Exploring Quality of Endoscopic Ultrasonography in Clinical Practice

Rutger Quispel

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Exploring Quality of Endoscopic Ultrasonography in Clinical Practice

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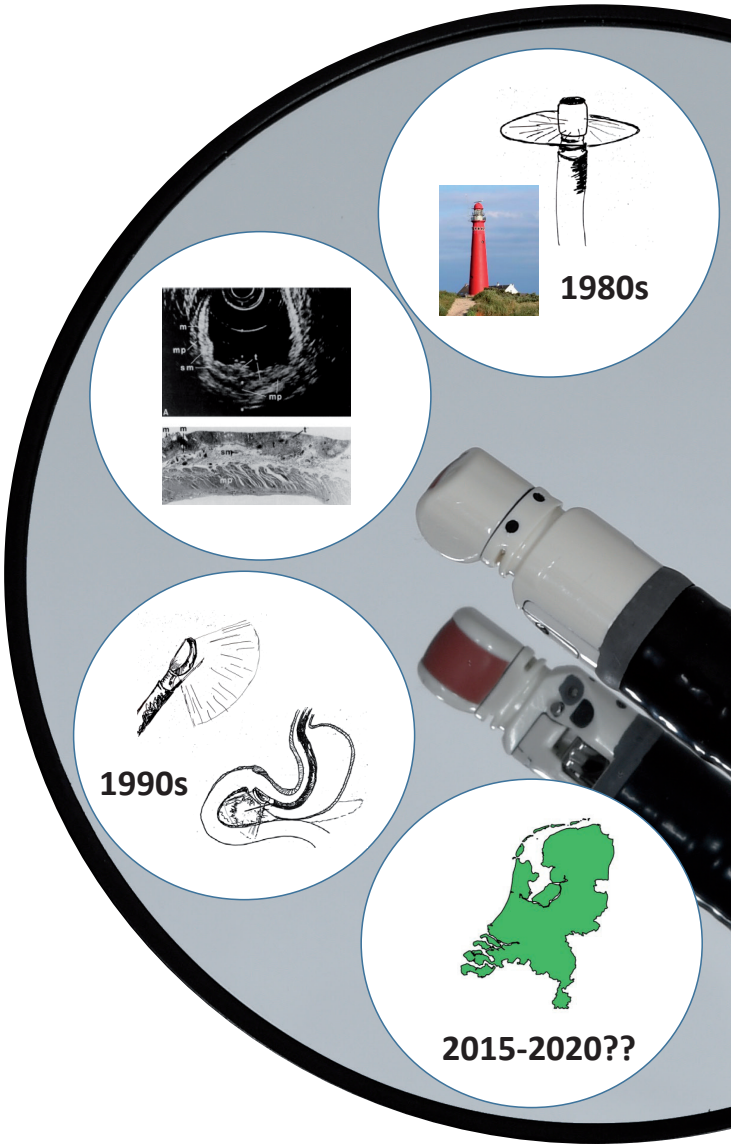
CHAPTER 1



Introduction and outline of the thesis

From radial EUS to EUS guided tissue acquisition

In 1980 a first article was published on a novel endoscopic technique called "endoscopic ultrasonography" (EUS). Di Magno et al from the Mayo Clinics described the use of a side-viewing gastroscope with an ultrasound probe mounted to its tip, a device they named "ultrasonic endoscope", in dogs[1]. These first echo-endoscopes created an ultrasound image from the around the ultrasound probe by projecting an ultrasound beam similar to the way a lighthouse projects its' light beam (Figure 1a and b). Olympus Company from Tokyo, Japan, manufactured the first commercially available prototype of an echoendoscope. These had been distributed to leading endoscopy centers around the world to gain experience and insight into the potential of this new technique[2]. This led to the first publications on radial endosonography in humans in the early 1980s, describing the endosonographic structure of the normal and pathologically altered gastrointestinal wall (Figure 2.) [3,4]. In 1984 Tio and Tytgat considered the possibility of using the biopsy channel of the echoendoscope for cytological puncture[5]. They hypothesized EUS guided tissue acquisition to be a valuable adjunct to the diagnostic value of EUS, although they also considered this difficult because of the perpendicular orientation of working channel and ultrasound beam in radial-scanning echoendoscopes.

In 1990 PENTAX introduced linear array endosonography[6]. In contrast to radial-scanning echoendoscopes, the ultrasound beam in these scopes is oriented alongside the endoscope and in the direction of its working channel (Figure 3a and b). The changed orientation of the

Figure 1a. Schiermonnikoog Lighthouse

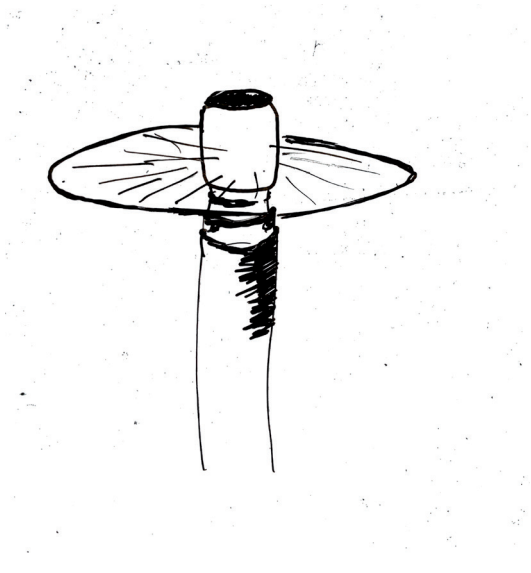


Figure 1b. Radial-array echoendoscope

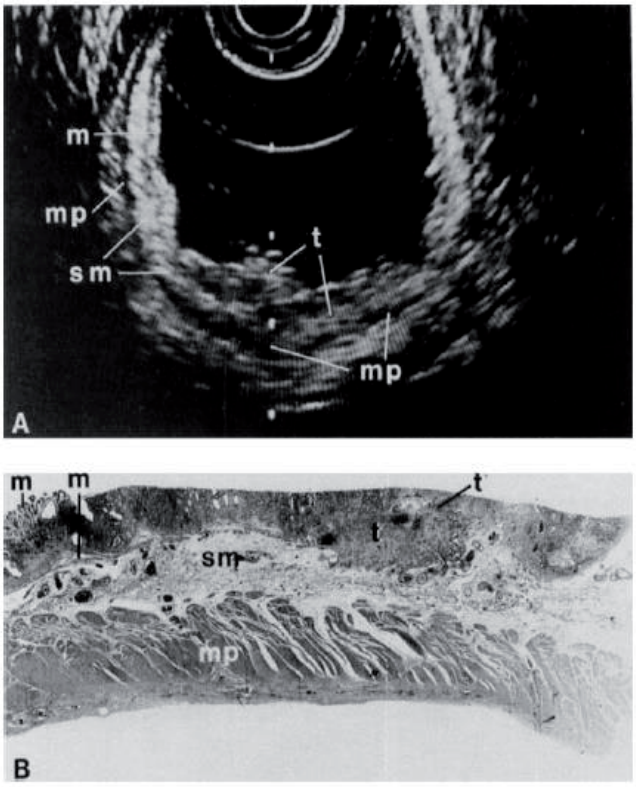


Figure 2a. EUS in vivo showing hypoechoic structure in the mucosa and submucosa (t) without penetrating into the muscularis propria bordering the normal gastric wall structure at both sides. **2b.** Corresponding histology of the resection specimen showing early gastric cancer (t) bordering the normal gastric wall. The resemblance between the EUS image and the corresponding histology is obvious.

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ultrasound beam allowed for introduction of a needle through the working channel into a lesion visualized with ultrasound. The first publication on Endoscopic Ultrasonography (EUS) guided Tissue Acquisition (TA) of solid pancreatic lesions was by Peter Villmann, from Kopenhagen, Denmark in 1992[7].

Types of publications and evidence on EUS

Initial publications on novel developments in healthcare usually consist of animal studies, followed by case reports and case series describing the use in humans focusing on safety and feasibility. For radial- and later linear EUS, these data were mainly published in the 80s

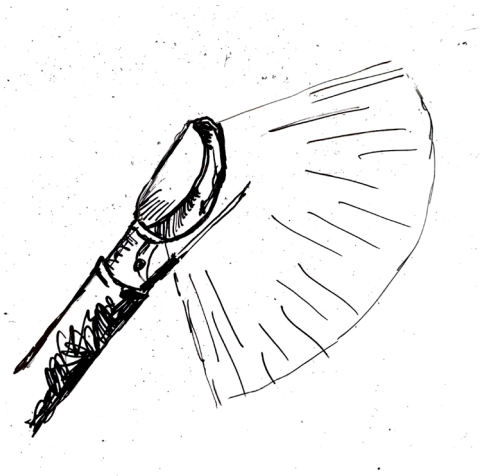

Figure 3a. Linear-array echoendoscope

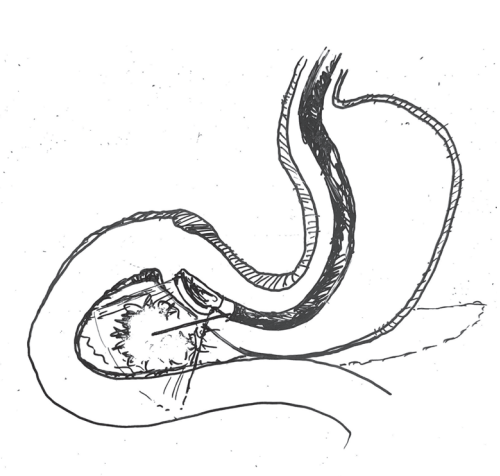

Figure 3b. EUS-guided tissue acquisition of solid pancreatic lesion from the stomach using linear-array echoendoscope

and 90s of the previous century. As EUS was being studied extensively in the following years, multiple publications on use and yield of EUS in different diseases came to light. In the late 90s of the 20th century, radial EUS had established itself as a tool for staging malignancies in and around the gastrointestinal tract, although this was debated by some[8]. In the first decade of the 21st century, the possibility of EUS guided TA, firmly established and expanded the role of EUS in clinical practice. This was confirmed by several randomized trials and meta-analyses, summarizing evidence from previous publications on specific topics such as the use of EUS in patients with suspected bile duct stones or the use EUS in patients suspected to have pancreatic cancer [9-12]. Nowadays, (inter)national endoscopy societies regularly publish evidence based guidelines on the use of EUS, aiming to guide practitioners throughout the world, on when and how to use EUS [13-16].

Developments in EUS

During the past 30 years, the pioneers and early adopters of EUS (most of them academic tertiary care facilities throughout the world), have studied EUS and a large sequence of new techniques and developments concerning EUS. Which type and diameter of EUS-needle should be used in specific types of lesions? Should suction be applied, when performing EUS guided TA? Does on-site cytopathological evaluation (ROSE) help to get better samples? Are liquid-based cytology techniques (Cellblock or Thinprep) helpful in getting a tissue diagnosis? What is the role of next generation sequencing (NGS) as an adjunct to EUS guided TA in suspected pancreatic cancer? These, and other important questions on the use and yield of EUS and additional techniques have been addressed and are summarized

in guidelines on EUS by both the American-, and European Societies of Gastrointestinal Endoscopy (ASGE and ESGE) [13-18].

Training and education

How to become an endosonographer? First, you have to be a skilled endoscopist. Second, you need a teacher. This teacher needs a curriculum: he or she needs to know what has to be taught (and how), to get a trainee to obtain the necessary skills. Third, teacher and trainee need a training environment, i.e. they need to perform endoscopy in a hospital with sufficient exposure to EUS, to provide necessary teaching, and learning opportunities. However, what is sufficient exposure, and how is this determined?

At the World Congress of Gastroenterology in Los Angeles, in October 1994, this topic was discussed. It was concluded that for tumor staging with a radial echoendoscope threshold numbers at which competence may be expected were 50 examinations each for the esophagus and stomach, and a 100 to 150 for the pancreaticobiliairy tract[19]. A scientific basis for these numbers was not specified. In 2001 the ASGE advised a minimum of 150 supervised EUS procedures, of which 75 for a pancreaticobiliary indication, before competency can be assessed [20]. These recommendations were based on expert opinion and limited data [21,22].

In 2013 Wani et al, published on learning curves of advanced endoscopy trainees learning EUS. They found substantial variability in achieving competency, and a need for more supervision in all trainees beyond the recommended number of procedures [23]. These findings were confirmed in later studies and systematic reviews, and indicate numbers of procedures performed, to be a poor measure of competency and quality [24-28].

Growth and dissemination of EUS

The use of EUS has increased tremendously throughout the last two decades. Today, EUS plays a pivotal role in diagnosing and/or obtaining tissue from a multitude of diseases in and around the gastrointestinal tract, and has a wide array of therapeutic applications [6,29]. Whereas in 1992, EUS was available in 5-10 hospitals in the Netherlands, today it is practiced in over 50 hospitals throughout the Netherlands by over a hundred endosonographers. Based on sales data from the main manufacturers of EUS needles (Cook medical, Boston scientific and Olympus), EUS guided TA was performed approximately 2500 times a year in Netherlands in 2006. From 2010 onwards, this remained stable at around 8000 EUS guided TA procedures annually.

Quality of EUS

What is quality? Although quality is often discussed in papers on endoscopic techniques, and at conferences, it was poorly defined until recently. Prior to being able to strive for quality, practitioners should agree on how to define quality and how this should be measured [30]. In 2007, Savides et al published their retrospective study of 1075 patients, from 21 centers, who underwent EUS-guided TA of solid pancreatic masses [31]. They concluded diagnostic yield of malignancy (the proportion of malignant diagnoses) of EUS guided TA of solid pancreatic masses to be a simple way to benchmark performance. However, not until recently, endoscopy societies have defined quality measures or key performance indicators (KPI) for most endoscopic procedures including EUS [32-34].

Aim and outline of this thesis

The aim of this thesis is **to explore the use and quality of care delivered by endoscopic ultrasonography in clinical practice**.

This thesis is divided into two sections. In section one, **EUS in patients with suspected bile duct stones,** the diagnostic value and limitations of EUS in these patients, are addressed. **Chapter 2** describes the utility and yield of endoscopic ultrasonography for suspected bile duct stones in common gastroenterology practice. In **chapter 3,** we study interobserver variability amongst endosonographers regarding EUS findings in these patients. **Chapter 4** describes the determination of the prevalence of bile duct sludge.

In section two, **EUS guided tissue acquisition (TA) in solid lesions of the pancreas**, measurements of use and quality both regional and national are covered, as well as a regional strategy aiming to improve the quality of care delivered. In **chapter 5,** we describe measurements of quality of EUS guided TA of solid pancreatic lesions from four community hospitals, followed by the initial steps of a regional quality initiative. The diagnostic yield and agreement on fine-needle specimens from solid pancreatic lesions: comparing the smear technique to liquid based cytology are described in **chapter 6. Chapter 7** describes the introduction of learning curves as a feedback tool to our multicenter multidisciplinary quality improvement initiative. In **chapter 8** the results of a nationwide assessment of the use and quality of EUS guided TA of resected pancreatic ductal adenocarcinoma are evaluated.

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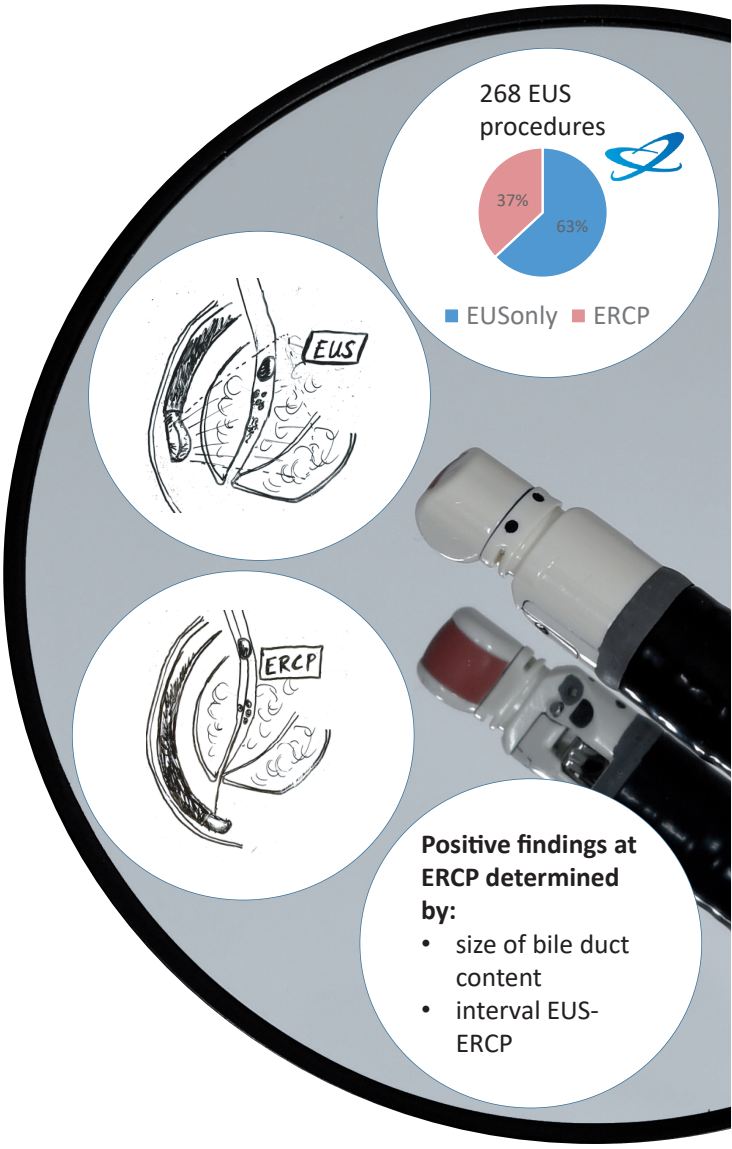
SECTION 1

EUS in patients with suspected bile duct stones

2

CHAPTER 2


268 EUS procedures
37%
63%
EUSonly
ERCP
EUS
ERCP
Positive findings at ERCP determined by:
• size of bile duct content
• interval EUS-ERCP

The utility and yield of endoscopic ultrasonography for suspected choledocholithiasis in common gastroenterology practice

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Abstract

Background and study aim

Endoscopic ultrasonography (EUS) is an established diagnostic modality for diagnosing common bile duct (CBD) stones. Its use has led to a reduction in the number of endoscopic retrograde cholangiopancreatography (ERCP) procedures performed for suspected choledocholithiasis. We aimed to explore the role of EUS in detecting CBD stones and/or sludge in common gastroenterology practice.

Patients and methods

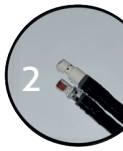
We reviewed case records of 268 consecutive patients who underwent (EUS) procedures performed to confirm or rule out the presence of CBD stones and/or sludge between November 2006 and January 2011 in the Reinier de Graaf Hospital, Delft, The Netherlands, which is a nonacademic community hospital.

Results

Based on EUS findings, 169 of 268 (63%) patients did not undergo ERCP and were therefore not exposed to its risk of complications. Patients with positive findings on EUS (n = 99) all underwent ERCP and endoscopic sphincterotomy. Only 57 of 99 (58%) had positive findings at ERCP. The main contributing factors to this finding seem to be time interval between EUS and ERCP and the type of CBD content (i.e. sludge, one CBD stone or more than one CBD stone) described.

Conclusion

In our common gastroenterology practice, EUS plays an important role in selecting patients suspected to have CBD stones or sludge for ERCP. Much is to be learned about the probability of spontaneous passage of CBD stones and sludge into the duodenum.



Introduction

Endoscopic ultrasonography (EUS) is an established diagnostic modality for diagnosing common bile duct (CBD) stones. Studies confirming this role of EUS show excellent sensitivity, specificity, and diagnostic accuracy [1–5], but were exclusively carried out at tertiary referral centers. CBD stones are estimated to be present in 5–10% of patients with symptomatic cholecystolithiasis, scheduled for cholecystectomy, and in 18–33% of patients with acute biliary pancreatitis [6]. A diagnostic work-up using EUS to rule out CBD stones has been proven to reduce the number of endoscopic retrograde cholangiopancreatography (ERCPs) and ERCP-related complications by 67% compared with an ERCP-alone strategy [7]. We have carried out a retrospective study to explore the role of EUS guiding the need to perform ERCP in patients with suspected choledocholithiasis in a large nonacademic community hospital practice.

Patients and methods

We have reviewed case records of 268 consecutive patients who underwent an EUS to confirm or rule out CBD stones and/or sludge between November 2006 and January 2011 in the Reinier de Graaf Hospital, Delft, The Netherlands, which is a 455-bed nonacademic community hospital. EUS was performed by three endosonographers with years of experience ranging from 1 to 10. An Olympus GF-UCT 140 linear echoendoscope (Olympus, Zoeterwoude, The Netherlands) with an Aloka SSD-4000 processor (Aloka Europe, Zug, Switzerland) was used.

The main objective was to evaluate the role of EUS in diagnosing CBD stones or sludge in our practice, thereby establishing a rightful indication for ERCP. A secondary objective was to explore the factors contributing toward negative findings at ERCP after EUS had established CBD stones or sludge. These factors included time interval to ERCP, characteristics of CBD content, and EUS operator. Biliary sludge was defined as mobile hyperechoic CBD content, without acoustic shadowing. The pretest probability of CBD stones was assessed using Barkun's classification [8]. This classification aims to predict the probability of CBD stones in patients in whom transabdominal ultrasonography does not show a CBD stone. It uses age (>55 years), plasma bilirubin level (>30 µmol/l), and CBD dilatation on ultrasound (≥6 mm diameter) as criteria. It predicts an intermediate probability of a CBD stone ranging from 19 to 38% in those with none or only one criterion present and a high probability ranging from 49 to 94% in those who fulfill two or three criteria.

After EUS had established CBD stones and/or sludge, an ERCP was performed. The timing of ERCP depended on the clinical presentation (i.e. frequency and severity of

symptoms), comorbidity (i.e. use of anticoagulant drugs), and the availability of ERCP facilities. At ERCP occlusion cholangiography was performed using a balloon catheter in a standardized manner. ERCP findings were considered positive if clearing the CBD with a balloon catheter and/or a Dormia basket led to either the observation of stones and/or sludge in the duodenum or the disappearance of stones from the CBD at repeat occlusion cholangiography. The study protocol was approved by the local ethics committee.

Statistical analysis

Statistical analysis was carried out using SPSS software, version 21 (IBM, Amsterdam, The Netherlands). The positive predictive value (PPV) was calculated by dividing the number of positive ERCP findings (CBD stones and/or sludge) by the total number of ERCPs performed. Logistic regression analysis was carried out to model the effects of independent explanatory variables: time interval to ERCP, characteristics of CBD content (i.e. sludge, one stone, more than one stone), and EUS-operator on the outcome of ERCP. Continuous numerical variables with a normal distribution are expressed as means with standard deviation (SD). Variables not normally distributed are expressed as median with interquartile range. A Cox proportional hazards model was used to analyze the multivariate predictors of time until spontaneous passage of CBD content (i.e. sludge and/or stones). Differences between the results were considered significant when P value was less than 0.05 using log-rank and $\chi 2$-tests. Kaplan–Meier survival analysis was carried out to illustrate the time-dependent survival of stones and/or sludge in the CBD.

Results

EUS was performed in 268 patients, ranging in age from 23 to 90 years. According to Barkun's classification, 17 of 268 (6%) patients had a high probability of CBD stones. The majority of patients (251 of 268, 94%) had an intermediate (pre-EUS) probability of CBD stones.

