Endosonography For Right-sided and Acute Upper Intestinal Misery: the EFRAIM study

A prospective, randomized, controlled, blinded study

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Abstract

Background: Acute upper abdominal pain is a frequent symptom leading to hospital admission.

Objective: To determine whether a primary intra- and extraluminal diagnostic approach enabled by endoscopic ultrasound is as effective as a conventional diagnostic algorithm of transabdominal ultrasound followed by oesophagogastroduodenoscopy.

Methods: A total of 240 patients who presented with acute right-sided and/or upper abdominal pain were prospectively recruited. Exclusion criteria were chronic pain, malignancy, prior abdominal surgery, bleeding, peritonitis, and elevated liver enzymes or lipase as defined 3-times higher than upper reference value. All patients underwent first transabdominal ultrasound and were then randomized (1:1) to either endoscopy followed by endoscopic ultrasound or vice versa. Patients and respective examiners were blinded to prior findings.

Results: A total of 223 patients were included. Endoscopic ultrasound provided a higher diagnostic yield than the combination of transabdominal ultrasound and endoscopy (62.3 vs. 50.7%; $p=0.001$). For mucosal/intraluminal lesions, we observed a very good agreement between both endoscopic modalities (kappa 0.89). The agreement for pancreatic and biliary causes was good between both ultrasound modalities (kappa 0.66).

Conclusions: Due to its high diagnostic yield, endoscopic ultrasound as a primary diagnostic modality appears to be a valuable option in patients with acute upper abdominal pain.

Keywords

Biliary, endoscopy, EUS, gastrointestinal, pain

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Introduction

Patients with abdominal symptoms represent a considerable group in any primary care clinical setting. In a recently published study on 34,333 patients seeking medical help in Berlin Charité's medical emergency department, 11.1% presented with the main symptom of abdominal pain.¹ Other studies report a prevalence of 1.5–5% of patients with abdominal symptoms in private practice or emergency departments in the USA.^{2,3}

Often faced with unspecific symptoms, inconclusive laboratory findings, and the numerous differential diagnoses of the chief symptom of upper abdominal pain, selection of an efficient diagnostic algorithm is challenging. In general, abdominal imaging applying

transabdominal ultrasound (TUS) or a computed tomography scan is the primary choice, followed by endoscopy if findings are inconclusive.^{4–6}

Taken under consideration that modern radial forward-viewing echoendoscopes should offer an adequate combined visualization of intraluminal mucosal lesions of the upper gastrointestinal tract and extraluminal findings of the pancreatobiliary tract, we designed this

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prospective study. The main study aim was to evaluate the diagnostic yield of a primary single-step diagnostic procedure with endoscopic ultrasound (EUS) in patients with acute upper abdominal pain vs. a conventional step-by-step algorithm consisting of TUS, oesophagogastroduodenoscopy (EGD), and EUS.

Given the non-inferiority of EUS vs. TUS and EGD, it would reaffirm the examiner to rely on one single diagnostic procedure to quickly rule out the most common conditions causing upper abdominal pain.

Methods

Study design

The EFRAIM study (Endosonography For Right-sided Acute Upper Intestinal Misery) was performed as a prospective diagnostic study randomized 1:1 to two diagnostic arms (Figure 1).

From January 2010 to August 2012, all patients with acute upper abdominal pain aged above 18 years who presented in the emergency department were asked to participate in the study. Acute abdominal symptoms

were defined as being present no longer than 48 hours before admission.

Exclusion criteria were: (i) selected pathological laboratory findings, defined as elevated liver enzymes at least 3-fold above the upper normal value and more than doubled lipase; (ii) all patients with known diseases that might otherwise explain the actual symptoms; (iii) patients with any history of chronic pain, malignant disease, and prior surgery/interventions in the upper gastrointestinal tract; (iv) patients with need for urgent treatment due to signs of gastrointestinal bleeding, peritonitis, or admission to intensive care unit for other reasons; (v) patients with ASA class 4 or 5; (vi) pregnancy; and (vii) inability to give informed consent.

The study was approved by the ethics committee of the Technical University of Munich and was registered with clinicaltrials.gov (NCT01080690).

After the validation of inclusion and exclusion criteria, 240 patients were randomized. Initially all patients underwent TUS. Figure 1 illustrates the diagnostic study algorithm: patients in the first arm were evaluated by EGD before EUS while patients in the second arm were evaluated by EGD after EUS. The endoscopy procedures were performed consecutively by different examiners who were blinded to all previous findings. Biopsies (standard forceps biopsies of antrum and corpus and other indicating findings) were only taken during the second procedure to avoid biased findings caused by the previous examination. Immediately after the respective examination and documentation of findings examiners were unblinded and further biopsies were taken, if necessary.

