, diagnosing a distinct pancreatic mass lesion other than ductal adenocarcinoma will significantly alter the patients management and prognosis — e.g., by indicating an organ-preserving surgical approach in small neuroendocrine tumors, a non-surgical treatment in mass-forming autoimmune pancreatitis or lymphoma or watchful-waiting in some cystic neoplasias and in the small World Health Organization Grade 1 neuroendocrine tumors.

On the other hand, even in recent studies from pancreatic surgical centers with high case load, incidence of benign

pathology after pancreaticoduodenectomy for presumed cancer was reported to be in the range of 9%-15.6%.<sup>47-49</sup>

Therefore, selection of patients for EUS-FNA with a high suspicion of diagnoses other than ductal adenocarcinoma is of crucial importance in order to avoid unnecessary pancreatic head resection with its inherent morbidity and mortality.

A typical pancreatic adenocarcinoma is a hypoechoic mass lesion with scarce irregular peripheral arterial vessels and lacks venous vessels.<sup>43,50-52</sup> A recent meta-analysis has shown that CE-EUS may discriminate pancreatic adenocarcinoma and other solid pancreatic lesions with a pooled sensitivity of 94% and specificity of 89%.<sup>53</sup>

In conclusion, complementary to the statements of the ESGE clinical guideline on EUS-guided biopsy, recent data suggest that patients with hyperenhancing or isoechoic solid pancreatic mass lesions in comparison with the surrounding pancreatic parenchyma should be referred to pre-therapeutic EUS-FNA.

### *Subepithelial gastrointestinal tumors*

The clinical guidelines<sup>1</sup> states that in hypoechoic subepithelial tumors (SET) of the stomach >20 mm the usefulness of EUS-guided biopsy is limited due to a moderate diagnostic yield and lacking the capability to determine the mitotic index. This conclusion is supported by several recent studies showing that retrieval of material suited for immunohistochemical phenotyping by EUS-FNA and EUS-TCB is successful only in about 70% of cases.<sup>54-56</sup>

In the stomach, the majority of hypoechoic SET are (potentially) malignant gastrointestinal stromal tumors (GISTs). On the other hand, approximately 25% of incidentally detected hypoechoic gastric SETs are benign leiomyoma or schwannoma and in those patients surgical treatment is not indicated. However, differential diagnosis of hypoechoic gastric SETs by means of EUS and other imaging methods is difficult.<sup>57</sup> There are several ways to make a presumptive diagnosis of a non-GIST gastric SET. In a study from Korea, differentiation of GISTs from leiomyomas was possible with a sensitivity of 89% and specificity of 86% if two of the following four EUS features were met: higher echogenicity compared with the muscularis propria, inhomogeneity, hyperechoic foci and halo sign. A typical leiomyoma is hypoechoic or isoechoic compared with the deep muscle layer, homogeneous, has a smooth contour and presents without a halo or hyperechoic spots. Conversely 60% of GIST are hyperechoic compared to the muscularis propria, 80% are surrounded by a hypoechoic halo, 80% are inhomogeneous and in 90% hyperechoic reflexes are found.<sup>58</sup> Preliminary data suggest that CE-EUS can discriminate GIST (hypervascular in all cases) from benign lesions (leiomyoma, lipoma: Hypovascular).<sup>59,60</sup> Moreover, GISTs with intermediate and high risk of malignancy present with highly irregular vascular patterns and avascular areas (necrosis).<sup>60,61</sup>

Summarizing these data, it would be a reasonable strategy



to use EUS features and CE-EUS to select those hypoechoic SETs for EUS-guided biopsy, which shows features typical for leiomyoma. Immunohistochemical proof of leiomyoma (Desmin and/or smooth muscle actin positive; CD177 and/or DOG-1 negative) would prevent unnecessary surgical treatment in approximately 20% of asymptomatic patients with hypoechoic SETs of the stomach.

The ESGE guidelines support individual and standardized management of patients under the rule of 30 years' experience and evidence. The application of CE-EUS and elastography has the potential to change indications and applications including biopsy techniques for pancreatic pathology, lymph nodes and subepithelial lesions. More details and practical hints about elastography and CEUS are published in current textbooks.<sup>62</sup>

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