EUS detected stones and/or sludge in the CBD in 99 of 268 cases (37%) (Table 1). These patients all underwent ERCP with endoscopic sphincterotomy. In the remaining 169 (63%) patients, all without stones or sludge according to EUS, no subsequent ERCP was planned. None of these patients underwent an ERCP at a later stage. The median time interval from EUS to ERCP was 4 days (interquartile range from 1 to 15 days). The majority (63%) of ERCPs were performed within a week following EUS. Patient files did not show any evidence of the occurrence of biliary complications (i.e. pancreatitis, cholangitis) while waiting for ERCP nor did rescheduling of ERCPs occur because of symptom progression and/or complications.

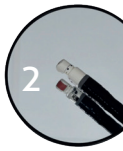


Table 1. Patient characteristics

	Total group (n=268) [n (%)]	Patients with stones and/or sludge on EUS (n=99) [n(%)]
Age (years)	57 (range 23-90)	61 (range 23-90)
Women	183 (68)	65 (66)
After cholecystectomy	88 (32)	39 (39)
High probability of CBD stones*	17 (6)	11 (11)
Intermediate probability of CBD stones*	251 (94)	88 (89)

CBD, common bile duct; EUS, endoscopic ultrasonography.
* according to Barkun's classification

Stones or sludge were detected at ERCP in 57 patients. The overall proportion of positive findings at ERCP (PPV) of patients with hyperechoic CBD content (i.e. stones or sludge) at EUS was 58%. In patients in whom ERCP was performed within 24 h after EUS had detected stones and/ or sludge, this figure reached 80%. A longer time interval to ERCP (either 1–6 days or ≥ 6 days) was associated with a lower proportion of stones or sludge in the CBD and hence lower PPV values (P = NS) (Table 2).

The finding of sludge in the CBD during EUS accounted for positive findings during subsequent ERCP in 48%, whereas the presence of more than one CBD stone on EUS yielded positive ERCP findings in 69% (P = NS) (Table 2 and Fig. 1).

Table 2. Positive findings at ERCP after EUS detected CBD stones or sludge + time-to-ERCP and characteristics of CBD content

	True positive	Total	PPV (%)
Overall	57	99	58
Time interval EUS-ERCP(days)			
≤1	8	10	80
1-6	31	51	61
≥6	18	38	47
Type/amount of CBD content			
Sludge	10	21	48
1 stone	29	52	56
>1 stone	18	26	69

CBD, common bile duct; ERCP, endoscopic retrograde cholangiopancreatography; EUS, endoscopic ultrasonography; PPV, positive predictive value.

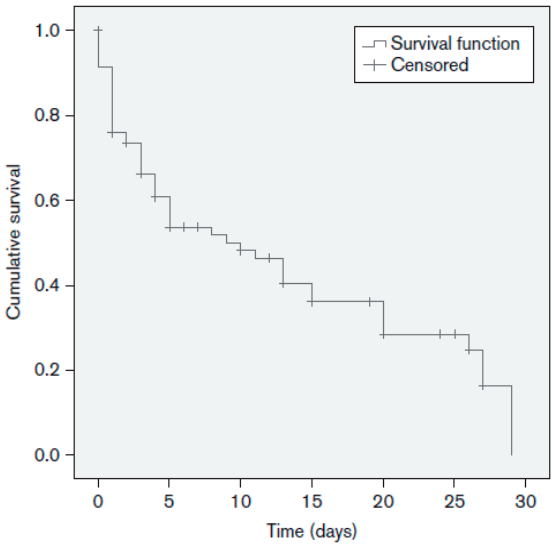


Figure 1. Kaplan-Meier curve showing time-dependent nature of sludge and stone survival in the CBD. On the x-axis, the time between EUS and ERCP is shown in days. On the y-axis, the proportion of stones and sludge detected at ERCP is shown. CBD, common bile duct; ERCP, endoscopic retrograde cholangiopancreatograpgy; EUS, endoscopic ultrasonography.

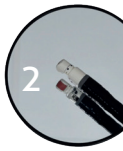
EUS was performed by one of three endosonographers (Willemien Erkelens, R.Q., and Claudia Rogge). EUS findings and policy on planning of subsequent ERCP procedures per operator did not differ significantly. EUS procedures were all without complications. Complications of ERCP occurred in seven of 99 (7.1%) patients. These complications consisted of five cases of post-ERCP pancreatitis (4 × mild, 1 × moderate) [9], one postsphincterotomy bleeding requiring both blood transfusion and repeat endoscopy, and one case of retroperitoneal perforation after sphincterotomy requiring prolonged hospitalization.

Discussion

EUS plays an important role in selecting patients suspected of having CBD stones and/or sludge for ERCP in our practice. On the basis of negative EUS findings, 169 of 268 (63%) patients did not undergo ERCP and therefore were not exposed to the risk of related complications. It is noteworthy that none of these patients needed to undergo an ERCP at a later stage or developed biliary complications. Of the patients with positive findings on EUS (n=99), only 58% had positive findings at subsequent ERCP, a considerably lower percentage than expected based on the available literature [1]. Probably the most important determinant is that in a relatively high proportion of patients, ERCP was performed at longer intervals after EUS in comparison with previous publications on this subject [1–5]. Moreover, extraction of small stones and sludge may have been missed during ERCP

[10]. Another potential contributing factor could have been the varying experience of the endosonographers, although performance characteristics did not differ significantly.

The longer interval between EUS and ERCP in this study has probably allowed for a higher rate of spontaneous clearance of stones and/or sludge from the CBD compared with studies in which ERCP followed directly after EUS. This is supported by the finding of a progressively lower probability of finding biliary stones or sludge at ERCP at longer time intervals between EUS and ERCP. This varying time interval was not associated with any complications (i.e. pancreatitis, cholangitis).



Spontaneous passage of CBD content across the duodenal papilla is known to occur in 21–33% of cases within 4–6 weeks [11,12]. Frossard and colleagues published a prospective study on the percentage of spontaneous CBD stone migration that occurred in 21%. In their study, symptoms of stone passage (pain) occurred in two out of 12 patients. For the rest of the patients, if spontaneous stone passage did occur, it occurred without any symptoms. In the study by Frossard et al. [12] smaller size stones (< 8 mm) were related to spontaneous passage.

If we assume the diagnostic accuracy of EUS for CBD stones in our series to be 100%, our data show spontaneous passage of CBD content of 20% (two out of 10) within 24 h, 36% (22 out of 61) between 1 and 6 days, and 42% (42 out of 99) when the interval between diagnostic EUS and ERCP is 6 days or more. Data on CBD stone size during EUS were not routinely recorded and therefore could not be analyzed. The assumed percentages of spontaneous CBD-clearance in our study are rather high in comparison with those in the study by Frossard and colleagues. The fact that we included biliary sludge as a positive finding of both EUS and ERCP may partially explain this difference.

Biliary sludge is considered an early and reversible state of bile stone disease only to be treated when causing biliary symptoms. Not much is known on the prevalence, pathophysiological role, and natural behavior of biliary sludge [13–15]. Biliary sludge is believed to play a role in acute idiopathic pancreatitis as well as in acalculous cholecystitis [13, 16–18]. In recent years, the number of publications mentioning CBD sludge has increased. This is probably related to improvements in EUS-imaging quality in the past decade. Only one of the previously mentioned studies confirming the role of EUS in diagnosing bile duct stones mentions the finding of sludge in the CBD in one of nine patients with positive findings at EUS performed before ERCP [3]. A recent study by Fusaroli et al. [19] describing the reliability of EUS in predicting the number and size of CBD stones before ERCP is the first to mention a prevalence of CBD sludge of 25% in their cohort of patients undergoing EUS to confirm or rule out CBD stones and/or sludge. This is similar to the prevalence that we found in our study (21/99, 21%). If smaller stones have a higher

chance of passing spontaneously, it is not unlikely that biliary sludge has an even greater chance of spontaneous passage into the small bowel.

This is the first study exploring the role of EUS for detecting CBD stones in a large community hospital. Our findings support the importance of EUS in selecting patients suspected of having CBD stones or sludge for ERCP. The limitations of this study are its retrospective design and the lack of standardized EUS and ERCP reporting.

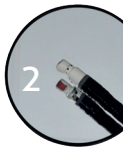
The results of this study have led us to implement standardized EUS reporting in our practice. We have also adopted a more conservative attitude toward patients with sludge in a nondilated CBD. Especially in cases with mild symptoms (for example after one episode of mild colicky pain in the previous 3 weeks, with decreasing mild liver biochemistry abnormalities), the choice for either watchful waiting or an ERCP is discussed with the patient. If future studies confirm spontaneous passage of bile duct content without any complications after 6 days in up to 50% of cases, such a watchful waiting approach may be the future strategy of choice [20,21].

Conclusion

The use of EUS for detecting CBD stones or sludge plays an important role in selecting patients for ERCP in our large community hospital and, in particular, that much is to be learned about the probability of spontaneous passage of CBD stones and sludge into the duodenum. Implementation of pre-ERCP EUS, in patients with intermediate probability of having CBD stones or sludge, reduces the number of ERCPs and therefore has high clinical relevance.

Acknowledgements

The authors thank both Claudia Rogge, MD, PhD, and Willemien Erkelens, MD, for performing EUS-procedures in the patients described in this study.



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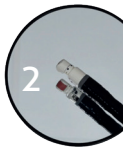
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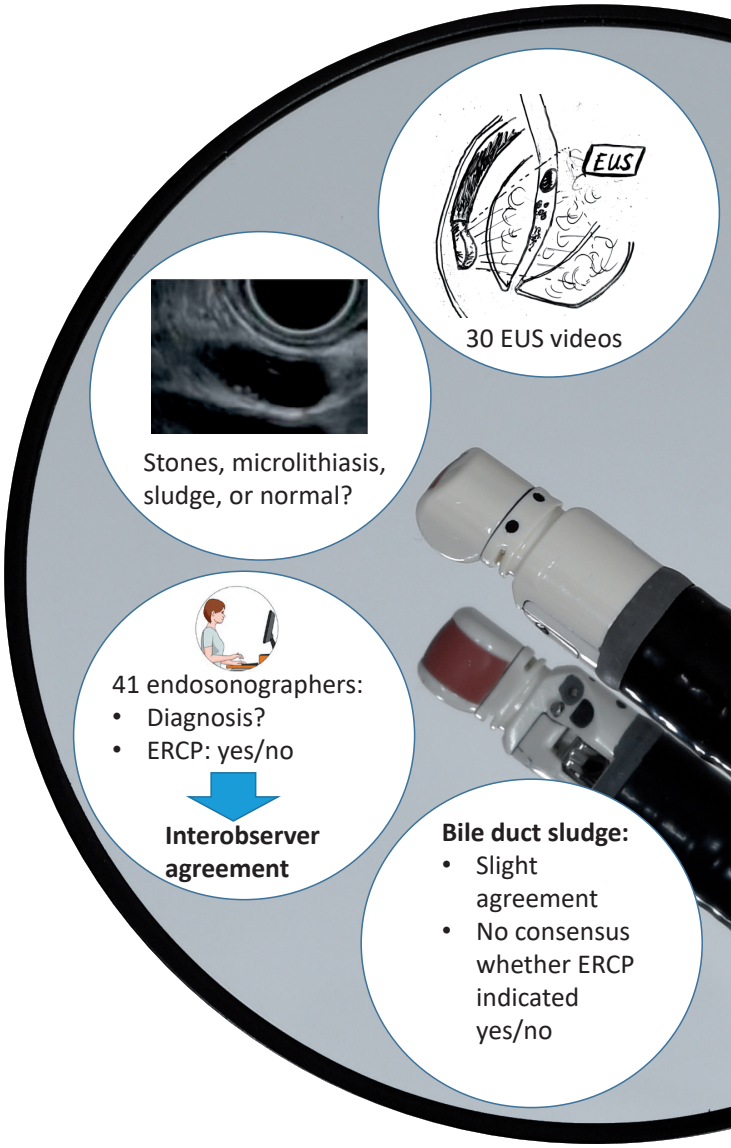
CHAPTER 3


EUS
30 EUS videos
Stones, microlithiasis, sludge, or normal?
41 endosonographers:
• Diagnosis?
• ERCP: yes/no
Interobserver agreement
Bile duct sludge:
• Slight agreement
• No consensus whether ERCP indicated yes/no

Do endosonographers agree on the presence of bile duct sludge and the subsequent need for intervention?

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Abstract

Background and aims

EUS is a tool widely used to diagnose bile duct lithiasis. In approximately one out of five patients with positive findings at EUS, sludge is detected in the bile duct instead of stones. The objective of this study was to establish the agreement among endosonographers regarding: 1. presence of CBD stones, microlithiasis and sludge, and 2. the need for subsequent treatment.

Patients and methods

30 EUS videos of patients with an intermediate probability of CBD stones were evaluated by 41 endosonographers. Experience in EUS and ERCP, and the endosonographers' type of practice were recorded. Fleiss' kappa statistics were used to quantify the agreement. Associations between levels of experience and both EUS ratings and treatment decisions were investigated using mixed effects models.

Results

A total of 1230 ratings and treatment decisions were evaluated. The overall agreement on EUS findings was fair (Fleiss' κ 0.32). The agreement on presence of stones was moderate (κ 0.46). For microlithiasis it was fair (κ 0.25) and for sludge it was slight (κ 0.16). In cases with CBD stones there was an almost perfect agreement for the decision to subsequently perform an ERC + ES. In case of presumed microlithiasis or sludge an ERC was opted for in 78% and 51% of cases, respectively. Differences in experience and types of practice appear unrelated to the agreement on both EUS findings and the decision for subsequent treatment.

Conclusion

There is only slight agreement among endosonographers regarding the presence of bile duct sludge. Regarding the need for subsequent treatment of bile duct sludge there is no consensus.

Introduction

In patients with suspected bile duct stones, endoscopic ultrasonography (EUS) is an excellent tool to prevent unnecessary Endoscopic Retrograde Cholangiography with Endoscopic Sphincterotomy (ERC with ES) and its complications. EUS in patients with suspected bile duct stones rules out the presence of bile duct stones in up to 65% of patients [1,2]. In patients without cholangitis, the 2019 ESGE guideline on endoscopic management of common bile duct (CBD) stones recommends to proceed to ERC + ES only when CBD stones are proven on imaging modalities that have a high specificity[3].

In approximately one out of five patients with positive findings at EUS performed for this indication, bile duct sludge is detected instead of stones [4,5]. Sludge is an ultrasound diagnosis usually described as layered, mobile, low-amplitude echoes without shadowing occurring in either the gallbladder and/or bile ducts [6,7]. Studies comparing EUS and microscopic examination of bile concluded that sludge represents bile precipitate out of solution [8,9]. Usually this precipitate consists of cholesterol monohydrate crystals, calcium bilirubinate granules and other calcium salts. Sludge is considered an early and reversible state of bile stone disease only to be treated when causing biliary symptoms [10,11]. Gallbladder sludge in symptomatic patients is considered an indication for cholecystectomy.

Sludge and small stones or microlithiasis (defined as stones < 3mm) in the CBD, are known to have an increased tendency to pass spontaneously into the bowel in comparison to stones > 3mm [5, 12-17]. They have also been associated with an increased incidence of biliary pancreatitis [18, 19]. However, since the likelihood of developing biliary complications in patients with bile duct microlithiasis or sludge is currently unknown, it is unclear if detection of sludge or microlithiasis in the bile duct at EUS should prompt for an ERC + ES, or whether a watchful waiting strategy can be adopted.

EUS is a known operator dependent technique [20]. Moreover, agreement regarding the presence of sludge or microlithiasis on EUS and the potential indication for treatment have not been investigated.

The purpose of the current study was to determine the interobserver agreement among endosonographers regarding the presence or absence of CBD stones, microlithiasis and sludge, and their advice for subsequent treatment. We also evaluated the role of the endosonographers' experience in EUS and/or ERCP, and the endosonographers' type of practice regarding EUS findings and treatment decisions.

Methods

Study aims

The objective of this study was to establish the agreement among endosonographers regarding: 1. presence of CBD stones, microlithiasis and sludge, and 2. the need for subsequent treatment.

Study design

The study protocol was approved by the local medical ethics committee (METC Leiden, Den Haag, Delft, Z19.050). Videos of linear EUS procedures of patients (>18 years old) with intermediate probability of bile duct lithiasis, according to the 2010 ASGE criteria[21], were recorded for the purpose of this study.

Video fragments

Videos were digitally recorded by 5 different endosonographers from different hospitals using linear EUS-endoscopes (GF-UCT 180 or GF-UCT 260, Olympus, Leiderdorp, the Netherlands) and different processors (Aloka F75, Aloka α10 or Aloka α7, Hitachi Medical Systems B.V., Reeuwijk, the Netherlands). All recording endosonographers had more than 10 years of clinical experience performing and teaching EUS. Aiming for a significant proportion of invited endosonographers to comply with our protocol and complete the evaluation we chose to limit the number of video fragments to 30 and the length of the fragments to 30 seconds. Fifteen EUS video fragments were filmed from the duodenal bulb, and 15 from the descending duodenum. Videos were edited by one endosonographer using Movavi® video editor plus, version 15.4.0 (Movavi Software Limited, Limassol, Cyprus). Video fragments were presented in the best possible video-format (mp4-files, framesize 1920x1080, speed 30 frames/sec) incorporated in a web-based survey using Castor® v2020.1.16 (Castor EDC, Amsterdam, the Netherlands). None of the endosonographers involved in recording and editing the videos was involved in rating the video fragments for the purpose of this study.

Endosonographers

Endosonographers in the Netherlands are all formally trained in endosonography for at least a year at a referral center. A total of 113 Endosonographers was invited to participate in this study by e-mail. Of the invited endosonographers 58 did not respond to the invitation, 3 responded not to be willing to participate, and 11 did not finish the survey before the deadline. For each of the 41 participants experience in both EUS and ERCP including the number of years performing these interventions, and number of procedures performed annually, were recorded. Types of practice (tertiary care/community hospital) were also registered.

Evaluation of video fragments

Each video fragment was rated by each observer independently for the presence or absence of stones, microlithiasis or sludge in the CBD (Figure 1). Sludge was defined as echoic, cloud shaped and mobile bile duct content, without acoustic shadowing. Microlithiasis was defined as stones < 3mm in size with or without acoustic shadowing (Table 1) [22-24]. The raters were asked whether or not they would proceed to ERC + ES in each case.

Primary endpoint was the interobserver agreement among endosonographers on the presence or absence of CBD stones, microlithiasis or sludge.

Secondary endpoints were the interobserver agreement on the need for ERC + ES (yes/no) and differences in interobserver agreement between experts and non-experts.

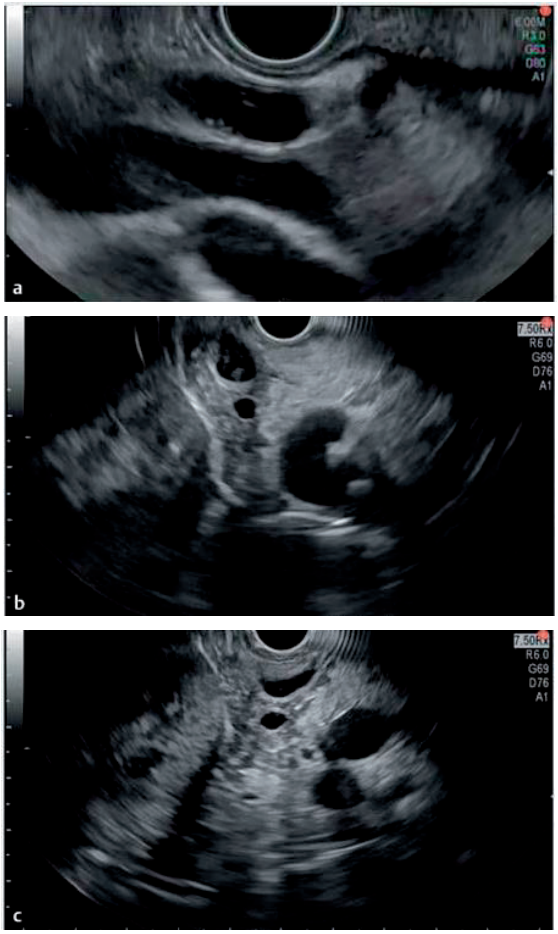

Figure 1. Images of EUS videos. Microlithiasis, sludge or artifact?

Table 1. EUS definitions of various presentations of bile duct lithiasis

	Definition
Sludge	Layered, cloud shaped, mobile echoic bile duct content, without acoustic shadowing
Microlithiasis	Hyperechoic circumscript bile duct content, < 3mm with or without acoustic shadowing
Stone(s)	Hyperechoic circumscript bile duct content, ≥3mm with or without acoustic shadowing

References: [21-23]

Statistics

The analyses were performed using R version 4.0.2 (2020-06-22) (R Core Team 2020). Assuming that 41 endosonographers would evaluate 30 videos, and that the prevalence of various EUS diagnoses would be "clean" (50%), "sludge" (15%), "microlithiasis" (5%), or "one or more stones" (30%), we performed a power calculation using simulation. A total of 500 datasets was generated with varying values of agreement from which Fleiss' κ and corresponding 95% confidence intervals were calculated. The resulting estimates are shown in Figure 1a and Table 1a (appendix). To approximate the values of the lower and upper bounds of the 95% confidence interval for any given κ-value, linear regression models were fitted in which the non-linear association with the corresponding κ-value was modeled using natural cubic splines with 3 degrees of freedom. The fitted values show that for slight agreement (κ 0.1), the 95% confidence interval can be expected to range from approximately 0.05 to 0.15, and that for moderate agreement (κ 0.4) the corresponding 95% confidence interval is expected to range from approximately 0.27 to 0.53.

Characteristics of the participating raters were summarized using medians and ranges or counts and proportions, as appropriate.

Multirater Fleiss' κ-values were calculated to quantify the agreement between raters. K-statistics were interpreted based on the convention by Landis and Koch, and compared with a two-sided paired t-test with level α=0.05, using the "linearization method" proposed by Gwet et al.[25,26]. The linearity correction is necessary since most agreement coefficients are not linear statistics which is a requirement for the standard t-test.

To estimate the expected proportion of videos for which an endoscopist would advise ERC + ES, while taking into account the correlation between the evaluations of multiple videos by the same endoscopist, we fitted a logistic mixed model for the advice of ERC + ES depending on the diagnosis and included endoscopist specific (random) effects for the intercept and diagnosis[27].

Associations between levels of experience and either the diagnosis of "sludge" or the advice for subsequent ERC + ES were investigated using logistic mixed effects models, that use the experience level as fixed effect covariate and take into account the correlation between repeated measurements within endoscopists (i.e., the same endoscopist scoring multiple videos) by including an endoscopist specific (random) intercept. The results are marginalized using the technique described by Hedeker et al., as implemented in the R package GLMMadaptive and can be interpreted on the population level[28,29].

Results

Endosonographers and their experience

The web-based survey and evaluation of the 30 EUS video fragments was completed by 41 endosonographers. Eight endosonographers (19%) worked in academic practice and the remaining 33 (81%) in community hospitals (table 2). Median post-training EUS experience was 6 years (range 1-25 years) while performing a median of 60 (20-300) procedures annually. The majority of endosonographers (27 out of 41, 66%) also performed ERCP procedures, with a median procedural experience of 10 years (range 1-30 years) while performing a median of 73 (20-300) ERCP procedures annually (Table 2).

Table 2. Endosonographers and their experience

Type of practice (n=41)	**n (%)**
Academic hospital	8 (19)
Community hospital	33 (81)
EUS experience (n=41)	Median (range)
Years	6 (1-25)
Procedures/year	60 (20-300)
ERCP experience (n=27)	Median (range)
Years	10 (1-30)
Procedures/year	73 (30-400)

Interobserver agreement on EUS diagnosis and treatment decisions

A total of 1230 ratings (41 x 30 video fragments) and 1230 treatment decisions were evaluated. The overall interobserver agreement on EUS findings was fair (Fleiss' κ 0.32). The agreement on presence or absence of stones was moderate (both κ 0.46). For microlithiasis the agreement was fair (κ 0.25) and for sludge there was slight agreement (κ 0.16) (Table 3).