After endoscopy, patients were followed up by reviewing their hospital charts and discharge letters. Furthermore, follow-up information was collected by telephone interviews after a 4-week period. These interviews focused on recovery, persistence, or aggravation of the symptoms or eventually performed other procedures in order to confirm or adjust the final diagnosis

Figure 1. Study protocol with the sequence of procedures according to the randomized study groups. EGD, oesophagogastroduodenoscopy; EUS, endoscopic ultrasound; TUS, transabdominal ultrasound.

Diagnostic procedures

Transabdominal ultrasound examinations were performed using a ACUSON Sequoia and Sonoline Elegra system (Siemens, Erlangen, Germany). Upper endoscopies were performed with a GIF H 180 or GIF Q 180 (Olympus, Hamburg, Germany). EUS examinations were done with digital radial scanners and forward-viewing echoendoscopes from Pentax (type EG3670URK) in combination with Hitachi Hi Vision Avius and EUB 5500 HV (Hitachi Medical Systems, Wiesbaden, Germany). Biopsies for histopathological analysis of gastritis and *Helicobacter pylori* were taken from the gastric antrum and body using pediatric forceps enabling passage through the

instrumentation channel of all endoscopes as used. Endoscopic examinations were performed under conscious sedation with propofol.

All examinations (TUS, EGD, and EUS) were performed in a standardized manner by experienced examiners having performed at least 500 examinations. TUS included examination of all intra-abdominal organs including large and small bowel as far as assessable.

Statistical analysis

Main study aim was the evaluation of a primary and single step diagnostic approach by EUS in patients with acute upper abdominal pain. The hypothesis was that EUS is not inferior to a standard diagnostic algorithm with transabdominal ultrasound followed by EGD.

A priori power calculation suggested a sample size of 240 patients. If the expected proportion of non-verified TUS and EGD diagnosis under EUS will be maximum 2%, with a test power of larger 80%, a type I error of 0.05 is assumed.

Statistical analysis was performed using SPSS software package, Version 18.0. A P-value below 0.05 was considered statistically significant.

Kappa coefficients for concordance were calculated to compare diagnostic agreement on mucosal findings by EUS vs. EGD and on non-mucosal/extraluminal findings by EUS vs. TUS. Furthermore, the diagnostic yields and miss rates of the respective test strategy (EUS vs. EGD/TUS) were tested for statistically significant difference using the McNemar test for dependent variables.

Patients were randomized for both groups according to a computer-generated list.

Results

A total of 240 patients were randomized for the study. Amongst those, 17 patients were not included after randomization due to violation of the study protocol (previous surgery, malignant disease, higher laboratory values than accepted). The baseline clinical characteristics of the study population are as shown in Table 1. Time of symptoms starting was (mean $\pm$ SD) 16.1 ± 13.7 hours before admission.

Findings of examinations as performed

Extraluminal findings were detected in 77 subjects in the EUS group and in 55 subjects in the TUS group. In detail, these findings were as follows: sign of cholecystitis (thickened wall of gall bladder) in 31 and 24 patients, gall stones in 24 and 24 patients, and common bile duct stones in 10 and four patients, respectively. Pancreatitis as defined by parenchymal

Table 1. Baseline characteristics of the study population

Characteristic	Study population (n = 223)
Female/male	118/105 (52.9/47.1)
Age (years)	44.6 $\pm$ 16.2
Pain onset before admission (hours)	16.1 $\pm$ 13.7
Main location of pain	
Epigastrium	131 (58.7)
Right upper abdomen	92 (41.3)

Values are n (%) or mean $\pm$ SD.

oedema, lobularity, hyperechoic strands, and/or dilation or irregular contour of the main pancreatic duct was diagnosed in 12 and three respective patients.

Intraluminal findings (oesophageal, gastric, or duodenal lesions) were detected in 43 patients of the EUS group and 41 patients of the TUS and EGD group. Amongst those, 24 and 21 respective patients had signs of erosive gastritis or duodenitis. Nine patients in both groups had reflux oesophagitis. Gastric and duodenal ulcers were detected in 10 patients of the EUS group and in 11 patients of the EGD group. One suspicious gastric ulcer (detected by both EUS and EGD) was confirmed a gastric cancer by histopathology.

Histopathological assessment of biopsies obtained during EUS or EGD revealed *H. pylori*-associated gastritis without mucosal lesions in 16 patients (7.2%).

Relevant pathological findings neither in EUS, TUS, nor EGD could be observed in the remaining 83 patients. Figure 2 summarizes the findings with respect to the different diagnostic modalities.

Agreement between the EUS and the EGD approaches

For mucosal lesions, we found a very good agreement for both approaches (EGD and EUS) with a kappa of 0.885. The detection of extraluminal/pancreaticobiliary pathological findings also showed a good agreement of TUS and EUS with a kappa of 0.569.