In 803 out of 1230 cases (65%) the evaluation of an EUS video fragment led to the advice not to proceed to ERC + ES. The overall interobserver agreement to proceed to ERC + ES was moderate (κ 0.41, 95% CI [0.25-0.55]). In cases with CBD stones or with a "clean" CBD there was almost perfect agreement for the decision to subsequently perform an ERC + ES or not. In patients with presumed microlithiasis or sludge it was chosen to perform ERC + ES in 78% and 51% of cases, respectively (Table 3).

Table 3. Ratings, interobserver agreement and advice for treatment

EUS diagnosis	n	Fleiss' κ (95%CI)	Advice ERCP	
			Yes (%)	No
Clean CBD	646	0.46 (0.32-0.60)	1 (0)	645
Sludge	235	0.16 (0.07-0.25)	120 (51)	115
Microlithiasis	194	0.25 (0.07-0.43)	152 (78)	42
One or more stone(s)	155	0.46 (0.13-0.78)	154 (99)	1
Overall	1230	0.35 (0.21-0.48)	427 (35)	803

In cases where microlithiasis was diagnosed the advice to proceed to ERC+ ES ranged from 20% to 100% among endosonographers. When sludge was diagnosed the advice to proceed to ERC + ES ranged from 0-100%. Seven out of 41 raters (17%) always advised against ERC + ES, and 13 raters (32%) always advised to proceed to ERC + ES in these cases (Figure 2 + 3).

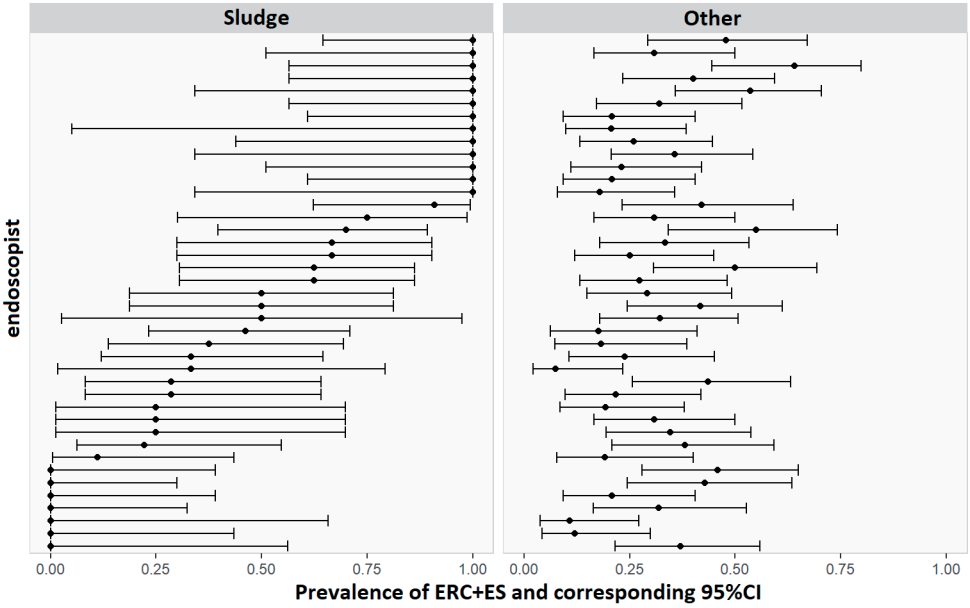

Figure 2. Proportion of videos for which ERCP was advised per endoscopist by EUS diagnosis (sludge vs other).

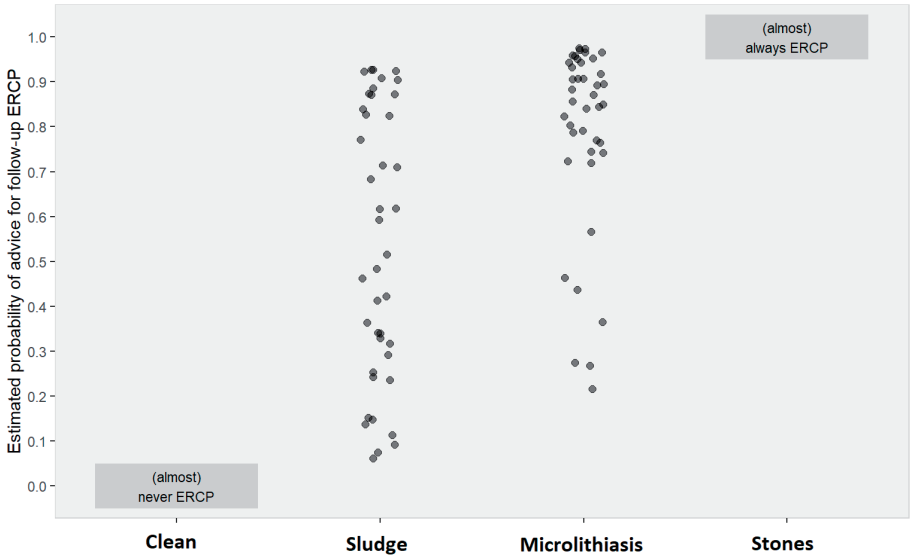

Figure 3. Estimated probability for advice to proceed with ERCP per endosonographer per diagnosis.
Since there was insufficient variation for cases diagnosed with bile duct stones and for cases diagnosed as clean analysis was restricted to diagnoses microlithiasis and sludge in the common bile duct.

Experience and interobserver agreement

Agreement for EUS diagnosis among academic hospital endosonographers was fair (κ 0.32, 95%CI [0.16-0.48]) as was agreement among community hospitals endosonographers (κ 0.32, 95%CI [0.20-0.43]). For the advice to proceed to ERC + ES there was moderate agreement amongst both academic and community hospital endosonographers, κ 0.41, 95%CI [0.23-0.59] vs κ 0.40, 95%CI [0.25-0.55] respectively.

There was no evidence for an association between differences in EUS experience (either in years or in number of procedures performed annually) and the proportion of sludge diagnoses (Table 4). There was no significant association between the advice to proceed to ERC + ES and whether or not the endosonographer performs ERCPs him- or herself, ERCP experience in years, or number of ERCPs performed annually.

Table 4. The effect of experience on sludge diagnosis and the decision to proceed to ERCP

EUS experience and sludge diagnosis (n=41)	OR	p-value	95% CI
Years of experience in EUS	0.99	0.66	0.96-1.03
EUS procedures/year	1.01	0.38	0.98-1.04
Advise to proceed to ERCP (n=41)	**OR**	**p-value**	**95% CI**
ERCP performers vs non-performers	1.26	0.23	0.87-1.8
ERCP experience and advice to proceed to ERCP (n=27)	**OR**	**p-value**	**95% CI**
Years of experience in ERCP	0.99	0.96	0.96-1.04
ERCP procedures/year	0.99	0.74	0.96-1.03

Endoscope position and interobserver agreement

The agreement on EUS diagnosis of video fragments recorded from both the duodenal bulb and the descending duodenum was fair (κ 0.36, 95% CI [0.17-0.56] and κ 0.28, 95% CI [0.14-0.43] respectively). There was no significant difference in agreement regarding video's from different scope positions (p=0.50).

Discussion

Endosonography plays a pivotal role in selecting patients with suspected bile duct lithiasis for ERC + ES. However, interobserver agreement among endosonographers regarding presence of CBD stones, which was the primary endpoint of this study, was only moderate. Moreover, there was only slight interobserver agreement among endosonographers regarding presence of microlithiasis and sludge, the second primary endpoint.

In cases with either stones or a clean bile duct there was an almost perfect agreement to either proceed to or refrain from ERC +ES. In cases with microlithiasis or sludge in the bile duct there was no consensus about the need for subsequent ERC + ES. There was no evidence for a relation between differences in experience in both EUS and/or ERC + ES, types of practice, and agreement on both EUS findings and the decision for subsequent treatment.

This is the first study to evaluate interobserver agreement of endosonographers rating EUS video fragments of patients with suspected bile duct lithiasis. Although interobserver agreement on gallbladder sludge is probably better than the only slight agreement among endosonographers on the presence of sludge in de CBD, the findings of this study shed a different light on previous publications regarding the finding of sludge (in gallbladder and/or CBD) at EUS.

Sludge accounts for 20-25% of the abnormalities detected in the CBD at EUS in patients with suspected bile duct lithiasis [4,5]. This estimate is based on two retrospective studies only and may be an overestimation of the true prevalence. Biliary sludge is detected in up to 75% of patients with idiopathic pancreatitis at EUS in patients with their gallbladder in situ. In idiopathic pancreatitis in postcholecystectomy patients CBD sludge is detected in 10-15% of cases [30]. In these patients initially suspected to have suffered from idiopathic pancreatitis the diagnosis of sludge in the CBD is relevant since it is considered an indication for cholecystectomy and ERC + ES respectively [31,32]. In the current study comprising of patients with an intermediate probability of gallstones but not having suffered from pancreatitis, ERC + ES was considered not indicated by the endosonographer in 65% of

the cases. This proportion is similar to the findings of two meta-analyses studying the role of EUS in patients with suspected bile duct lithiasis in clinical practice [1,2].

Strengths of the current study are the substantial number of endosonographers involved when compared to previously published EUS interobserver studies on chronic pancreatitis, findings in familial pancreatic cancer kindred's and pancreatic cysts [33-36]. The 41 contributing endosonographers from 27 different hospitals represent approximately 25% of the total number of endosonographers in the Netherlands. The results of our study therefore signify a rational representation of how findings of biliary sludge are diagnosed and interpreted throughout the Netherlands.

Limitations of our study are the fact that 30 second video fragments were used. Having a second look when in doubt means playing the video again, which is very different from repositioning the endoscope to confirm or reject a potential diagnosis from another angle.

The only moderate agreement on the presence or absence of bile duct stones is likely to be a reflection of the known operator dependency of EUS[37]. Not only have learning curves of advanced endoscopy trainees proven to be highly variable in prospective studies [38,39], good or even excellent interobserver agreements are rarely found in studies on interobserver variability in EUS [33-36].

Improving interobserver agreement of EUS in patients with suspected bile duct lithiasis starts with basic knowledge regarding the limitations of EUS imaging and potential pitfalls of image interpretation and 'tricks' to overcome this. All this should be taught as part of a formal training program learning EUS. Evaluation of the CBD with a linear EUS scope requires careful tracing of the CBD from the liver hilum all the way down to the ampulla by means of different scope positions. It may be difficult to distinguish sludge from EUS imaging artifacts caused by, for example the cystic duct junction or the crossing of vessels, especially in a non-dilated duct and/or a non-stable position of the endoscope. Side-lobe artifacts, off-axis secondary projections of the ultrasound beam, can be misinterpreted as sludge[40]. Repositioning the transducer can cause these artifacts to disappear. Adherence to the simple rule that "when a EUS finding cannot be reproduced it does not exist", prevents a lot of over interpretation and false positive findings.

Knowledge regarding the natural behavior of bile duct stones is limited. The Swedish Gallriks study describes an increased likelihood of biliary complications (biliary pancreatitis, cholangitis or bile duct obstruction) of up to 25% during a follow-up of 4 years after cholecystectomy when leaving bile duct stones in situ, in comparison to a likelihood of 13% of complications after clearance of the bile duct (Odds Ratio [OR] 0.44, 95%CI 0.35-0.55) [41]. This justifies performing ERC + ES in all patients with bile duct stones, regardless of the

risk of complications [3]. However, the advantage of an intervention aiming to remove bile duct stones is less clear in stones <4mm, which may be related to the increased possibility of spontaneous passage into the bowel. Although bile duct sludge is increasingly detected with the growing use of EUS in recent years, its natural behavior is currently unknown. To answer the question whether the EUS findings CBD sludge and microlithiasis in patients with an intermediate probability of bile duct stones justify a subsequent ERC + ES, or that a watchful waiting strategy can be adopted, further studies are needed.

In summary, our study demonstrates that there is moderate interobserver agreement regarding presence or absence of bile duct stones, and only limited agreement regarding the presence of CBD sludge and microlithiasis among endosonographers. In cases with either sludge or microlithiasis in the bile duct at EUS, there is a lack of consensus whether a subsequent ERC + ES should be performed. Agreement regarding EUS findings or treatment decisions appear unrelated to experience of the rating endosonographer. In order to guide clinicians and prevent potentially unnecessary ERC + ES, further research into the reliability of an EUS diagnosis of biliary sludge and the need for intervention is indicated.

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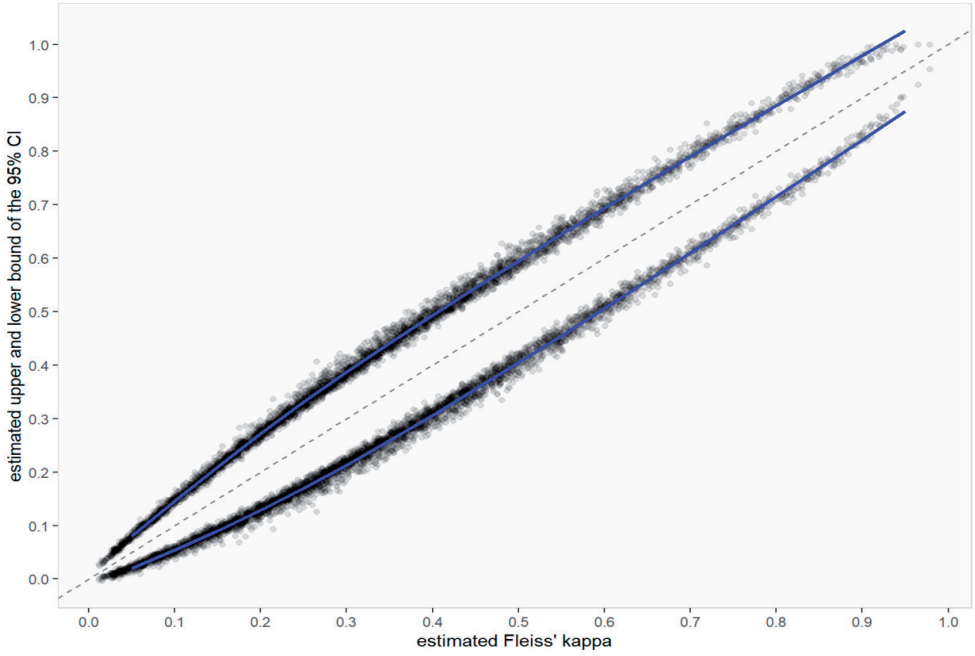
Supplemental table 1a. Estimated bounds of the 95% confidence intervals for a range of possible kappa values.

kappa	lower bound	upper bound
0.1	0.05	0.15
0.2	0.11	0.29
0.3	0.19	0.41
0.4	0.27	0.53
0.5	0.37	0.63
0.6	0.47	0.73
0.7	0.58	0.82
0.8	0.70	0.90

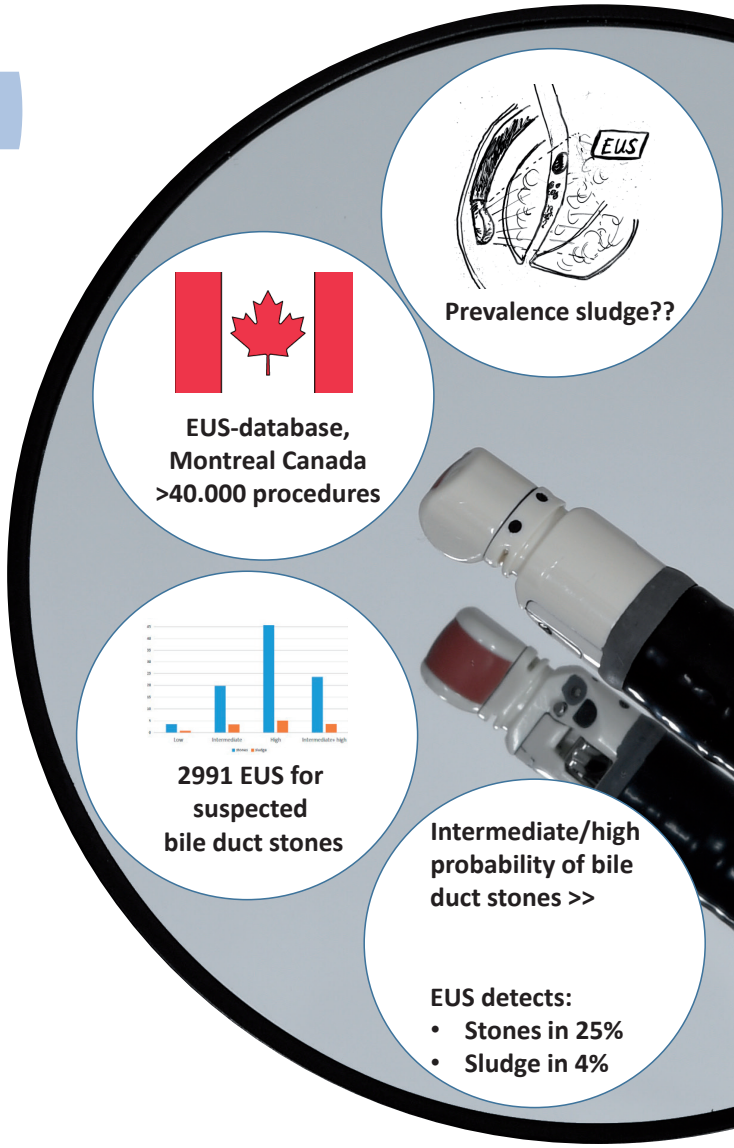


Supplemental figure 1a: Estimates of Fleiss kappa and corresponding 95% confidence intervals from simulated data.


3

4

CHAPTER 4


EUS
Prevalence sludge??
EUS-database,
Montreal Canada
>40.000 procedures
2991 EUS for
suspected
bile duct stones
Intermediate/high
probability of bile
duct stones >>
EUS detects:
• Stones in 25%
• Sludge in 4%

The prevalence of bile duct sludge in patients with suspected bile duct stones

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Techniques and Innovations in Gastrointestinal Endoscopy 2021; 288-289

Introduction

Endoscopic Ultrasonography (EUS) in patients with suspected bile duct stones rules out the presence of stones in up to 65% of patients, thus preventing unnecessary Endoscopic Retrograde Cholangiography with Endoscopic Sphincterotomy (ERC with ES) and its complications in the majority of cases [1]. Increased use of EUS for ruling out bile duct stones has led to more cases in which bile duct sludge is detected. Sludge is an ultrasound diagnosis usually described as layered, mobile, low-amplitude echoes without shadowing, representing bile precipitate out of solution [2,3]. In presumed idiopathic pancreatitis the finding of bile duct sludge is considered an indication to perform a cholecystectomy [4]. The clinical relevance and significance of detecting bile duct sludge in patients with suspected bile duct stones is currently unclear. Based on two retrospective studies including a total of 215 EUS procedures with positive findings (sludge or stones), bile duct sludge is estimated to account for 20-25% of the abnormalities detected in the CBD in patients with suspected bile duct lithiasis [5,6].

Methods

Aiming for a better estimate of the prevalence of bile duct sludge at EUS in patients with suspected bile duct lithiasis, we analyzed all consecutive EUS procedures in patients with suspected bile duct stones from a large prospectively maintained EUS database from a tertiary referral center in Montreal, Canada. Cases were stratified based on serum bilirubin and findings at transabdominal ultrasound according to the 2010 ASGE criteria into low, intermediate, and high probability of bile duct stones [7]. Pancreatitis and suspected cholangitis cases were excluded. Linear array EUS was performed by either one of two experienced endosonographers (SP and AS).

Results

Between October 2000 and June 2020 41259 upper gastrointestinal EUS procedures were performed in patients >18 years of age, of which 2991 cases were performed for suspected bile duct lithiasis. Overall, bile duct stones were detected in 403 (13.5%) out of 2991 cases and sludge was detected in 65 (2.2%) cases. EUS detected bile duct sludge or stones (positive findings) in 468 cases. Sludge was detected in 13.8% (65 out of 468) of these cases. A total of 1511 (51%) patients had low probability, 1265 (42%) patients had intermediate probability, and 215 (7%) patients had high probability of bile duct stones according to 2010 ASGE criteria. In patients with intermediate or high probability of bile duct stones EUS detected stones in 349/1480 (24%) and sludge in 54/1480 (3.6%) of cases

(Table 1, Figure 1). The prevalence of both bile duct stones and sludge increases with the estimated probability.

Table 1. Probability of bile duct stones and findings at EUS for suspected bile duct lithiasis.

Probability	n(%)	CBD stone(s) n(%)	CBD sludge n(%)
Low	1511 (51)	54 (3.5)	11 (0.7)
Intermediate	1265 (42)	251 (19.8)	43 (3.4)
High	215 (7)	98 (45.6)	11 (5.1)
Total	2991	403 (13.5)	65 (2.2)

Probability according to 2010 ASGE criteria

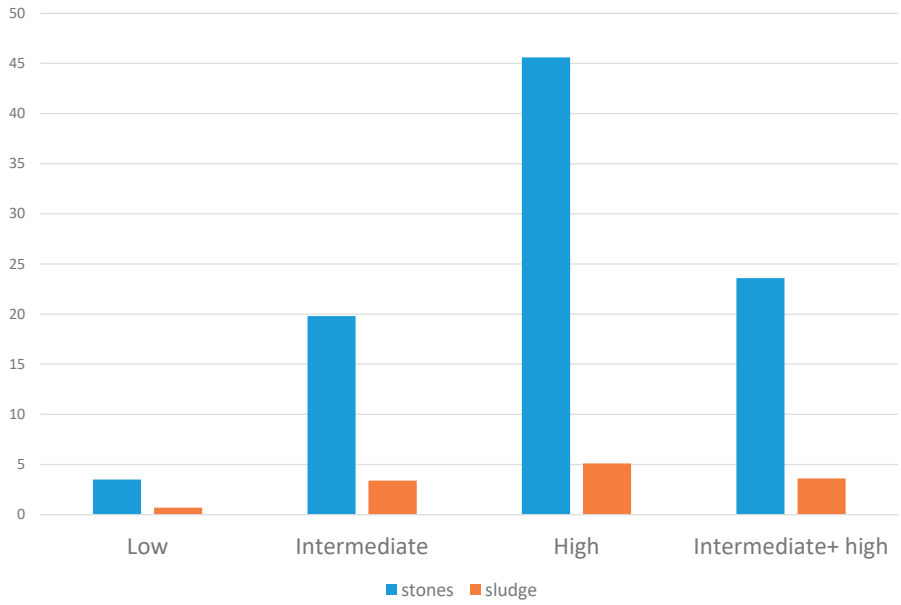

Figure 1. Estimated probability of bile duct stones and prevalence of stones and sludge at EUS
Proportion of patients with low, intermediate, high and intermediate + high probability of bile duct stones according to 2010 ASGE criteria with stones and sludge at EUS.

Discussion

Based on this retrospective analysis of a large, prospectively maintained EUS database, we estimate the prevalence of bile duct sludge in patients with intermediate or high probability of bile duct stones to be 3.6%.

Previous estimates of the prevalence of bile duct sludge ranged from 20-25% and were calculated using the number of positive findings at EUS (sludge or stones) as the denominator in studies with limited numbers of cases (116 and 99 cases respectively)[5,6].

In the current study, sludge was detected in 65 (13.8%) out of 468 cases with positive findings at EUS.

The larger sample size in comparison to previous studies and the use of number of cases with intermediate or high probability of bile duct stones as the denominator are the main strengths of the data presented, providing a more solid estimate of the prevalence of bile duct sludge in patients with suspected bile duct lithiasis. Of critical note, EUS is known to be associated with interobserver variability[8]. In the current study, only two experienced endosonographers performed all EUS interventions.

Endosonography plays an important role in selecting patients with suspected bile duct lithiasis for ERC with ES. Performing EUS in patients with an intermediate or high probability of bile duct stones may yield bile duct sludge in 1 out of 25 cases, posing endosonographers the intriguing and unsolved question whether it is indicated to proceed to ERC and ES. Further research into the natural behavior of biliary sludge is needed to guide clinicians in making the right treatment decision in these patients.

Detecting hyperechoic, dependent, non-shadowing bile duct content at EUS in patients with suspected bile duct lithiasis, should prompt the endosonographers to confirm the diagnosis by repositioning the endoscope to rule out artifacts. In our practice, we only schedule ERC with ES in these patients after a thorough pro- and con discussion with the patient. An endoscopic intervention is scheduled 3-10 days after diagnosis. Prior to this ERC+ ES we schedule a second EUS in the same session to re-confirm the sludge diagnosis and rule out spontaneous passage.

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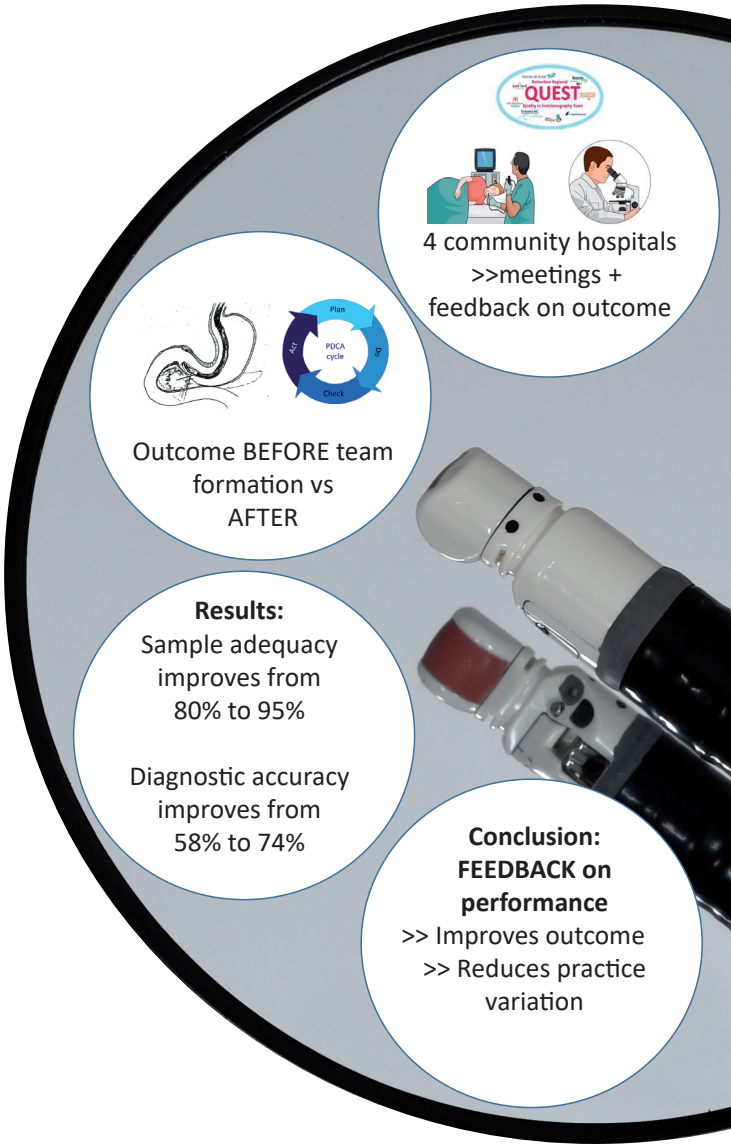
4

SECTION 2

EUS guided tissue acquisition in solid lesions of the pancreas

5

CHAPTER 5


QUEST
4 community hospitals
>>meetings +
feedback on outcome
Plan
Do
Check
Act
PDCA
cycle
Outcome BEFORE team
formation vs
AFTER
Results:
Sample adequacy
improves from
80% to 95%
Diagnostic accuracy
improves from
58% to 74%
Conclusion:
FEEDBACK on
performance
>> Improves outcome
>> Reduces practice
variation

Collaboration of community hospital endosonographers improves diagnostic yield of endoscopic ultrasonography guided tissue acquisition of solid pancreatic lesions

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Abstract

Background and aims

Endoscopic ultrasound (EUS) guided tissue acquisition (TA) is the method of choice to establish a pathological diagnosis of solid pancreatic lesions. Data on quality and yield of EUS guided TA performed in community hospitals are lacking. A study was performed to determine and improve the diagnostic yield of EUS guided TA in a group of community hospitals.

Methods

Following analysis of the last 20 EUS guided TA procedures of solid pancreatic lesions performed in each of 4 community hospitals, a collaborative EUS interest group was formed and a prospective registry was started. During meetings of the interest group feedback on results per center were provided and strategies for improvement were discussed.

Results

In the BEFORE team formation cohort 80 procedures were performed in 66 patients. In the AFTER team formation cohort 133 procedures were performed in 125 patients. After team formation the rate of adequate sample increased from 80% (95%CI [0.7-0.9]) to 95% (95%CI [0.9-1.0]) , diagnostic yield of malignancy improved from 28% (95%CI [0.2-0.4]) to 64% (95% CI [0.6-0.7]), and sensitivity of malignancy improved from 63% (95%CI [0.4-0.8]) to 84% (95%CI [0.8-0.9]). Multivariate regression analysis revealed team formation to be the only variable significantly associated with an increased rate of adequate sample.

Conclusions

The formation of a regional EUS interest group with regular feedback on results per center, and discussions on methods and techniques used, significantly improved the outcome of EUS guided TA procedures in patients with solid pancreatic lesions in community hospitals.

Introduction

The use of endoscopic ultrasound (EUS) guided tissue acquisition (TA) of pancreatic lesions has increased dramatically over the last 20 years [1]. Following the initial publication on this subject, EUS guided TA has become the method of choice to establish a pathological diagnosis of solid pancreatic lesions [2].

EUS guided TA of solid lesions of the pancreas is reported to have a sensitivity of 85%, a specificity of 98% and a diagnostic accuracy of 88% [3,4]. In 2015, the ASGE published quality indicators defining performance targets for EUS fine needle aspiration (FNA) of solid pancreatic lesions: 1. rate of adequate sample 85%, 2. diagnostic yield of malignancy 70%, and 3. sensitivity of malignancy 85% [5]. EUS guided TA of solid pancreatic lesions is a complex multistep process in which several equipment and operator variables may impact the diagnostic yield. Factors such as: needle size, needle type, amount and type of suction applied, number of passes, presence of on-site cytopathogical evaluation, and operator experience have been extensively studied in well-designed randomized trials [6-16]. These studies have almost exclusively been performed in tertiary referral centers.

Data regarding practice variation of pancreatic EUS guided TA are limited. In a large multicenter retrospective study, including 1075 patients with solid pancreatic lesions from 21 centers, they found the diagnostic yield of malignancy per center ranging from 39% to 93% (1st quartile 61%; 3rd quartile 85%). The majority of these (81%) were academic centers, all but one located in the United states[17]. A recent publication found marked regional differences regarding the use of EUS and EUS guided TA in the province Ontario, Canada[18]. These publications both show significant differences regarding EUS practice and yield between different centers and different regions.

In the Netherlands, as in many other countries, EUS guided TA is nowadays also practiced in the majority of larger community hospitals. Literature data on the results of EUS guided TA from solid pancreatic lesions in community hospitals are lacking. We performed a study in patients with solid pancreatic lesions aiming to: 1. determine practice variation regarding yield of EUS guided TA in patients with solid pancreatic lesions, and 2. to improve quality and yield of EUS guided TA in a collaborative group of 4 community hospitals in the Rotterdam region, Zuid-Holland, the Netherlands.

Methods

First, we retrospectively analyzed the diagnostic performance of the last consecutive 20 EUS guided TA procedures of solid pancreatic lesions in each of the 4 community hospitals

in the province of Zuid-Holland in the Netherlands (the BEFORE cohort). These procedures had all been performed in 2014.

Next, from January 2015 onwards, a regional EUS interest group was formed and regular team meetings were organized. The formation of this interest group and its 3 annual meetings was initiated and organized by community hospital endosonographers. Endosonographers and trainees from the local tertiary center were involved from the beginning and attended all meetings. At the first meeting, the results of the retrospective analysis were extensively discussed, as were possible strategies to reduce practice variation and improve diagnostic yield. At subsequent meetings guidelines, techniques and materials, and tips & tricks were exchanged by means of formal presentations and open discussions, and EUS case video recordings were presented and discussed.

Prospective data were collected between January 2015 and September 2016 (The AFTER cohort). During this episode 5 EUS interest group meetings were organized. Feedback on performance per center was provided once a year. Based on data provided during team meetings each local endosonography team decided to change or maintain their practice. No specific protocols or materials were prescribed by the regional team or any of its members.

Primary outcome variable for both cohorts was : 1. rate of adequate sample, defined as proportion of procedures yielding specimen sufficient for cyto- and/or histological analysis. Secondary outcome variables were: 2. diagnostic yield of malignancy: proportion of procedures yielding a malignant diagnosis, 3. sensitivity for malignancy: true positives divided by the sum of true positives and false negatives, and 4. diagnostic accuracy defined as the sum of true positives and true negatives divided by the total number of diagnostic procedures. Item 1 , 2 and 3 were previously defined as ASGE quality indicators.

Data on EUS guided TA procedures collected both the BEFORE, and AFTER cohorts included: patient demographics, localization of the pancreatic mass, hospital, endosonographer, needle diameter (19-22-25 G), number of passes, use of any suction technique (yes/no) and the result of the cyto- and/or histopathological evaluation of the EUS guided TA specimen, and whether or not an EUS guided TA procedure was repeated following the initial procedure. The results of cyto- and/or histopathological evaluation were stratified as follows: malignant, non-malignant, unclear, and non-diagnostic i.e. insufficient material for diagnosis. As a reference standard the final diagnosis based on a minimum of 12 months of clinical follow-up and/or histopathology and/or surgical resection specimen was used.

In the AFTER cohort, additional data were collected including tumor size, ultrasonography characteristics of the mass (echogenicity, vascularity, delineation, homogeneity), consistency of the mass, puncture location (ie. stomach or duodenum), type of EUS needle (FNA/FNB),

type of suction (vacuum/slow withdrawal of stylet), type of liquid based cytology (LBC) medium used (cytolyt®, cytotich red®, other), and presence of on-site cytopathological evaluation during EUS guided TA.

In each of the collaborating hospitals 200-300 EUS procedures are performed annually. All endosonographers were formally trained in endosonography for at least a year at a referral center. During formal training each endosonographer performed at least 250 EUS procedures, including 100 pancreaticobiliary cases and at least 50 EUS guided TA procedures. Post-training EUS experience ranged from 1-12 years while performing an average of 80 procedures per year (range 60-200). Patient selection, and techniques and materials used, were all at the discretion of the local clinicians and according to local availability of equipment and hospital standards.

Statistics

In order to detect a significant difference in the rate of adequate sample from 80% to 95%, with α=0.05 and power of 0.9, the required number of procedures in the AFTER cohort is 97.

Data are presented as median and range for continuous variables, and as counts with percentages for categorical variables. Point estimates are presented with 95% confidence intervals (CIs). Categorized variables were analyzed using Fisher's exact test or chi-square test, as appropriate. Quantitative variables were analyzed using Welch's t-test. A Mann-Whitney U Test was used for not normally distributed variables.

Sensitivity and diagnostic accuracy were calculated using 2x2 contingency tables and compared using n-1 chi-square testing [19].

Univariate logistic regression analysis was performed to identify factors associated with rate of adequate sample. Variables with $p<0.1$ during univariate analysis were tested in a multivariate model.

The study protocol was approved by the local ethics committees of the 4 hospitals.

Results

Between September 2014, and September 2016, 213 consecutive EUS guided TA procedures of solid pancreatic lesions were included in our study. The BEFORE cohort consisted of 66 unique patients who underwent a total of 80 EUS guided TA procedures. The AFTER cohort consisted of 125 unique patients who underwent a total of 133 procedures.

In the BEFORE cohort patients were significantly younger in comparison to the AFTER cohort. In the AFTER cohort the proportion of patients with a final diagnosis of pancreatic malignancy (= reference standard) was higher in comparison to the BEFORE cohort (89%, (95%CI [0.8-0.9]) vs 72%, (95%CI [0.6-0.8]) (Table 1).

The number of patients in which a second procedure was performed to achieve diagnostic accuracy decreased from 14 out of 80 (18%, 95%CI [0.1-0.3]) in the BEFORE cohort to 9 out of 133 (7%, 95%CI [0.03-0.13]) in the AFTER cohort. Twenty of 22 (91%, 95%CI [0.7-1.0]) patients with a non-diagnostic procedure were finally diagnosed with a pancreatic malignancy.

Table 1. Demographics, tumor localization and reference standard per EUS guided TA procedure in BEFORE and AFTER cohorts.

	Total (n= 213)	BEFORE (n = 80)	AFTER (n = 133)	p-value (BTF vs ATF)
Sex male, n (%)	116 (54%)	46 (58%)	70 (52%)	0.5
Median age in years (range)	69 (24-87)	67 (24-86)	70 (43-87)	**0.02**
Location mass pancreatic head, n (%), [95%CI]	125 (59%) [0.5-0.7]	50 (63%) [0.5-0.7]	75 (56%) [0.5-0.7]	0.4
Reference standard malignant, n (%), [95%CI]	177 (83%) [0.8-0.9]	58 (72%) [0.6-0.8]	118 (89%) [0.8-0.9]	**<0.01**

BEFORE= before team formation
AFTER= after team formation
Significant results are bolded

In the BEFORE cohort the rate of adequate sample per hospital differed significantly (55% (95% CI [0.3-0.8]) to 100% (95% CI [0.8-1.0]) (Table 2). In the AFTER cohort the overall rate of adequate sample increased from 80% (95% CI [0.7-0.9]) to 95% (95% CI [0.9-1.0]). Nevertheless, the significant differences in rate of adequate sample between individual hospitals remained, ranging from 83% (95% CI [0.6-0.9]) to 100% (95% CI [0.9-1.0]).

In the BEFORE cohort diagnostic yield of malignancy per hospital ranged from 0% (95% CI [0.0-0.2]) to 55% (95% CI [0.3-0.8]), compared with 59% (95% CI [0.4-0.8]) to 67% (95% CI [0.5-0.8]) in the AFTER cohort. In the AFTER cohort differences between the hospitals regarding diagnostic yield were no longer statistically significant (difference 18%, 95%CI [-0.2-0.3], p=0.5) Overall, diagnostic yield of malignancy in the AFTER cohort improved significantly from 28% (95% CI [0.2-0.4] to 64% (95% CI [0.6-0.7]), (difference 36%, 95%CI [0.2-0.5]).

Sensitivity for malignancy was significantly different between hospitals in the BEFORE cohort , ranging from 50% (95%CI [0.1-0.9]) to 89% (95%CI [0.5-1.0]), (difference 39%, 95%CI [0.1-0.6]). In the AFTER cohort it ranged from 62% (95%CI [0.4-0.8]) to 92% (95%CI [0.7-1.0]),

(difference 30%, 95%CI [0.1-0.5]). Overall, sensitivity for malignancy improved from 63% (95%CI [0.4-0.8]) to 84% (95% CI [0.8-0.9]), (difference 21%, 95%CI [0.1-0.3]).

Diagnostic accuracy was also different between hospitals in the BEFORE cohort ranging from 36% (95%CI [0.1-0.6]) to 70% (95%CI [0.5-0.9], (difference 34%, 95%CI [0.0-0.6]). In the AFTER cohort the overall diagnostic accuracy improved from 58% (95%CI [0.4-0.7]) to 74% (95%CI [0.7-0.8]), (difference 16%, 95%CI [0.0-0.3]).

Table 2. Performance characteristics per hospital BEFORE and AFTER

	A	*B*	*C*	*D*	*Difference (min-max)*	*95% CI*	*p-value*	*Total*
Procedures BEFORE	20	20	20	20				80
Rate of adequate sample	70% [0.5-0.9]	95% [0.7-1.0]	100% [0.8-1.0]	55% [0.3-0.8]	45%	[0.2-0.7]	**<0.001**	80% [0.7-0.9]
Diagnostic yield of malignancy	0% [0.0-0.2]	40% [0.3-0.7]	55% [0.3-0.8]	15% [0.1-0.7]	55%	[0.3-0.7]	**<0.001**	28% [0.2-0.4]
Sensitivity for malignancy	…..	89% [0.5-1.0]	79% [0.5-0.9]	50% [0.1-0.9]	39%	[0.1-0.6]	**<0.01**	63% [0.4-0.8]
Diagnostic accuracy	36% [0.1-0.6]	68% [0.4-0.9]	70% [0.5-0.9]	45% [0.2-0.8]	34%	[0.0-0.6]		58% [0.4-0.7]
Procedures AFTER	24	23	49	37				133
Rate of adequate sample	83% [0.6-0.9]	96% [0.8-1.0]	100% [0.9-1.0]	97% [0.8-1.0]	17%	[0.0-0.4]	**<0.01**	95% [0.9-1.0]
Diagnostic yield of malignancy	60% [0.4-0.8]	59% [0.4-0.8]	65% [0.5-0.8]	67% [0.5-0.8]	18%	[-0.2-0.3]	0.5	64% [0.6-0.7]
Sensitivity for malignancy	75% [0.5-0.9]	62% [0.4-0.8]	84% [0.7-0.9]	92% [0.7-1.0]	30%	[0.1-0.5]	**<0.01**	84% [0.8-0.9]
Diagnostic accuracy	70% [0.5-0.9]	64% [0.4-0.8]	73% [0.6-0.8]	83% [0.7-0.9]	19%	[0.0-0.4]	0.09	74% [0.7-0.8]

A, B, C and D represent collaborating community hospitals.
Rate of adequate sample: proportion of procedures yielding specimen sufficient for cyto- and/or histopathological analysis (%, [95% CI]).
Diagnostic yield of malignancy: proportion of procedures yielding a malignant diagnosis (%, [95% CI]).
Sensitivity of malignancy: true positives divided by the sum of true positives and false negatives (%, [95% CI]).
Diagnostic accuracy: true positives + true negatives divided by total number of procedures (%, [95% CI]).
Significant results are bolded

The effect of team formation on behavior of endosonographers

In the AFTER cohort the median number of passes increased significantly from 2.0 (range 1-5) to 3.0 (range 1-6) (Table 3). In the BEFORE cohort only 1 pass was performed in 29 out of 80 cases (36%) compared to 14 out of 131 (11%) in the AFTER cohort (Figure 1). Overall the diagnostic yield for malignancy of 1 pass was 32% (95%CI [0.2-0.5]) compared to a

diagnostic yield of >1 pass (range 2-6) of 51% (95% CI [0.4-0.6]), (difference 19%, 95%CI [0.0-0.3]).

In hospitals B and C the median number of passes did not significantly change. In hospital A the median number of passes increased from 2.0 to 3.0 in the AFTER cohort (95%CI [0.3-1.4]). In Hospital D the median number of passes increased from 2.5 to 3.0 in the AFTER cohort (95%CI [0.6-1.6]).

In the AFTER cohort the use of 19G needles overall decreased from 18% to 8% (difference 10%, 95%CI [0.01 –0.2]) and a trend was observed towards a more frequent use of the 25G needle (Table 3). In hospitals B and C needle diameters did not significantly change. In hospital A the 25G needle was introduced after team formation and used in 10 out of 24 cases (42%). The use of 22G needles in this hospital was reduced from 100% to 58% accordingly (difference 42%, 95%CI [0.2–0.6]). In hospital D the use of the 19G needles decreased from 65% to 8% in the AFTER cohort (difference 57%, 95% CI [0.3–0.7]).

Although the use of suction in the BEFORE cohort was only reported in 53% of cases (with 38 out of 80 missing), the use of any type of suction overall increased from 35% to 96% in the AFTER cohort (difference 61%, 95%CI [0.5-0.7]). In the BEFORE cohort hospitals B and D did not report on the use of suction in the majority of cases. In hospitals A and C the use of suction was reported in both cohorts (Table 3).

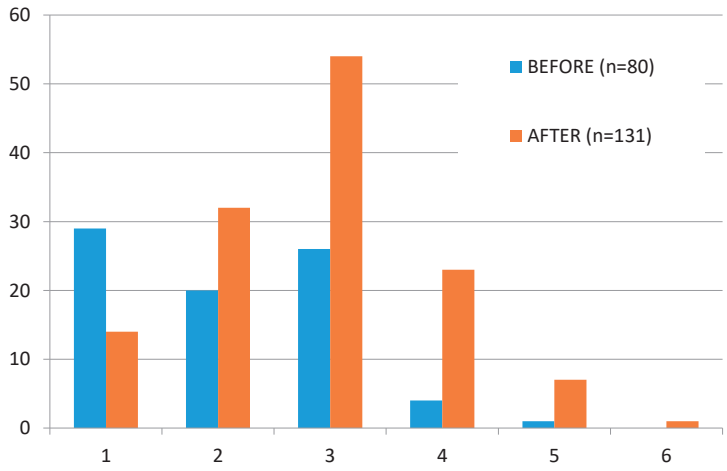

Figure 1. Number of passes performed in BEFORE and AFTER cohorts.
On the X-axis the number of passes performed per procedure. On the Y-axis the number of procedures performed.

Table 3: Number of passes, needle diameters and suction applied per hospital BEFORE and AFTER

BEFORE		AFTER		
A:	N=20	N=24	p-value	95%CI
Passes (median (range))	2.0 (1 – 4)	3.0 (2 – 4)	**<0.01**	0.3–1.4
25G	-	10 (42%)	**<0.01**	0.2 -0.6
22G	20 (100%)	14 (58%)	**<0.01**	0.2 – 0.6
19G	-	-		
Needle not reported	-	-		
Any suction	16 (80%)	24 (100%)	0.02	0.02 -0.4
Suction not reported	-	-		
B:	N=20	N=23		
Passes (median (range))	1.0 (1 – 2)	1.0 (1 – 2)	0.1	-0.1 – 0.5
25G	18 (90%)	15 (65%)	0.06	-0.01 – 0.5
22G	1 (5%)	2 (9%)	0.6	-0.2 – 0.2
19G	1 (5%)	4 (17%)	0.2	-0.1 – 0.3
Needle not reported	-	2 (9%)		
Any suction	-	21 (91%)	(a)	
Suction not reported	20 (100%)	2 (9%)		
C:	N=20	N=49		
Passes (median (range))	3.0 (1 – 5)	3.0 (2 – 5)	0.4	-0.3 – 0.6
25G	6 (30%)	23 (46.9%)	0.2	-0.1 – 0.4
22G	14 (70%)	23 (46.9%)	0.08	-0.03 – 0.4
19G	-	3 (6.1%)	0.3	-0.1 – 0.2
Needle not reported	-	-		
Any suction	11 (55%)	47 (96%)	**<0.001**	0.2 – 0.6
Suction not reported	-	-		
D:	N=20	N=37		
Passes (median (range))	2.5 (1 – 4)	3.0 (2 – 6)	**<0.001**	0.6-1.6
25G	-	2 (5%)	0.3	-0.1 –0.2
22G	5 (25%)	32 (87%)	**<0.001**	0.6 – 0.9
19G	13 (65%)	3 (8%)	**<0.001**	0.3 – 0.7
Needle not reported	2 (10%)	-		
Any suction	1 (5%)	36 (97%)	(a)	
Suction not reported	18 (90%)	1 (3%)		
Total	N=80	N=133		
Passes (median (range))	2.0 (1-5)	3.0 (1-6)	**<0.001**	0.5 – 1.0
25G	24 (30%)	50 (38%)	0.2	-0.1 –0.2
22G	40 (50%)	71 (54%)	0.7	-0.1 – 0.2
19G	14 (18%)	10 (8%)	**0.03**	0.01 – 0.2
Needle not reported	2 (3%)	2 (2%)		
Any suction	28 (35%)	128 (96%)	**<0.001 (a)**	0.5 – 0.7
Suction not reported	38 (48%)	3 (2%)		

A, B, C and D represent collaborating community hospitals.
a) In the BEFORE cohort the use of suction was not reported in 38 out of 80 cases (48%). P-values and 95% confidence interval are therefore only given for the total cohorts.
Significant results are bolded

Variables associated with non-diagnostic procedures in uni-and multivariate analysis.