Final diagnoses, diagnostic yield, and miss rate

Based on clinical findings, initial cause, and course of symptoms, the final diagnoses as stated at discharge of patients were as shown in Table 2. No conclusive findings could be obtained in 83 patients. These were categorized as patients with an acute dyspeptic episode of unknown origin. Overall, solely EUS provided a higher diagnostic yield than the combination of TUS and EGD (62.3 vs. 50.7%; $p = 0.001$). EUS failed to detect findings observed by TUS and EGD in four patients (miss rate 3.5%). In contrast, TUS and EGD missed

Figure 2. Frequency of pathological findings (pancreaticobiliary and endoluminal findings) as detected by EUS vs. TUS and EGD. EGD, oesophagogastrroduodenoscopy; EUS, endoscopic ultrasound; TUS, transabdominal ultrasound.

Table 2. Final diagnosis of patients based on the diagnostic approach

Diagnosis	EUS	TUS or EGD
Symptomatic gall stone disease	24/25	24/25
Cholecystitis	31/32	24/32
Common bile duct stones	10/10	4/10
Pancreatitis	12/12	3/12
Reflux oesophagitis	9/10	9/10
Erosive gastritis and/or duodenitis	23/24	21/24
Peptic ulcer disease ^a	9/11	11/11
Other ^b		1

Values are n/total patients.

^aAdenocarcinoma of the stomach in one patient. ^bSmall bowel ileus due to obstruction of an unclear mass (as detected by TUS).

relevant findings observed by EUS in 28 patients (17.5%) (Figure 3). The higher diagnostic yield of EUS was mainly attributed to its more accurate detection of pancreaticobiliary causes (Figure 2 and Table 2). For mucosal lesions, EUS missed the detection of a relevant pathological finding in four patients: in two patients benign gastric ulcers were overlooked, in a further two patients EUS missed to detect gastric erosions. For pancreaticobiliary lesions, EUS missed a single patient with cholecystitis and another patient with small stones in the gall bladder.

Figure 3. Diagnostic yield and miss rate of endoscopic ultrasound compared to transabdominal ultrasound combined with EGD. EGD, oesophagogastrroduodenoscopy; EUS, endoscopic ultrasound; TUS, transabdominal ultrasound. Any pathological finding of the respective method was considered a positive diagnosis, whereas miss rate summarizes patients with an overlooked finding by one method that was, however, detected by the other respective method.

Follow-up data

Four weeks after inclusion, follow-up data were available from 164 of the 223 patients included (74%) and

we were able to contact 39 of the 83 patients with no findings (47%). Here, diagnosis continued to be indistinct and functional disorders have been assumed in all those patients. Follow-up data could be obtained from 125 of the 140 patients with specific pathological findings (89%). The final discharge diagnosis could be confirmed in 121 of those 125 cases (97%) but had to be modified in four patients. One patient was operated the day after discharge for a left-sided appendicitis not diagnosed by TUS. Another patient with suspected symptomatic gallstones was readmitted to another hospital for equivalent upper abdominal and was diagnosed an adhesions ileus. Two male patients who presented with upper abdominal pain were transferred to urgent surgery for a perforated appendicitis 18 hours and 6 days after the initial pain episode.

The patient with an undetermined mass in the ileum (as detected by TUS) proved to suffer from a jejunal metastasis of a malignant melanoma not detected before admission.

Discussion

In this large prospective diagnostic study, we were able to demonstrate that EUS using forward-viewing echoendoscopes as a single diagnostic procedure for further evaluation of acute abdominal pain is not inferior to EGD in combination with transabdominal ultrasound. Furthermore, the diagnostic yield of EUS proved to be significantly higher compared to EGD and TUS without a significant lack of accuracy in detecting luminal endoscopic findings. In addition, EUS as a primary procedure might be more cost-effective compared to TUS followed by EGD. Costs for various examinations may vary in various hospitals in various countries or regions. However, in accordance to published data from Germany on that topic⁷ and based on the internal cost allocation of our hospital, costs for single diagnostic EUS are somewhat lower compared to the summed up costs of TUS followed by diagnostic EGD (EUS ~95€ vs. TUS and EGD ~40€ + ~80€).

All these data suggest that EUS as a primary diagnostic approach appears to be a valuable option in patients with acute upper abdominal pain.