In univariate regression analysis the formation of a regional team of endosonographers and decreased use of 19G needles were associated with a reduced proportion of non-diagnostic procedures i.e. an increased rate of adequate sample (Table 4). Multivariate regression analysis, including the use of 19G needles (yes/no), and before/after team formation in the model, showed only the latter variable to be significantly associated with an increased rate of adequate sample (Odds ratio 5, 95%CI [2-13], p<0.01).

Table 4: Variables associated with non-diagnostic procedures in univariable and multivariable analysis

	Univariate (1)		Multivariate	
Variable	Odds ratio with 95%CI	p-value	Odds ratio with 95%CI	p-value
Needle diameter 19G (yes/no)	0.4 (0.1-1.1)	0.08	0.7 (0.2-2.3)	0.6
AFTER (yes/no)	5 (2-14)	0.001	5 (2-13)	**<0.01**

Results of univariate logistic regression analysis investigating 9 variables as potential predictors of non-diagnostic procedures, and of the multivariate analysis using variables significant at p<0.1 in the univariate analysis.
Age, sex, mass localization (pancreatic head yes/no), number of passes (<3 yes/no), use of any type of suction (yes/no), endosonographers experience (> 3 years post-training yes/no), endosonographers training program (Erasmus Medical Center yes/no) had p-values >0.1 in univariate analysis and were therefore not included in the multivariate analysis.
Significant results are bolded

Practice variation in the AFTER cohort

In the AFTER cohort significant differences between the centers remained regarding choice of type and diameter of needle, number of passes performed, use of suction, type of suction, presence of on-site cytopathological evaluation, and choice of liquid based cytology medium.

The median number of passes performed per hospital ranged from 1.0 in hospital B to 3.0 in hospitals D (difference 2.0, 95%CI [1.8 – 2.6]) (Table 3). Center A used FNA needles only, compared to center C using FNB needles in 80%. Centre B used 25 G FNA needles in 78%, whereas center D mostly used 22G FNA and/or FNB needles. In 42 out of 133 cases (32%) on-site cytopathological evaluation was available during EUS guided TA, ranging from 0-47% in the different hospitals. In two out of 4 centers no on-site cytopathological evaluation was available. We observed a trend towards performing less passes with FNB/core needles in comparison to FNA needles.

None of the technical aspects of the procedure (i.e. puncture location, type of needle, type of suction, the use of stylet, type of liquid based cytology medium used, or the presence of on-site cytopathological evaluation) were significantly related to rate of adequate sample or diagnostic yield for malignancy in univariate and multivariate regression analysis.

Adverse events

One case of post EUS guided TA pancreatitis was reported in the AFTER cohort, requiring hospitalization for 2 days. No other adverse events were reported.

Discussion

The formation of a regional EUS interest group with regular team meetings that include presentations of EUS case video recordings, literature discussions, and feedback on performance per center pending this study, significantly improved the outcome of EUS guided TA in patients with solid lesions of the pancreas in community hospitals and reduced practice variation.

By means of this intervention the adequacy of the samples increased from 80% to 95%. Diagnostic yield of malignancy increased from 28% to 64%. Sensitivity for malignancy increased from 63% to 84%, and diagnostic accuracy from 58% to 74%. As a consequence, the proportion of patients requiring a second EUS guided TA procedure to achieve an adequate diagnosis was reduced from 18% to 7%.

Practice variation was reduced regarding techniques used (behavior of endosonographers) and outcome. The two hospitals that initially were underperforming, showed an improvement up to the level of the two other hospitals. In the AFTER cohort only minor differences between hospitals regarding outcome of EUS guided TA remained.

Team formation led to changes in the behavior of endosonographers. Significant changes in behavior were made in both initially underperforming hospitals A and D. After team formation EUS guided TA procedures in patients with solid pancreatic lesions in these hospitals involved: 1. more passes, 2. the use of less 19G and, 3. more 25G needles, 4. a more consequent use of suction, and is therefore more in line with the guidelines[20]. It remains unclear, whether and to what extent these changes affected outcome.

The fact that hospitals B and C, both with reasonable outcome in both BEFORE and AFTER cohorts also deviated from the guidelines, does not add to clarity regarding this subject. This is illustrated by the low median number of passes in hospital B, in both BEFORE and AFTER cohorts (1.0 in both cases) in contrast with the guidelines suggesting to perform three to four passes with an FNA needle and two to three passes with an FNB needle.

Besides, multivariate logistic regression does not support the changes regarding behavior to have led to an improved outcome. This may be due to the limited sample size, but may also suggest non-measured variables to play a role. It appears the improved yield in our

study is related to more than just the "technical" variables measured. The endosonographers (post-graduate) learning curve, the quality of the preparation of smears, the techniques used at the cytopathology lab, the experience of the local cytopathologist, and the quality of communication with the local cytopathologist are examples of variables likely to be involved.

Taking into consideration the differences in median age and reference standard between the groups BEFORE and AFTER, case selection was also affected. A partial explanation of the increased proportion of patients with a malignancy after team formation is the current higher demand for EUS guided TA in patients with solid pancreatic lesions planned for neo-adjuvant chemotherapy.

The rate of adequate sample is the most valuable outcome measure since it is independent of the prevalence of malignancy in both groups. Multivariate regression analysis showed that team formation was significantly associated with an increased rate of adequate sample. Number of needle passes, needle type, needle diameter, use of suction, presence of on-site cytopathological evaluation, endosonographers experience and endosonographers training program were not significantly associated with the increased rate of adequate sample. It has to be noted however, that limitations in sample size for each individual parameter prohibit a more detailed analysis.

This is the first study to explore the quality and ways to improve quality of EUS guided TA of pancreatic lesions in community hospitals. It is the first study to promote a regional multicenter team based approach to improve outcome[21].

The retrospective nature of data collection in the BEFORE cohort is a potential limitation of the current study. Nevertheless, we selected consecutive cases in an attempt to limit selection bias. Another potential limitation is the variety of techniques and materials used. Choice of needles and other technical aspects of the procedure where at the discretion of the local clinicians. However, this was intentional as we were not testing the implementation or change of a single variable, for example a specific needle type and size, but the behavior of the whole endosonography team within a hospital when regularly exposed to contact and interaction with colleagues from other hospitals jointly discussing potential ways to improve outcome.

A meta-analysis performed in 2012 showed higher sensitivity in prospective compared to retrospective studies, as well as in multicenter compared to monocenter studies[4]. We also observed this effect which is most likely because of regular feedback and communication between centers. Moreover, the EUS team comprising of endosonographers, nursing staff, cytotechnicians and pathologists were aware that their performance was being monitored

and compared to others. This effect on healthcare providers behavior is also known as the Hawthorne effect and is usually regarded as bias [22]. We argue that in the current study it is a desired effect, because of its positive effects on the quality of EUS-FNA while taking into consideration that it is not a one-time stimulus to behave differently, but a continuous incentive to do better as education and comparative performance measurements continue.

The results achieved after team formation are largely in line with performance targets regarding EUS guided TA of solid pancreatic lesions proposed by the ASGE in 2015 [16]. Sensitivity after team formation is comparable to the pooled sensitivity of 85% reported by Hewitt et al. in their meta-analysis, and also in line with the ASGE performance target of 85%. However, with a diagnostic yield of malignancy of 64% our results do not yet meet the proposed performance target of 70%. Clearly this is an area for future improvement. The proposed ASGE performance targets are based on a multicenter retrospective study by Savides et al, with 1075 patients who underwent EUS-FNA of solid pancreatic lesions at 21 centers of which 81% were tertiary referral centers. In this publication it is stated that a diagnostic yield of less than 52% should prompt centers to evaluate the reasons of their low yield[17].

The current study including solely community hospitals, all of which can be considered low-volume centers, shows that significant progress can be made regarding quality and yield of EUS guided TA of solid pancreatic lesions by means of the formation of regional EUS interest group. We intend to continue and expand our collaborative activities including prospective registration of data on EUS procedures aiming for continuous improvement of outcome and care. We hope that expanding our prospective registry will allow us to clarify questions regarding the value of specific materials and techniques, such as the presence of on-site cytopathological evaluation in EUS guided TA of solid pancreatic lesions in community hospital practice in the future.

We would recommend all centers performing EUS guided TA to continuously monitor their yield as a quality indicator. The most simple and straightforward way is to monitor the rate of adequate sample. If more than 1 out of 7 procedures yields an inadequate sample, additional measures should be undertaken including scrutinizing each aspect of the local protocol, initiate detailed communications with the local cytopathologist, and consult local and/or regional colleagues.

In summary, the formation of a regional EUS interest group with regular team meetings that include feedback on performance per center, significantly improved the outcome of EUS guided TA in patients with solid lesions of the pancreas in community hospitals and provides a framework for continuous improvement of care for these patients.

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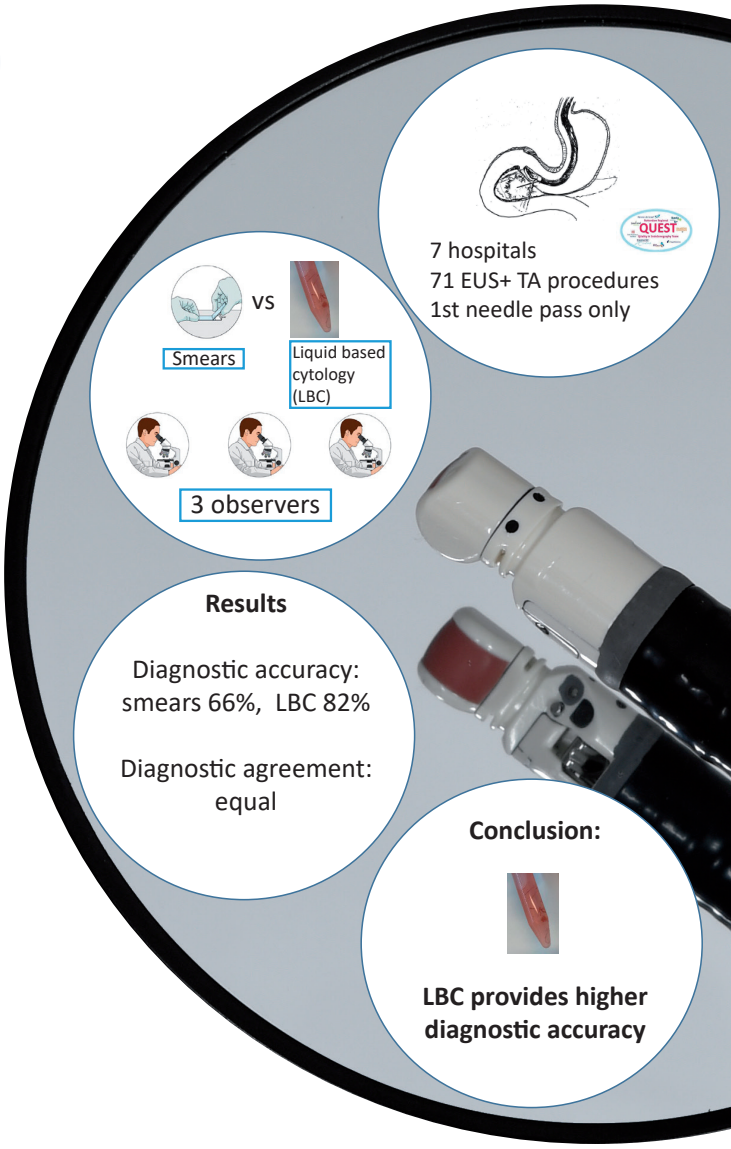
CHAPTER 6


7 hospitals
71 EUS+ TA procedures
1st needle pass only
vs
Smears
Liquid based cytology (LBC)
3 observers
Results
Diagnostic accuracy: smears 66%, LBC 82%
Diagnostic agreement: equal
Conclusion:
LBC provides higher diagnostic accuracy

Diagnostic yield and agreement on fine-needle specimens from solid pancreatic lesions: comparing the smear technique to liquid- based cytology

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ABSTRACT

Background and study aims

The traditional "smear technique" for processing and assessing endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA) is sensitive to artifacts. Processing and evaluation of specimens collected in a liquid medium, liquid-based cytology (LBC) may be a solution. We compared the diagnostic value of EUS-FNA smears to LBC in pancreatic solid lesions in the absence of rapid on- site evaluation (ROSE).

Patients and methods

Consecutive patients who required EUS-FNA of a solid pancreatic lesion were included in seven hospitals in the Netherlands and followed for at least 12 months. Specimens from the first pass were split into two smears and a vial for LBC (using ThinPrep and/or Cell block). Smear and LBC were compared in terms of diagnostic accuracy for malignancy, sample quality, and diagnostic agreement between three cytopathologists.

Results

Diagnostic accuracy for malignancy was higher for LBC (82 % (58/71)) than for smear (66 % (47/71), P = 0.04), but did not differ when smears were compared to ThinPrep (71 % (30/42), P = 0.56) or Cell block (62 % (39/63), P = 0.61) individually. Artifacts were less often present in ThinPrep (57 % (24/42), P = 0.02) or Cell block samples (40 % (25/63), P < 0.001) than smears (76 % (54/71)). Agreement on malignancy was equally good for smears and LBC (κ =0.71 versus κ = 0.70, P = 0.98), but lower for ThinPrep (κ =0.26, P = 0.01) than smears.

Conclusion

After a single pass, LBC provides higher diagnostic accuracy than the conventional smear technique for EUS-FNA of solid pancreatic lesions in the absence of ROSE. Therefore, LBC, may be an alternative to the conventional smear technique, especially in centers lacking ROSE.

Introduction

Pancreatic cancer is one of the most lethal solid tumors [1, 2], but individualized therapies have improved progression-free survival [3, 4]. Because these therapies depend on pre-therapeutic tissue analysis [5], endoscopic ultrasound (EUS)-guided tissue collection is increasingly being used for this purpose.

Although EUS-guided tissue sampling can reach diagnostic accuracy rates over 90 %, its outcome strongly depends on performer skills, sampling tools and techniques, and tissue processing [6]. Traditionally, fine-needle aspiration (FNA) needles have been used to collect cytological samples, which were smeared onto glass slides, the so-called smear technique. This technique is cheap, easy to use and available to the majority of EUS centers [7]. The downside of smears is that they are very sensitive to preparation artifacts [8, 9]. A dedicated on-site pathologist (ROSE) can improve smear quality and hence diagnostic accuracy. However, in many EUS centers ROSE is not readily available due to costs and logistic issues [7]. As a result, FNA samples are often handled by the endoscopy staff, with varying diagnostic outcomes [10–13].

An alternative for ROSE is to collect FNA samples in a liquid- based medium, the so-called liquid-based cytology (LBC) technique. This technique makes samples less vulnerable to contamination or artifacts, as debris, blood, and exudates can easily be removed [14]. There are different LBC techniques, i. e. ThinPrep, Surepath, Cellprep plus, and Cell block. LBC slides mimic the in situ 3-dimensional tissue architecture and provide a homogeneous cell dispersion. They also allow pathologists to perform ancillary tissue tests that could previously only be performed on histological samples.

Although, LBC is more accurate than the conventional smears for the cytological diagnosis of cervical bile duct and gall bladder cancers [15, 16], its superiority for pancreatic cancer has not been proven. The outcome of studies that compared smear to LBC for pancreatic lesions vary greatly, and are difficult to compare due to heterogeneity in the used LBC techniques (i. e. ThinPrep, Surepath, Cellprep plus, and Cell block) [9, 17–26]. As the ThinPrep and Cell block technique are two commonly used LBC techniques, we compared their diagnostic performance to the conventional smear technique for processing of FNA specimens from solid pancreatic lesions in the absence of an on-site pathologist.

Patients and methods

Study design and patient selection

This prospective multicenter study assessed whether LBC could replace smears for processing of pancreatic FNA specimens in centers lacking ROSE. For this, we compared EUS sample processing using the smear and LBC technique in terms of diagnostic accuracy, sample quality, and agreement on these parameters. Consecutive patients scheduled for EUS-FNA of a suspected solid pancreatic malignancy were included in a tertiary referral center and six regional community hospitals in the Netherlands between April 2016 and September 2017. Patients were followed for at least 12 months, until September 2018. Prior to the study, the endoscopy personnel underwent 1-day FNA tissue preparation training to optimize their knowledge and skills. All harvested and prepared FNA samples were collected and reviewed by an expert cytopathologist and two experienced cytotechnicians from the pathology department at the Erasmus MC University Medical Center in Rotterdam, the Netherlands. The Medical Ethics Committee reviewed the study and granted a waiver of consent as the protocol did not interfere with local EUS-FNA sampling protocols (MEC-2016-022).

EUS-guided tissue sampling

All EUS-FNA procedures were performed according to a stand- ard protocol, using a convex array echoendoscope (Pentax EG- 3870 UTK, Pentax EG-3270 UK, Olympus UTC 140/180, Olympus linear GF-UCT180, Table 1).

Tissue sampling was performed by endosonographers who were formally trained for at least 1 year at a tertiary referral center, had 1 to 20 years of EUS experience, and perform at least 25 EUS-guided tissue sampling procedures annually. Patients were sampled using a 19-, 22- or 25-gauge FNA needle (EchoTip; Cook Medical or Expect; Boston Scientific). The number of passes, sampling technique, and use of additional techniques (e. g. applying negative suction with a syringe) were at the discretion of the performer.

Specimen handling

EUS-FNA specimens from the first pass were expelled from the needle using a stylet. Then, the specimen was split to prepare two separate glass slides using the smear technique. The remainder specimens from the same pass was collected in a liquid-based medium. Smears were performed using the "sandwich method" [27]. LBC was processed using thin layer preparation (ThinPrep, (Hologic) and/or the Cell block technique (Cel- lient automated Cell block system [Hologic]), the Agar technique, or Aalfix Cellblock, depending on local tissue handling protocols (Table 1). Subsequent passes were handled according to local standards and not included in the study. Smears and LBC were prepared on-site, by the endoscopy

Table 1. EUS-guided FNA and tissue processing specifics per center

Center	EUS-scope type	Annual EUS-FNAper endosonographer	ROSE available	Additional techniques	SMEARpreparation	Liquidcytology medium	Thin-layer cytology technique	Cellblock technique
Albert Schweitzer Hospital, Dordrecht	Olympus linear GF-UCT180	25	Yes	Slow pull or Suction	Air dry, Hemocolor	Cytolyt	ThinPrep	Cellient Hologic
Reinier de Graaf Hosptial, Delft	Olympus linear GF-UCT180	30	No	Slow pull	Air dry No stain	Cytolyt, or Polytransportbuffer*	ThinPrep	Agar
Erasmus MC University Medical Center Rotterdam	Pentax EG-3870 UTK Olympus UTC 140/180	50	Yes	Slow pull or Suction	Air dry Diff quick	Cytolyt	ThinPrep	Cellient Hologic
Haga Hospital, The Hague	Olympus linear GF-UCT180	25	Yes	Slow pull	Air dry Diff quick	Formalin	None	Paraffin cellblock
Ijsselland Hospital, Rotterdam	Olympus linear GF-UCT180	25	Yes	Slow pull	Air dry Diff quick Giemsa	CytoRichRed	None	Agar
Maasstad Hospital, Rotterdam	Pentax EG-3270 UK Olympus linear GF-UCT180	30	No	Slow pull	Air dry Diff quick	CytoRichRed	None	Aalfix cellblock*
Sint Franciscus Hospital, Rotterdam	Pentax EUS-scope	20	No	Slow pull or Suction	Air dry No stain	CytoRichRed	None	Agar

*medium/technique developed locally.

personnel (endoscopy nurse or endosonographer). On-site pathological assistance was only allowed after the first pass, once study material was collected.

Sample reviewing

All study samples were anonymized and sent to the Erasmus MC University Medical Center in Rotterdam for review by an expert cytopathologist and two cytotechnicians who were specialized in pancreaticobiliary diseases. Reviewers were blinded to the final clinical and pathological outcome. Sample assessment and scoring were done individually by the reviewers. Case discussion was not allowed. Smears, thin layer samples, and Cell blocks were analyzed consecutively.

Endpoints, scoring variables and definitions

The primary endpoint was comparison of diagnostic accuracy of the conventional smear method to the LBC technique of FNA specimens from solid pancreatic lesions. Sample diagnosis was based on the Bethesda classification, and scored as non-diagnostic, benign, atypical, or malignant [28]. The reviewing expert cytopathologist determined the final sample diagnosis. Gold standard diagnosis was based on the surgical resection specimens in operated patients, or on a compatible clinical dis- ease course during a 12-month follow-up period. Solid pseudo- papillary neoplasms (SPN) and NET grade 2 and 3 were classified as malignant [29, 30].

Secondly, we compared sample quality, defined as sample cellularity (< or > 50 % target cells) and presence of preparation artifacts, such as poor fixation, thick smear/clots, obscuring blood or inflammation, or cytolysis (no/yes). In addition, we compared interobserver agreement on sample diagnosis and quality among the three reviewers between the two techniques.

Other parameters that were scored included needle size, target lesion characteristics (location, size), number of needle passes performed, type of LBC medium used, and procedure-related complications (pancreatitis, infection, bleeding, other).

Statistics

Diagnostic accuracy and sample quality were compared between the smear and LBC technique, and were analyzed using logistic mixed effects models [31] with subject- and study center-specific (random) intercepts. This method allows taking into account the clustering structure of this multicenter trial, i. e., that observations from the same study center may be correlated. Separate models were fitted for comparison of SMEAR vs LBC and SMEAR vs ThinPrep vs Cell Block. Statistical significance was established as $P < 0.05$ (two-tailed).

Interobserver agreement among reviewers was calculated using kappa statistics [Fleiss' κ-statistic and 95 % confidence intervals (CIs)]. κ- statistics were interpreted according to convention of Landis and Koch; < 0, no agreement; 0–0.20 slight agreement; 0.21–0.40, fair agreement; 0.41–0.60, moderate agreement; 0.61–0.80, substantial agreement; and 0.81–1.0; almost perfect agreement. Because not all samples were eval- uated for both LBC methods, ThinPrep and Cell block, some of the ratings were missing. To compare agreement coefficients, the coefficient was then calculated based on the samples for which all ratings of the methods in the current comparison were available. In settings where the agreement coefficients of three methods were compared, three pairwise tests were used and P values were corrected for multiple testing using Holm's procedure [32]. For this, the P-values presented in this manuscript have been multiplied by the number of comparisons. Analyses were carried out using R version 3.5.1 [33], and SPSS version 23, Statistical Package for the Social Sciences, SPSS Inc., Chicago, Illinois, United States.

Power calculation

To determine the power needed for this study, we first performed a pilot study to assess the diagnostic accuracy for malignancy for pancreatic EUS-FNA specimens prepared using the smears and LBC method in the Erasmus MC University Medical Center. A difference in diagnostic accuracy of 20 % between smear and LBC was found, and considered clinically relevant. We estimated that to find such a difference, a sample size of 59 to 72 pairs would have 80 % power to detect a difference in proportions of 0.250 when the proportion of discordant pairs is expected to be between 0.500–0.600 and the method of analysis is a McNemar's test of equality of paired proportions with a 0.050 two-sided significance level.

Results

Case characteristics

A total of 71 cases were included, of which lesion and sampling characteristics are listed in Table 2. No procedure-related complications were recorded. Final diagnosis comprised 64 (90 %) malignancies, three (4 %) atypical cases, including two neuroendocrine tumors and one case of pancreatitis, and four (6 %) benign cases. This diagnosis was based on resection specimens in 19 (29 %), additional tissue biopsy (i. e. peritoneal, brain, lymph node biopsy) in 13 (20 %), and follow-up in 33 (51 %) cases.

Diagnostic accuracy and sample quality for smear versus LBC

Overall, diagnostic accuracy for malignancy of the first pass was 86 % (61/71). Accuracy was higher for samples processed using LBC than with the conventional smear technique (82 % versus 66 %, OR 2.62 95 % CI 1.13–6.79, P = 0.03). Overall diagnostic accuracy according to Bethesda was 80 % (57/71). For this classification, smears and LBC performed equally

Table 2. Case characteristics

Variables	Cases (n=71)
Target lesion location, n (%)	
Head	34 (48)
Uncinate process	6 (9)
Neck	4 (6)
Corpus	14 (20)
Tail	13 (18)
Target lesion size (mm), mean ± SD	31.0 ± 1.37
FNA needle size, n (%)	
19-gauge	1 (1)
22-gauge	27 (38)
25-gauge	43 (61)
Number of passes, median (IQR)	3 (2–3)
Gold standard diagnosis	
Benign	4 (6)
Atypical (NET, pancreatitis)	3 (4)
Malignant	64 (90)

well (51 % versus 59 %, OR 1.44 95 % CI 0.73–2.92, P = 0.30). Comparing the diagnostic accuracy for malignancy and the Bethesda classification of smears to both LBC techniques individually did not result in a significant difference in diagnostic accuracy (Table 3). Cell block had lower sample cellularity than smear (OR 0.39 95 % CI 0.18–0.82, P = 0.01,Table 4), but there was no clear evidence of a difference between ThinPrep and smear (OR 0.51 95 % CI 0.21–1.16, P = 0.11). Sample quality, in terms of artifacts, was better for both LBC techniques as compared to the smears (Table 4).

Diagnostic agreement for smear vs LBC

The diagnostic agreement among the cytopathologist and the two cytotechnicians was equally good for identifying malignancy in smears (κ = 0.71, 95 % CI 0.57–0.84) and LBC samples (κ = 0.70, 95 % CI 0.55–0.86, P = 0.98). The same was true for their agreement on the Bethesda classification (κ = 0.70, 95 % CI 0.57–0.83 vs κ = 0.64, 95 % CI 0.50–0.78, P =

Table 3. Overall diagnostic accuracy, and per tissue processing technique compared to smear.

Tissue preparation technique	Accuracy for malignancy n (%)	OR (95% CI)	p-value	Accuracy for Bethesda n (%)	OR (95% CI)	p-value
Overall (n=71)	61 (86)			57 (80)		
Smear (n=71)	47 (66)	1.92 (0.75-4.83)	*	36 (51)	1.03 (0.62-1.71)	*
LBC (n=71)	58 (82)	2.62 (1.13-6.79)	0.03	42 (59)	1.44 (0.73-2.92)	0.30
ThinPrep (n=42)	30 (71)	1.29 (0.52-3.26)	0.59	26 (62)	1.61 (0.74-3.76)	0.24
Cell block (n=63)	39 (62)	0.78 (0.78-1.69)	0.53	22 (35)	0.51 (0.24-1.03)	0.07

*reference category

Table 4. Sample quality per tissue processing technique, compared to smear.

Tissue preparation technique	Artifacts n (%)	OR (95% CI)	p-value	Cellularity n (%)	OR (95% CI)	p-value
Smear (n=71)	54 (76)	4.09 (1.54-15.16)	*	35 (49)	0.97 (0.43-2.04)	*
LBC (n=71)						
ThinPrep (n=42)	24 (57)	0.32 (0.12-0.82)	0.02	14 (33)	0.51 (0.21-1.16)	0.11
Cell block (n=63)	25 (40)	0.15 (0.05-0.35)	<0.001	18 (29)	0.39 (0.18-0.82)	0.01

*reference category

0.55). When ThinPrep (κ = 0.26, 95 % CI 0.04–0.48) and Cell block (κ = 0.79, 95 % CI 0.66–0.92) were assessed separately, agreement on presence of malignancy was comparable for Cell block and smears (κ = 0.79 vs. κ = 0.73, adjusted P = 0.53), but lower for ThinPrep than smears (κ = 0.261 vs κ = 0.640, adjusted P = 0.04). Similar results were found for the Bethesda classification (Fig. 1).

Agreement on presence of artifacts was low for all processing techniques, and did not differ significantly between processing techniques (Fig. 2). Agreement on cellularity was highest for Cell block (κ = 0.64, 95 % CI 0.48–0.81) and smears (κ = 0.60, 95 % CI 0.46–0.75), and lowest for ThinPrep (κ = 0.35, 95 % CI 0.14–0.56).

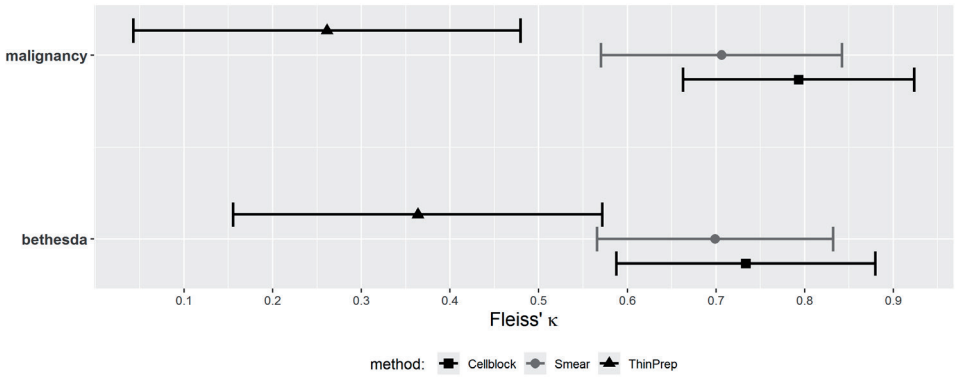

Figure 1. Agreement on diagnostic accuracy of malignancy and the Bethesda classification for smear, ThinPrep and cell block technique.

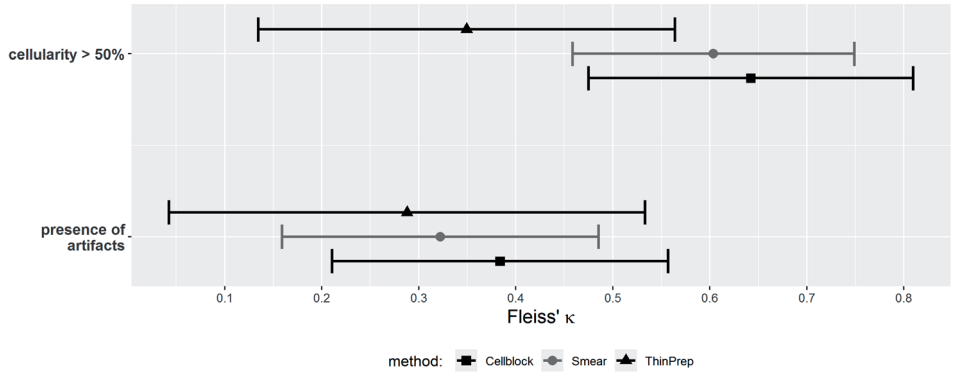

Figure 2. Agreement on sample cellularity and presence of artifacts for the smear, ThinPrep and cell block technique.

Discussion

Liquid-based cytology using ThinPrep and Cell block provides higher diagnostic accuracy than and a comparable agreement to the conventional smear technique after a single FNA pass from solid pancreatic lesions in the absence of an on-site pathologist. LBC, therefore, is a good alternative to the smear technique in the absence of ROSE. The higher diagnostic agreement for Cell block than ThinPrep advocates for implementation of the Cell block technique for LBC.

The first explanation for the higher diagnostic accuracy of LBC than smear seems to be its lower artifact rate. It is generally accepted that smears are vulnerable to preparation artifacts, which induces interpretation errors, and may result in a lower diagnostic accuracy [25]. Despite the fact that the endoscopy staff in the current study participated in smear preparation training to optimize their performance before initiation of the study, 76 % of the smears still contained artifacts. This was much higher than the artifact rate for the Cell block (39.7 %) and ThinPrep samples (57.1 %).

Besides a low artifact rate, the histology-like look of Cell block samples likely contributes to easier interpretation and matching interobserver agreement. It has previously been reported that pathologists prefer histology or Cell block over conventional cytology preparation, as its appearance is much closer to the in situ tissue architecture [8]. Furthermore, LBC allows for additional testing, such as immunohistochemistry, which may be decisive in challenging diagnostic cases such as autoimmune pancreatitis, or differentiation between metastatic or primary disease. Although agreement was higher for Cell block than for ThinPrep, it should also be taken into account that special training of cytotechnicians and pathologists is a prerequisite for accurate interpretation of these different LBC techniques [8]. Therefore,

choosing the optimal LBC technique will depend upon the preference and experience of the local pathologists.

The finding that sample cellularity was lower for LBC than for smears does not seem to match with its high diagnostic accuracy and agreement. It may be explained by the more homogeneous cell dispersion of LBC samples. This allows for better assessment of cell morphology, but may give the impression of a less "cellular sample." On the other hand, highly cellular smears may be scored as containing more than enough target cells, but if cells are packed in thick layers, this only hampers the interpretation. Despite the lack of a clear definition of "FNA sample cellularity," higher cellularity has been associated with higher DNA yield for molecular testing [14]. Therefore, it is crucial to determine the specific purpose of EUS-guided tissue collection in advance, and discuss this with the involved pathologist.

It is challenging to compare our findings to previous reports, since EUS-FNA protocols and tissue handling and processing techniques vary greatly. So far, 11 studies have compared the smear to the LBC technique for solid pancreatic lesions [9, 17– 26]. Six of them reported a higher diagnostic accuracy for smears than LBC [9, 18, 21–23, 26]. Half of these studies used ROSE [18, 21, 22]. Overall, only three of the 11 studies that compared smear to LBC were performed without ROSE [9, 20, 26]. Of these studies, two found a benefit of smear over LBC [9, 26] and one found a benefit for LBC, using another ThinPrep-like solution (Surepath) [29]. Each study used different ThinPrep solutions, limiting a direct comparison with our results. Of the studies that reported a diagnostic benefit for LBC, two of three used the Cell block rather than the ThinPrep technique, which seems to correspond with our findings [17, 24, 25]. Lastly (or finally), none of the above-mentioned studies assessed diagnostic agreement on the different techniques.

Compared to results in other studies, our overall diagnostic accuracy rate of 86 % is rather high, considering the fact that material was collected from the first needle pass only. Previous studies mostly based their results on several passes. Moreover, we split the material from this first pass for smear and LBC. As a result, our samples likely contained less material as compared to other study settings. Therefore, our diagnostic accuracy rates underestimate the true diagnostic accuracy rates in our practices. Furthermore, the diagnostic accuracy of each preparation technique alone was somewhat lower than LBC overall. The most likely explanation for this is that ThinPrep and Cell block are complementary techniques that provide samples with a different phenotype and diagnostic possibilities.

Our study has some limitations. An important limitation of studies on EUS-guided tissue sampling is lack of uniform guidelines on optimal sampling and tissue-handling techniques. Therefore, the resulting intercenter variation should always be considered, and may hamper general extrapolation of our findings. Second, we did not power our study to perform

additional subgroup analysis. Furthermore, although the participating endosonographers who performed the smears participated in hands-on FNA tissue preparation training, their experience is not comparable to that of on-site pathologists. Therefore, this may have limited the diagnostic accuracy of the smears. Another limitation is that the reviewing pathology staff could not be blinded to the processing technique, as their appearance differs accordingly. Furthermore, we did not perform a cost-effectiveness analysis due to differences in local EUS-protocols between the participating centers. Last, we only assessed the performance for both processing techniques for the first FNA pass, as our study was primarily designed to verify the concept that LBC could replace smears in clinical practice, not to evaluate the absolute diagnostic accuracy of the two techniques. Our data suggest that, in the absence of ROSE, LBC may replace smears.

Although LBC may replace smear preparation of pancreatic FNA specimens, in the absence of ROSE, its clinical importance may be questioned because there is growing evidence of the superiority of FNB over FNA [34, 35]. It would be interesting to directly compare the diagnostic accuracy of FNA specimens in liquid-based cytology to FNB cores in formalin, preferably in an international multicenter setting. Furthermore, it should be noted that tissue collection for liquid preparation techniques is easy for the endosonographer, but requires a well-equipped pathology laboratory and trained personnel. Therefore, introducing and implementing novel techniques and innovations for EUS-guided tissue sampling should always be done in close co- operation with the pathology department.

Conclusion

In conclusion, absent an on-site pathologist, the diagnostic accuracy of EUS-FNA for solid pancreatic lesions can be increased with the LBC technique as compared to the conventional smear technique. Because LBC provided for higher diagnostic accuracy and comparable interobserver agreement than smears, it may be routinely implemented in EUS centers lacking ROSE. The higher agreement for Cell block advocates for implementation of Cell block rather than ThinPrep. However, providing optimal EUS-tissue sampling depends on many factors, including experience and skills of the involved endoscopy and pathology team, and starts with the determination of the diagnostic or therapeutic purpose of tissue acquisition.

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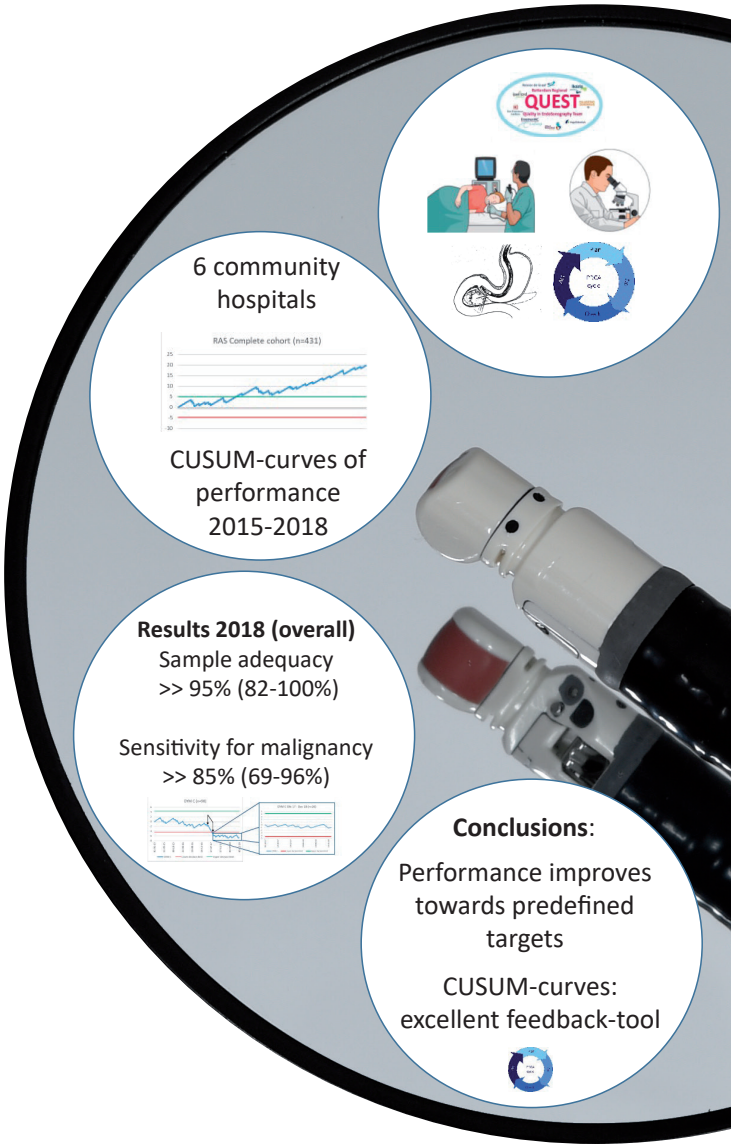
CHAPTER 7


6 community hospitals
RAS Complete cohort (n=431)
CUSUM-curves of performance 2015-2018
Results 2018 (overall)
Sample adequacy >> 95% (82-100%)
Sensitivity for malignancy >> 85% (69-96%)
Conclusions:
Performance improves towards predefined targets
CUSUM-curves: excellent feedback-tool

Cumulative sum learning curves guiding multicenter multidisciplinary quality improvement of EUS-guided tissue acquisition of solid pancreatic lesions

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Abstract

Introduction and aim

In this study we evaluated the performance of community hospitals involved in the Dutch quality in endosonography team (QUEST) regarding yield of EUS-guided tissue acquisition (TA) of solid pancreatic lesions using cumulative sum (CUSUM) learning curves. The aim was to assess trends in quality over time, and explore potential benefits of CUSUM as a feedback-tool.

Methods

All consecutive EUS-guided TA procedures of solid pancreatic lesions were registered in five community hospitals between 2015-2018. CUSUM learning curves were plotted for overall performance and for performance per center. ASGE defined key performance indicators (KPI), rate of adequate sample (RAS) and diagnostic yield of malignancy (DYM) were used for this purpose. Feedback regarding performance was provided on multiple occasions at regional interest group meetings during the study period.

Results

A total of 431 EUS-guided TA procedures in 403 patients were included in this study. The overall and per center CUSUM curves of RAS improved over time. CUSUM curves of DYM revealed gradual improvement, reaching the predefined performance target (70%) overall, and in 3 out of 5 contributing centers in 2018. Analysis of a sudden downslope development of the CUSUM curve of DYM in one center revealed temporary absence of a senior cytopathologist to have had a temporary negative impact on performance.

Conclusion

CUSUM derived learning curves allow for assessment of best practices by comparison amongst peers in a multidisciplinary multicenter quality improvement initiative and proved to be a valuable and easy to interpret means to evaluate EUS performance over time.

Introduction

EUS-guided TA is first choice for establishing a tissue diagnosis in suspected pancreatic cancer [1]. The increasing use of neoadjuvant chemotherapy for pancreatic carcinoma, and the fact that neoadjuvant treatments require pathological confirmation of the diagnosis, have rendered quality of EUS-guided TA of solid pancreatic lesions ever more important[2,3]. Proficiency in EUS-guided tissue acquisition can only be reached in centers in which all its aspects including tissue acquisition, tissue handling, microscopic assessment and reporting are safeguarded. Feedback on performance is key in order to improve quality [4].

In 2015 the American Society of Gastrointestinal Endoscopy (ASGE) defined the following key performance indicators (KPI) for EUS-guided TA in solid pancreatic lesions: rate of adequate sample (RAS) with a performance target of 85%, diagnostic yield of malignancy (DYM) with a performance target of 70% and sensitivity for malignancy (SFM) with a performance target of 85% [5]. RAS mainly reflects the quality of the process within the endoscopy suite (tissue acquisition, preparation of smears, including transport to the cytopathology lab), whereas DYM and SFM reflect the quality of the entire process, including patient selection, specimen preparation, microscopic assessment and reporting.

Currently, quality control for the yield of EUS-guided TA is not customary or required for centers performing EUS-guided TA. Quality measurements of EUS-guided TA procedures were previously described as a monitoring tool during the development of academic or regional EUS programs [6-8]. Wani et al. used CUSUM curves to describe the development of competence of advanced endoscopy trainees performing both EUS and ERCP [9-13]. CUSUM curves reflect development of quality delivered in time relative to predefined performance targets.

In 2015 the Dutch quality in endosonography team (QUEST) was founded. This is a regional EUS interest group, consisting of endosonographers and pathologists from five community hospitals in the Netherlands. QUEST aims to improve performance of EUS-guided TA by providing feedback on KPIs of individual centers based on a prospective registration of consecutive EUS-guided TA procedures of solid pancreatic lesions. This has led to an improvement in RAS (80% to 95%), in DYM (28% to 64%) and in SFM (63% to 84%) comparing the results of an initial retrospective analysis of yield of EUS-guided TA to the first 21 months of prospective registration [14].

This study evaluated the use of CUSUM curves to monitor performance of contributing centers regarding the yield of EUS-guided TA of solid pancreatic lesions. Using this tool, we aimed to assess trends in KPI over time, and explore potential benefits of CUSUM curves as a feedback-tool.

Patients and methods

This was a prospective multicenter quality improvement study of consecutive EUS-guided TA procedures of solid pancreatic lesions conducted in 5 community hospitals in the Netherlands. The local medical ethics committee (METC Zuidwest Holland 17-038) approved the study protocol. Informed consent was obtained from all patients. The Study is registered in the Dutch trial registry (NTR) with trial number NL9470.

Study population and data collection

All patients from the age of 18 with a solid pancreatic lesion with high suspicion of malignancy who underwent an EUS-guided TA procedure were eligible for this study. Primary outcome parameters were CUSUM derived learning curves with RAS and DYM as input parameters. RAS was defined as proportion of procedures yielding specimen sufficient for cytopathological and/or histopathological analysis. DYM was defined as the proportion of procedures yielding a 'suspicious for malignancy' or a 'malignant' diagnosis. The secondary outcome parameter was sensitivity for malignancy (SFM). SFM was defined as the total of true positives ('suspected malignancy' or 'malignancy' based on EUS-guided TA with a malignancy as final diagnosis) divided by all patients with a final diagnosis of malignancy.

Collected data on EUS-guided TA procedures included: patient demographics, localization of the pancreatic mass, hospital, endosonographer, pathologist, needle diameter (<22G or 22G), type of needle (FNA/FNB), number of passes, use of suction (slow withdrawal of stylet or vacuum suction), availability of ROSE, and the result of the cytopathological and/or histopathological evaluation of the EUS-guided TA specimen. Based on current practice guidelines and previous experience of our group endosonographers were advised to perform at least three passes with FNA-needles or at least two passes with FNB-needles (unless ROSE detected sufficient material for diagnosis earlier), and to use vacuum suction [14,15]. All other techniques and materials used, were at the discretion of the local clinicians and according to local availability of equipment and hospital standards.

The results of cytopathological and/or histopathological evaluation were classified as follows: non-diagnostic, benign, atypical, suspicious for malignancy and malignant. Neuroendocrine tumors were classified as malignant. For the purpose of this study 'suspicious for malignancy' and 'malignant' were both considered malignant. All types of pancreatic- and periampullary malignancies were considered a malignant reference standard. The gold standard for a malignant diagnosis was based on either histopathological diagnosis after surgical resection or progression of disease compatible with malignancy during a minimum of 12 months follow-up.

Feedback on performance

Regional interest group meetings were organized three times a year. Prior to meetings all contributors received data regarding the performance of their individual center accompanied by (anonymized) benchmark data from the other centers. At the regional interest group meetings the results of prospective registration, best practices, guidelines, and difficult cases were discussed. Up to 2017, feedback on performance overall and per center was provided as RAS, DYM and SFM (proportions). From 2018 onwards visual feedback by means of CUSUM curves of RAS and DYM was also provided. At meetings all data (numbers and CUSUM curves) were presented (in an anonymized fashion) and subsequently discussed. Participating endosonographers and pathologists were invited to reflect on changes in directions of the curves provided. Significant changes in the direction of the curve were subjected to further analysis of which the results were discussed separately with the practitioners from the centers involved, prior to the next general meeting. At a subsequent meeting, the results of these analyses were presented and discussed, with emphasis on potential learning opportunities for all participants. All gastroenterologists and pathologists involved had completed their training at least 3 years before the start of this study [14].