Our results stand in agreement with a previously published study comparing the diagnostic yield of EGD and EUS vs. EGD and TUS. The authors concluded that EGD combined with EUS should be considered in the first-line diagnostic evaluation of patients with upper abdominal pain because of its higher diagnostic yield especially in chronic pancreatitis.⁸ In an accompanying editorial, it was postulated that EUS/EGD as first line procedure for the evaluation of the dyspeptic patient seems to be reasonable and warranted

if the patient's symptoms suggest a possible pancreatic or biliary source of pain.⁹ Although these data already strengthened the role of EUS in the diagnostic work up of patients with upper abdominal symptoms, our study highlights the fact that, due to the additional integrated endoscopic imaging system, EUS can serve as a single diagnostic tool for mucosal and non-mucosal findings. Moreover, the study population in the manuscript of Chang et al.⁸ comprised patients with abdominal symptoms for more than 4 weeks, while we focused on patients with an acute episode of pain.

That EUS as a single diagnostic step for determination of dyspepsia might be valuable has already been reported before using fiberoptic echoendoscopes.¹⁰ Authors assumed that EUS enables an adequate endoscopic and ultrasound examination leading to a relevant overall cost-reduction since detection of relevant mucosal and non-mucosal findings prevents further additional testing.¹¹ However, such an approach was not prospectively assessed in an acute setting when a correct diagnosis is essential before further therapeutic procedures are initiated.

As we focused in our analysis on the diagnostic accuracy of both diagnostic approaches, it is necessary to take a closer look on the missed diagnosis with therapeutic relevance. With the EUS approach, gastric ulcers were missed in two cases: one located beneath the angulus in the antrum; the other at the posterior wall of the gastric body. We assume that this endoscopic shortcoming is related to the stiffer handling of echoendoscopes. Retroflexion of the endoscope's tip can be difficult and complete inspection of the gastric mucosa appears to be more complex and time consuming. Newer, more flexible echoendoscopes might help to overcome these shortcomings. Other technical limitations of the echoendoscopes during the procedure were not documented. Adequate biopsy samples could be obtained in all cases using thinner, pediatric biopsy forceps. Herein our study contradicts the work of Chang et al.⁸ where the standard endoscope was preferred for biopsies.

Overall detection of mucosal lesions showed a very good agreement with a kappa of 0.89. Nevertheless disagreement in mucosal findings was documented most often for erosions and reflux-oesophagitis. In our opinion, this can be explained by interobserver variability in detecting and classifying endoscopic findings. This stands in agreement with other reports mentioning a inter-observer agreement with a kappa value of 0.59 for erythematous gastric mucosa, a kappa of 0.72 for gastric erosions, and a kappa of 0.85 for gastric ulcers.¹² Therefore, non-equivalent findings of small intraluminal changes of the mucosa should not query a valid mucosal evaluation performed by a radial echoendoscope.

One of the important findings is a higher accuracy of EUS for pancreaticobiliary causes (Table 2). Of interest, EUS more often detected a wall thickening of the gallbladder, suggestive for cholecystitis. Typically, TUS uses also pain on palpation or compression of the gallbladder as an important and sensitive criterion but this is impossible to judge with EUS. One might therefore doubt whether all these EUS diagnoses of cholecystitis are correct. However in such cases with a wall thickening solely found by EUS, an antibiotic therapy was given and patients' complaints significantly improved at follow up leading to the assumption that indeed cholecystitis was the cause of primary admission. For subtle changes of the pancreas (parenchymal oedema, lobularity, hyperechoic strands, and/or dilation or irregular contour of the main pancreatic duct), we can only assume that these were indeed related to painful but mild episodes of pancreatitis, since more than doubled lipase was considered an exclusion criterion. Nevertheless, even if these patients were excluded from analysis, EUS still performed better compared to TUS.

The present study also included assessment of follow-up data to obtain better information on the final diagnosis and outcome. In almost all cases, the initially obtained data were sufficient to guide subsequent therapy. Of interest, three patients with continuing aggravated symptoms suffered from acute appendicitis as diagnosed after readmission. These examples highlight the necessity of at least a close clinical monitoring of patients with severe symptoms that initially cannot sufficiently be explained by indistinct findings. Furthermore, it reflects that transabdominal ultrasound can also fail to detect other, non-pancreaticobiliary causes.

Nevertheless, in summary, we think that our present study supports the preferred use of radial EUS with forward-viewing optics in the diagnostic work up for the majority of all patients seeking help due to acute upper abdominal misery or distress. The logistic disadvantages of EUS when comparing with TUS such as need for sedation and need for availability of endosonographers might be outweighed by the fact that the usual standard sequence – TUS followed by EGD followed by computed tomography, MRI, or EUS as long as diagnosis is inconclusive – can be omitted in most cases. The diagnostic accuracy of echoendoscopes for detecting mucosal lesions allows a reliable endoluminal evaluation of the upper gastrointestinal tract, while their use for evaluation of the pancreaticobiliary system offers a significantly higher diagnostic yield compared to TUS. Hence, we conclude that our results

serve to extend the indication for an early use of EUS in patients with acute upper abdominal pain.

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Conflict of interest

The authors declare that there is no conflict of interest.

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