Statistics

Cumulative sum analysis (CUSUM)

Each EUS procedure is scored as a success (adequate sample/malignant outcome) or a failure (inadequate sample/non-malignant outcome). Each success is rewarded with adding score s, each failure results in subtraction of (1–s). Each procedure is a dot in the learning curve that is created by a plot of the cumulative sum of all cases in chronological order.

The acceptable rates (P0) and unacceptable rates (P1) were defined based on the ASGE KPI and a previous publication by Eltoum et al. [16]. For inadequate samples we designated 10% as acceptable (P0) and 15% as unacceptable (P1) rates. For a non-malignant outcome of the EUS the P0 was defined as 25% and the P1 as 30%.

Decision limits

Two decision limits (h1 and h0) were calculated. The decision limits are calculated based on type I (α) and type II (β) errors. A type I error is the risk of rejection of a true null hypothesis and a type II error is the risk of non-rejection of a false null hypothesis. The formulae that are used to calculate h0 and h1 were previously described [16]. The meaning of the decision limits in relation to the curve can be explained as follows: [17,18]

1. If the learning curve crosses the upper decision limit, the failure rate is within the preset acceptable range and it reflects high quality.
2. If the learning curve crosses the lower decision limit, the failure rate is above the preset unacceptable rates and an intervention is needed.
3. If the learning curve remains between the two decision limits, the performance is within the preset acceptable range.

CUSUM charts

CUSUM charts were constructed using Excel™. Each success (adequate sample/malignant outcome) contributes to an upwards slope of the CUSUM curve. Each inadequate sample will contribute to a downwards slope of the CUSUM curve. A downslope curve means that the key performance indicator is not met. A horizontal curve indicates that quality is up to standards. An upslope curve signifies quality is above the predefined key performance indicator threshold.

Multivariable analysis

To investigate the association of RAS and DYM with procedure characteristics, we fitted logistic mixed models. Due to the limited number of inadequate samples only two parameters (suction: yes/no and ROSE: yes/no) could be included in the RAS model.

The model for the diagnostic yield of malignancy included the variables suction type (no, slow withdrawal of stylet or vacuum), ROSE, number of passes (continuous), needle size (<22G, 22G) and needle type (FNA or FNB). In both models we used endoscopist specific (random) intercepts to take into account that samples obtained by the same endoscopist may not be independent, the model for DYM additionally included a pathologist specific (random) intercept. Both models were fitted in the Bayesian framework which allowed us to include observations for which some of the covariates were missing. We used normal priors with mean 0 and standard deviation 100 for all regression coefficients. The Bayesian models were fitted using Markov chain Monte Carlo (MCMC), with the help of the freely available and widely used "JAGS" software [19] that uses Gibbs sampling and provides a wide range of samplers to sample from full-conditional distributions that do not have a closed form. Results are presented as posterior mean and 95% credible interval (CI). Calculations were performed in R version 4.0.2 (2020-06-22) (R Core Team 2020) and the package JointAI 1.0.0.9000 [20].Missing observations were imputed during the analysis.

Results

From January 2015 until December 2018, 431 EUS-guided TA procedures of solid pancreatic lesions in 403 individual patients, were included. The median age of the patients was 68

years (range 27-88), and 51% were male. During follow-up, a pancreatic or periampullary malignancy (reference standard) was diagnosed in 87% of all cases. Per hospital 2-4 endosonographers were involved in these procedures. A wide range of 8-16 pathologists per hospital were involved (Table 1).

Rate of adequate sample (RAS) overall and per hospital

A total of 399 out of 431 procedures yielded an adequate sample. Hence, RAS was 93% for the complete cohort (range 86%-99% amongst individual hospitals). The ASGE defined KPI of RAS ≥85% was met overall and in each of the individual hospitals (Table 2). This can also be appreciated from the upslope direction of the overall learning curve drawn for this parameter (Supplementary figure 1). The RAS learning curves of the individual hospitals indicate adequate and stable quality (curves between the decision limits) in hospitals A, B, and E, and adequate and improving quality in hospitals C and D (Supplementary figures 2-6).

Table 1. Characteristics of the participating patients and hospitals.

	Total cohort (n=403)	A (n=79)	B (n=88)	C (n=81)	D (n=94)	E (n=61)
Sex male, n (%)	206 (51%)	43 (54%)	42 (48%)	40 (49%)	54 (57%)	27 (44%)
Median age in years (range)	68 (27-88)	70 (42-86)	68 (43-86)	68 (27-87)	67 (33-88)	68 (35-88)
Reference standard malignant, n (%)	351 (87%)	69 (87%)	77 (88%)	68 (84%)	81 (86%)	56 (92%)
Number of endoscopists involved	15	2	4	2	3	4
Number of pathologists involved	39	16	8	8	8	14

Table 2. Values of RAS, DYM and SFM for the complete cohort and per hospital.

Hospital	Number of procedures	RAS	DYM	SFM
A	87	*75 (86%)*	53 (61%)	68%
B	91	*82 (90%)*	57 (63%)	71%
C	90	*87 (97%)*	59 (66%)	79%
D	100	*99 (99%)*	75 (75%)	*87%*
E	63	*56 (89%)*	41 (65%)	73%
Total cohort	431	*399 (93%)*	285 (66%)	76%

Italics and underlined: equal or above ASGE performance target.
RAS: rate of adequate sample
DYM: diagnostic yield of malignancy
SFM: sensitivity for malignancy

Diagnostic yield of malignancy (DYM) overall and per hospital

A total of 285 out of 431 procedures yielded a malignant diagnosis. Therefore, the overall DYM was 66% (ranging from 61%-75% in the individual hospitals). This is below the KPI of DYM ≥70% (Table 2). The overall learning curve of this parameter has a downslope direction (crossing the lower decision limit) up to January 2018 (Figure 1a). From this point onwards the curve has a more horizontal direction between the newly constructed decision limits, indicating an adequate and stable quality throughout 2018 (Figure 1a and 1b).

In only one of the contributing hospitals (hospital D) the KPI of DYM ≥70% is met overall (Table 2). However, the learning curves of the individual hospitals for this parameter develop from an initial downslope (hospitals B and E) or horizontal direction (hospitals C and D) into a horizontal (B, C, and E) or an upslope (hospital D) direction (Figure 2a-3a, supplementary figure 7a-9a). This indicates a gradual improvement in these centers up to an adequate quality level in 2018.

The CUSUM curve of hospital B starts with a downwards slope, in January 2018 the curve suddenly improves to a horizontal slope (Figure 2a and 2b).

The curve of hospital C initially shows a stable and adequate quality up to May 2017. From this point onwards there is a remarkable short and sharp downslope development of the curve, which again develops in a more horizontal direction from September 2017 onwards (Figure 3a and 3b). This indicates a 4 months episode during which a significantly lower number of malignant diagnoses were made. During these 4 months a high proportion of specimens with atypia (40%) was graded in comparison to the episodes prior to May 2017 (4%) and from September 2017 onwards (11%) (Supplementary table 1). The four-month episode coincided with the temporary absence of the most experienced cytopathologist in this center, who had been involved in all cytopathological evaluations of pancreatic lesions in the previous years in this hospital.

Sensitivity for malignancy (SFM) overall and per hospital

The overall SFM for the contributing hospitals throughout the 4 years of this study was 76%, ranging from 68-87% amongst different hospitals. The KPI of SFM ≥85% is not met in 4 out of 5 contributing hospitals. The developments in the learning curves regarding DYM suggest improvement of quality in the majority of these centers. In 2018, the final year of this study, the overall SFM was 85%, ranging from 69-96% amongst the centers. In this year the KPI of SFM ≥85% was met in 3 out of 5 centers (Supplementary table 2).

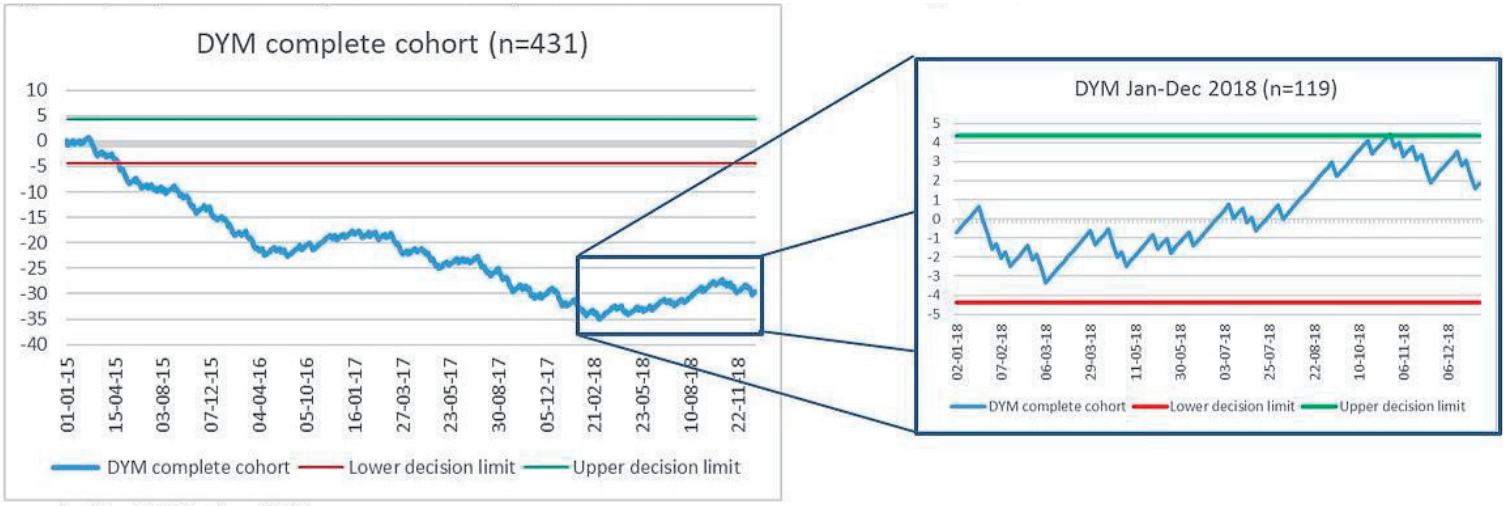
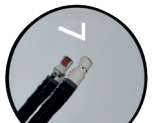


Figure 1a. **DYM** CUSUM learning curve of the complete cohort. Figure 1b.
a: period Jan 2015 – Dec 2018
b: period Jan 2018 – Dec 2018
DYM: diagnostic yield of malignancy



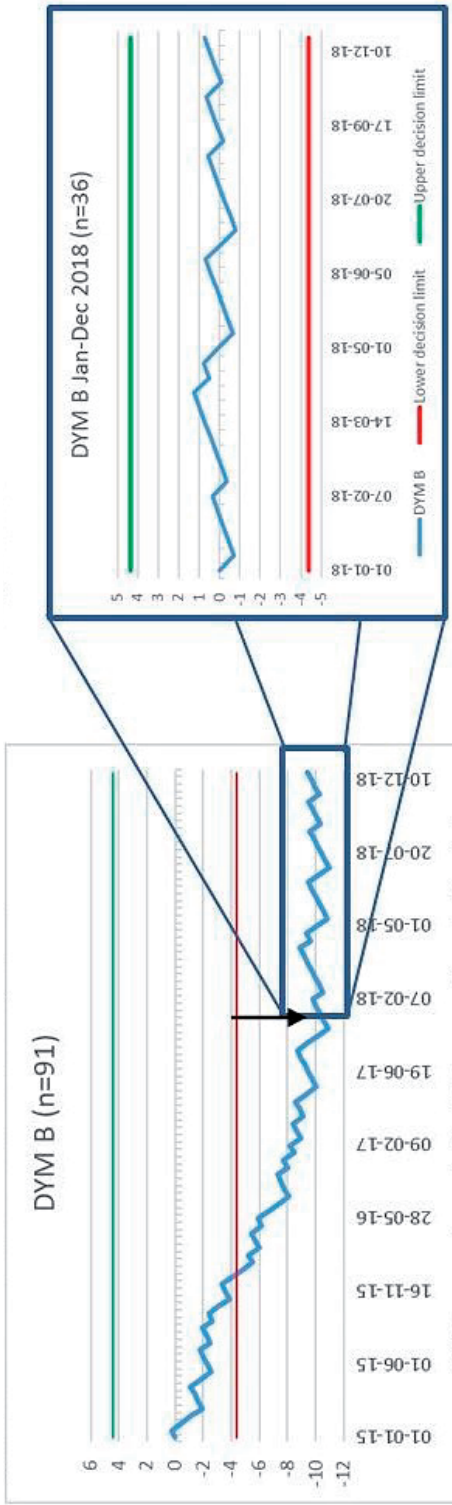


Figure 2a. **DYM** CUSUM curve of hospital B. Figure 2b.
a: period Jan 2015 – Dec 2018
b: period Jan 2018 – Dec 2018
Black arrow marks the decrease in evaluating pathologists from 9 to 3.
DYM: diagnostic yield of malignancy

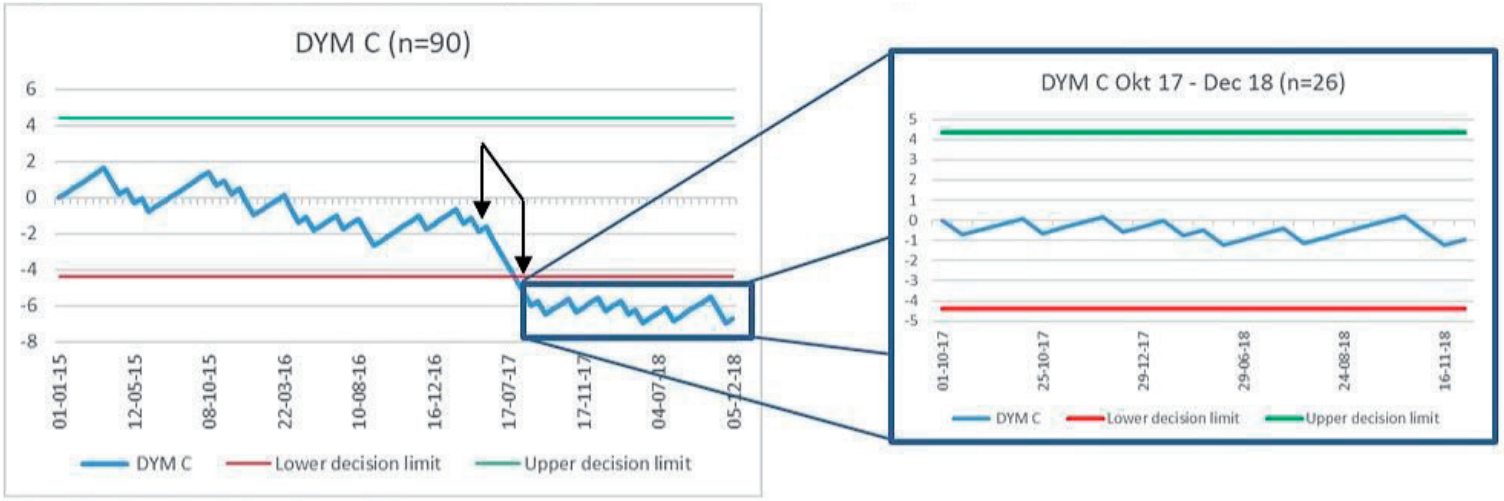


Figure 3a. **DYM** CUSUM curve of hospital C. Figure 3b.
a: period Jan 2015 – Dec 2018
b: period Oct 2017 – Dec 2018
Black arrows mark the temporarily absence of one experienced cytopathologist
DYM: diagnostic yield of malignancy

FNB versus FNA needles

A total of 282 FNA procedures and 127 FNB procedures were performed. Outcome of FNA and FNB procedures was similar (Supplementary table 3). The use of FNB needles did not increase over time.

Multivariable analysis

Nine observations for which all covariates were missing were excluded from the analysis. Missing values in the remaining 422 observations were imputed (missing values: suction type 4.7%, needle brand 2.8%, number of passes 2.1%, needle size 1.7%, needle type 0.9%, ROSE 0.2% and suction 0.2%). The use of any type of suction and the presence of ROSE was positively associated with RAS, with Odds Ratios of 3.2, 95% CI (1.1-7.8) and 2.8, 95% CI (1.1-8.4) respectively (Table 3). There was no clear evidence that any of the co-variates considered was associated with DYM (Table 3).

Feedback and interpretation of curve deflections

During the four years of prospective registration, the following changes were reported by contributing practitioners. Hospital A, D and E requested ROSE on a regular basis which they did not do before. Hospital A started with ROSE halfway 2016, hospital D from January 2018 onwards and hospital E from the beginning of 2016. In hospital B and C there were changes in the number of pathologists involved in EUS-guided TA procedures of the pancreas. In hospital B the group of pathologists that reviewed pancreatic samples collected with EUS was downsized from 8 to 3 in January 2018. The most experienced cytopathologist from hospital C was temporarily absent during a four month period in 2017.

The time that the above described events took place are marked with an arrow in (Figure 2a-3a, supplementary figure 6, 8, 7a-9a).

Discussion

This study evaluated the performance of 5 community hospitals regarding the yield of EUS-guided TA of solid pancreatic lesions using CUSUM curves in order to assess trends in quality over time and explored potential benefits of CUSUM curves as a feedback-tool. Throughout the 4 years of this study all three ASGE defined KPI improved. KPI of RAS ≥85% was met consistently in most of the centers and overall (93%). KPI of DYM ≥70% was not met overall throughout the study episode 2015-2018, but eventually yielded 75% overall in 2018. Similarly the KPI of SFM ≥85% was not met overall from 2015-2018, but improved up to 85% in 2018. Since not all ASGE defined KPI are yet consistently met in each center, feedback on performance and analyses for potential improvements are indicated and ongoing.

Table 3. Odds ratios and corresponding 95% CIs for the logistic mixed models for RAS and DYM.

RAS			DYM		
Covariate	**OR**	**95% CI**	**Covariate**	**OR**	**95% CI**
Use of suction (vacuum and/ or slow-withdrawal of stylet)	3.2	1.1–7.8	**No suction**	0.7	0.3–1.6
ROSE	2.8	1.1–8.4	**Vacuumsuction**	1.1	0.5–2.3
			ROSE	1.5	0.9–2.4
			Number of passes	1	0.8–1.4
			<22G needle (FNA and/or FNB)	1.5	0.4–4.9
			22G needle (FNA and/or FNB)	0.9	0.6–1.5
			FNB	1.1	0.7–2.1

There were missing values in 7 covariates, with a percentage of missing observations per variable ranging from 0% to 5%. These missing observations were imputed during the analysis.
RAS: rate of adequate sample
DYM: diagnostic yield of malignancy
OR: odds ratio
CI: confidence interval
FNA: fine needle aspiration
FNB: fine needle biopsy
ROSE: rapid on-site evaluation

The diagnostic yield of EUS-guided TA in solid pancreatic lesions is considered a benchmark for quality measurements in EUS [1]. However, the majority of studies on which the ASGE defined KPI are based, were performed in tertiary care facilities [21]. Moreover, the majority of publications on EUS-guided TA of solid pancreatic lesions were controlled trials focusing on discrete factors influencing the yield, i.e. different types and diameters of needles, use of suction, the use of rapid on-site cytopathological evaluation (ROSE), or the optimal number of passes to perform [22-34]. Therefore, when comparing the current study to these previous publications, it cannot be ruled out that differences regarding patient selection may have influenced yield of EUS-guided TA. Nevertheless, questioning the generalizability of the benchmark data may never be an excuse to stop monitoring and improving your performance.

To improve quality of EUS-guided TA it is necessary to provide feedback on performance. For providing feedback, CUSUM derived learning curves have several advantages over tables with numbers. First, their interpretation is easy and does not require any knowledge on specific key performance indicator values (a downward trend is not good, a horizontal line is good, and an upward trend is better). Second, they allow determination of best practices and comparison amongst peers. Third, they provide a more detailed picture of development over time, allowing for focused analysis of performance within specific timeframes [35]. The analysis of the sudden downslope deflection in the DYM curve of hospital C, coinciding with the 4 months absence of a senior cytopathologists is an excellent example of this. Analysis

of this specific example teaches us how vulnerable the multi-step process of EUS-guided TA is, being dependent on each factor or operator involved. Therefore, the discriminating advantage of learning curves for feedback over tables with numbers is that they provide additional learning opportunities.

RAS and DYM are obviously related. However, since CUSUM curves of these variables reflect quality relative to a predefined quality target, they do not necessarily develop in the same direction. An upward RAS curve does therefore not mean the DYM curve has to be upward as well. In other words: having a sample that contains at least a couple of cells from the target organ (adequate sample), does not automatically mean that a pathologist will be confident about the malignant origin of the lesion. This can lead to a rate of adequate sample above the performance target and a diagnostic yield of malignancy and sensitivity for malignancy below the performance target.

Supported by feedback provided by CUSUM analyses, several changes regarding protocols and/or staff involved were made in individual hospitals. In hospital C nowadays, a pathology report regarding pancreatic cytology or histopathology can only be finalized after consent of a dedicated cytopathologist. Several hospitals implemented routine use of ROSE and the number of pathologists involved was reduced in one of the centers. Although multivariable analysis supports the use of suction and ROSE to be beneficiary to RAS, an overall positive effect of these changes can be assumed. After all, with a RAS of 85%, the lowest acceptable level according to ASGE definitions, the SFM can never exceed 85%, and makes DYM ≥70% in patients with solid pancreatic lesions difficult to achieve.

To our knowledge this is the largest prospective multicenter study of EUS-guided TA of solid pancreatic lesions from community hospitals and the first to implement CUSUM derived learning curves as a tool for monitoring and improving KPI of these procedures. Previous publications on the use of CUSUM curves in EUS-guided TA investigated performance of either cytopathologists or endoscopy trainees [9-13,16]. In contrast to these studies we used CUSUM curves to evaluate the entire process defining quality and yield of these procedures, including the work of both endosonographers and cytopathologists. A part of the data presented in this study (133 procedures, performed from January 2015 to September 2016) were previously described in the initial publication on this community hospital quality initiative [14]. The current study shows ongoing and persistent improvement in performance and introduces learning curves as a feedback and monitoring tool.

Main limitation of this study is the fact that feedback, either in tables with numbers or as learning curves was not provided real-time. Ideally CUSUM curves would have been drawn 3 times a year, enabling contributing centers to respond more quickly to changes in curve directions. Due to logistic challenges and the time consuming nature of data

collection, this could not be realized in the current study. Another limitation is the fact that in the current study no subtypes of FNB-needles were recorded. Recent publications indicate improved outcome of a subtype of FNB needles over FNA needles [36]. The fact that no difference between FNA and FNB was detected in our study, may be related to the unclear mix of subtypes of FNB needles used. However, other confounders such as the endosonographers learning curve for a new type of needle, or the pathologists learning curve for evaluating tissue cores may have been involved.

Future directions

Performing EUS-guided TA comes with the responsibility to measure KPI regarding these procedures. In order to facilitate this, an automated system is needed allowing EUS-procedural parameters and concomitant pathology reports to be added on regular basis. Subsequently CUSUM curves can be constructed based on KPI data at any point in time, allowing for constant trend analysis thereby providing the fundament for quality improvement. We believe that feedback on KPI is an essential first step for quality improvement. If KPI are not up to par this should be followed by a cycle of protocol changes, continued KPI measurements and evaluations (Plan-do-check-act cycle), aiming for continuous improvement of quality and life-long learning opportunities for all collaborators.

Changes of protocol are to be tailored center specific depending on KPI measurements and available resources. A measure aiming to increase a low adequate sample rate in a center using 22G FNA needles, 3 passes and suction, for example could be: 1. the introduction of ROSE or 2. the introduction of an FNB needle. If the hospital involved does not have its own cytopathology lab, implementation of FNB needles could solve their problem. A measure aiming to increase DYM, with current adequate RAS and high proportions of atypia diagnoses, might for example be: 1. to reorganize the workflow in the pathology lab to have all samples evaluated by two cytopathologists instead of seven, 2. to introduce liquid based cytology instead of smears only, or 3. to introduce the use of FNB needles. There is evidence to support that changes made "bottom-up" are more likely to sustain in comparison to changes implemented "top-down" [37]

In conclusion, this prospective multicenter study using CUSUM derived learning curves for both quality monitoring and feedback, demonstrates consistent improvement of KPIs RAS, DYM and SFM over time. It illustrates the benefits of using learning curves with easy to interpret feedback regarding performance of a whole process or its individual components while also allowing comparison with peers. Use of CUSUM curves is an excellent way for responsible staff to monitor and scrutinize their performance and improve the outcome of key performance indicators up to the desired level.

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Supplementary table 1. RAS, rate of atypia, DYM and SFM before, during and after a period of absence of a senior pathologist in hospital C.

Period	RAS	Rate of atypia	DYM	SFM
Before 12-05-2017 (n=53)	51 (96%)	2 (4%)	38 (72%)	81%
Between 12-05-2017 and 12-09-2017 (n=10)	10 (100%)	4 (40%)	2 (20%)	40%
After 12-09-2017 (n=27)	26 (96%)	3 (11%)	19 (70%)	83%

RAS: rate of adequate sample
DYM: diagnostic yield of malignancy
SFM: sensitivity for malignancy

Supplementary table 2. RAS, DYM en SFM per year, per hospital

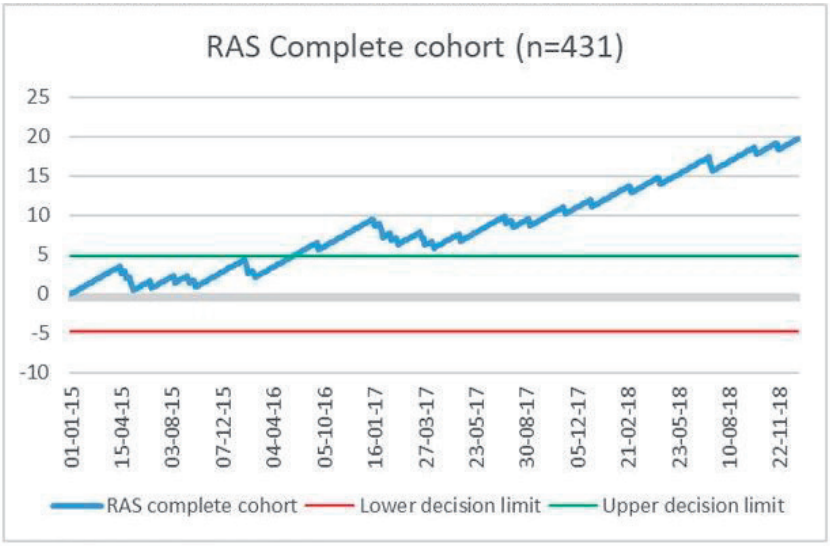
Period	2015–2018				2015				2016				2017				2018			
Hospital	**Number of procedures**	**RAS**	**DYM**	**SFM**	**Number of procedures**	**RAS**	**DYM**	**SFM**	**Number of procedures**	**RAS**	**DYM**	**SFM**	**Number of procedures**	**RAS**	**DYM**	**SFM**	**Number of procedures**	**RAS**	**DYM**	**SFM**
A	87	*75 (86%)*	53 (61%)	68%	23	*20 (87%)*	12 (52%)	55%	8	*8 (100%)*	*7 (88%)*	*88%*	39	*33 (85%)*	23 (59%)	70%	17	14 (82%)	11 (65%)	69%
B	91	*82 (90%)*	57 (63%)	71%	24	*33 (96%)*	12 (50%)	52%	13	*11 (85%)*	7 (54%)	64%	18	14 (78%)	11 (61%)	73%	36	*34 (94%)*	*27 (75%)*	*87%*
C	90	*87 (97%)*	59 (66%)	79%	24	*23 (96%)*	*18 (75%)*	*90%*	27	*26 (96%)*	18 (67%)	72%	23	*23 (100%)*	12 (52%)	75%	16	*15 (94%)*	11 (69%)	79%
D	100	*99 (99%)*	*75 (75%)*	*87%*	18	*18 (100%)*	*13 (72%)*	*87%*	18	*18 (100%)*	12 (67%)	80%	34	*33 (97%)*	*25 (74%)*	83%	30	*30 (100%)*	*25 (83%)*	*96%*
E	63	*56 (89%)*	41 (65%)	73%	9	6 (67%)	1 (11%)	20%	12	*11 (92%)*	*10 (83%)*	83%	22	*19 (86%)*	15 (68%)	71%	20	*20 (100%)*	*15 (75%)*	83%
Total cohort	431	*399 (93%)*	285 (66%)	76%	98	*90 (92%)*	56 (57%)	66%	78	*74 (95%)*	54 (69%)	76%	136	*122 (90%)*	86 (63%)	75%	119	*113 (95%)*	*89 (75%)*	*85%*

Italics and underlined: equal or above ASGE performance target.
RAS: rate of adequate sample
DYM: diagnostic yield of malignancy
SFM: sensitivity for malignancy

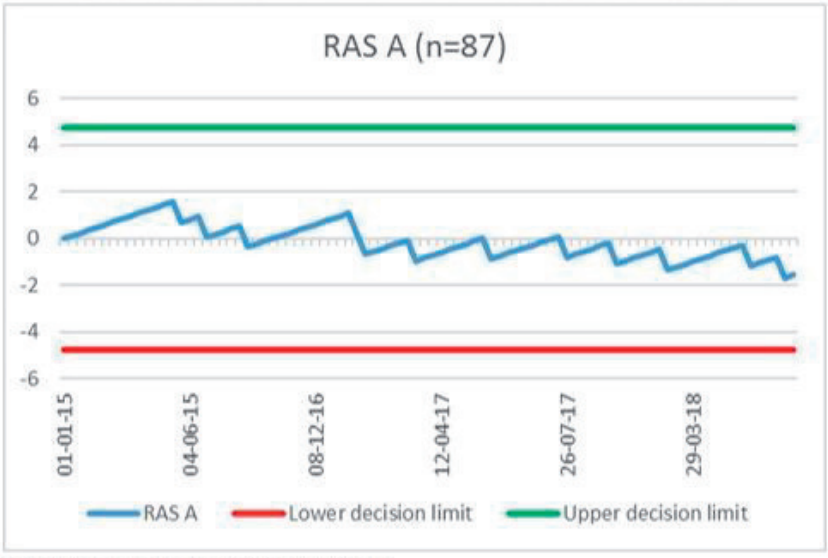
Supplementary table 3. Key performance indicators for both FNA and FNB.

	Total				2015				2016				2017				2018			
Needle type	**Number of procedures**	**RAS**	**DYM**	**SFM**	**Number of procedures**	**RAS**	**DYM**	**SFM**	**Number of procedures**	**RAS**	**DYM**	**SFM**	**Number of procedures**	**RAS**	**DYM**	**SFM**	**Number of procedures**	**RAS**	**DYM**	**SFM**
FNA	**282**	**93%**	**67%**	**75%**	57	95%	58%	60%	50	96%	72%	80%	93	87%	62%	73%	82	95%	74%	86%
FNB	**127**	**95%**	**69%**	**82%**	26	92%	73%	95%	27	96%	67%	72%	39	95%	62%	77%	35	94%	77%	84%

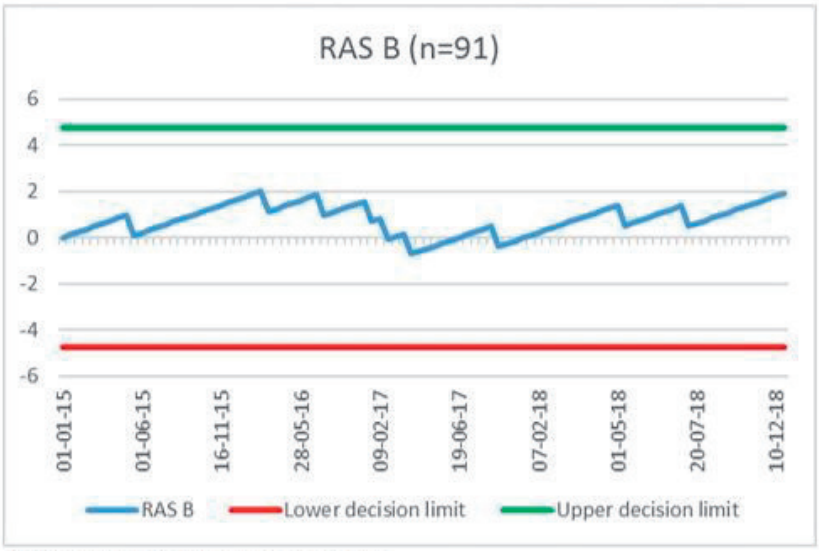
RAS: rate of adequate sample
DYM: diagnostic yield of malignancy
SFM: sensitivity for malignancy
FNA: fine needle aspiration
FNB: fine needle biopsy



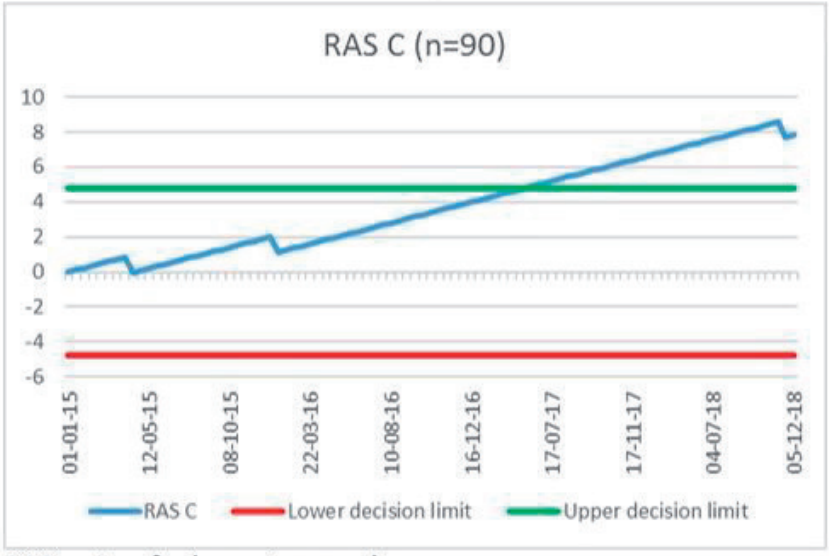
Supplementary figure 1. **RAS** CUSUM learning curve of the complete cohort.
RAS: rate of adequate sample



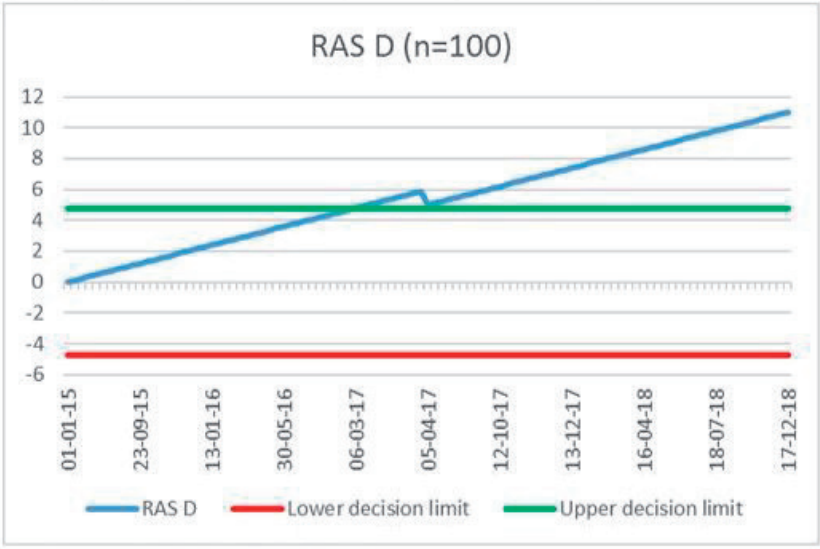
Supplementary figure 2. **RAS** CUSUM curve of hospital A.
RAS: rate of adequate sample



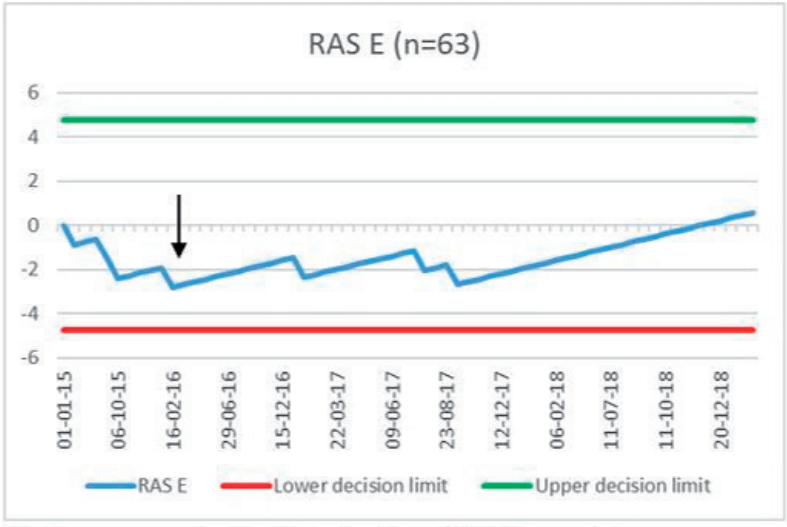
Supplementary figure 3. **RAS** CUSUM curve of hospital B.
RAS: rate of adequate sample



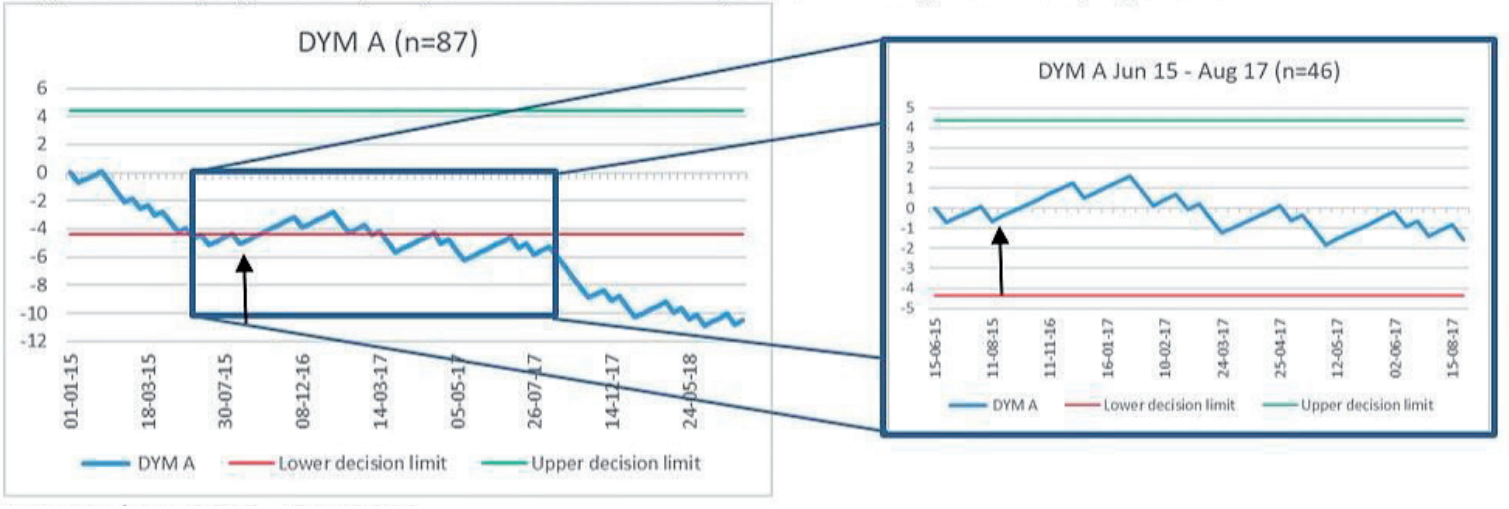
Supplementary figure 4. **RAS** CUSUM curve of hospital C.
RAS: rate of adequate sample



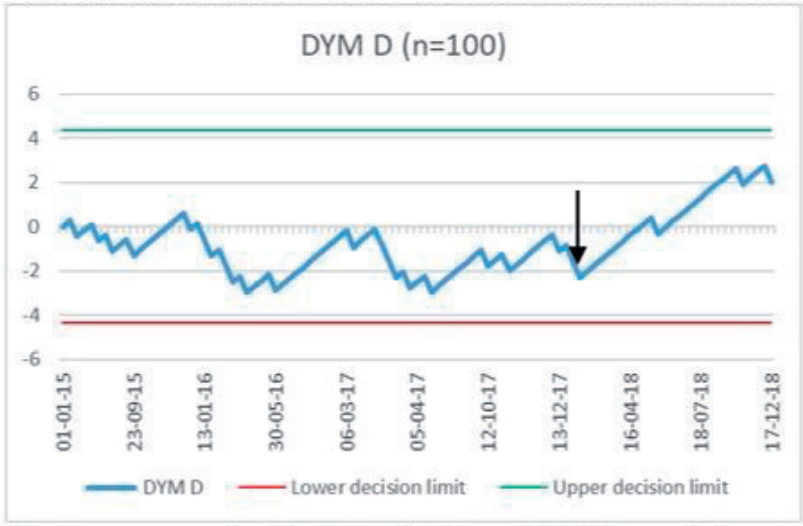
Supplementary figure 5. **RAS** CUSUM curve of hospital D.
RAS: rate of adequate sample



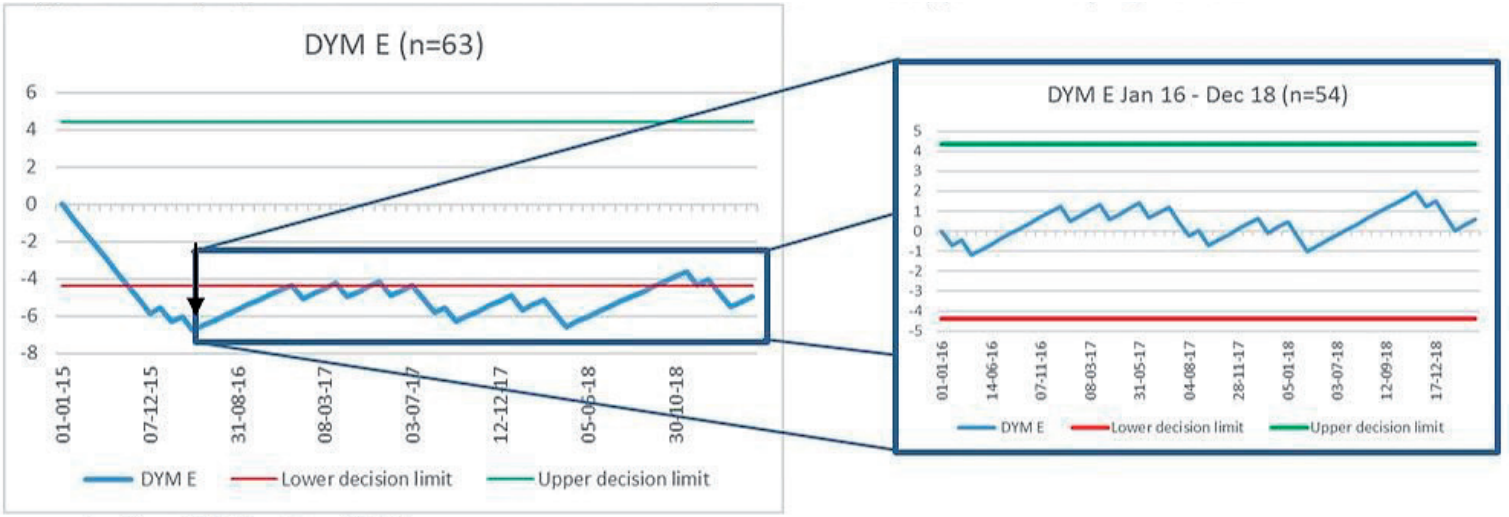
Supplementary figure 6. **RAS** CUSUM curve of hospital E.
Black arrow marks the introduction of ROSE regularly.
RAS: rate of adequate sample



Supplementary figure 7a+b. **DYM** CUSUM curve of hospital A.
a: period Jan 2015 – Dec 2018
b: period June 2015 – Aug 2017
Black arrow marks the introduction of ROSE regularly.
DYM: diagnostic yield of malignancy



Supplementary figure 8. **DYM** CUSUM curve of hospital D.
Black arrow marks the introduction of ROSE regularly.
DYM: diagnostic yield of malignancy

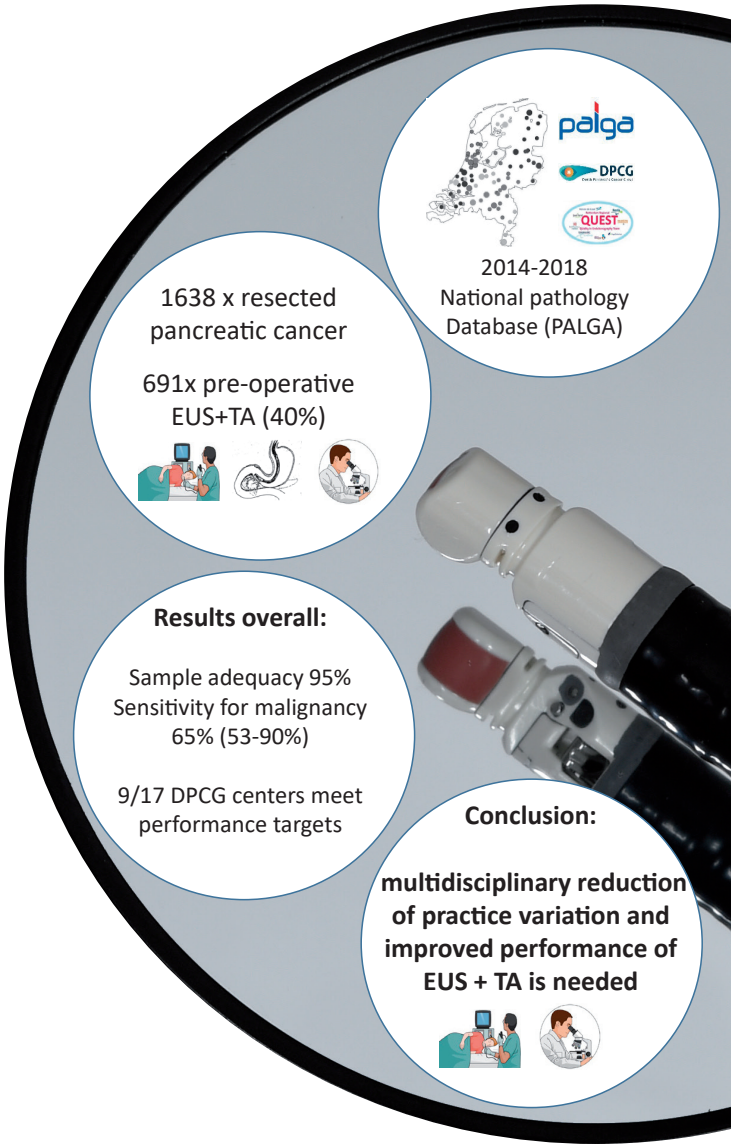


Supplementary figure 9a+b. **DYM** CUSUM curve of hospital E.
a: period Jan 2015 – Dec 2018
b: period Jan 2016 – Dec 2018
Black arrow marks the introduction of ROSE regularly
DYM: diagnostic yield of malignancy


7

8

CHAPTER 8


palga
DPCG
QUEST
2014-2018
National pathology
Database (PALGA)
1638 x resected
pancreatic cancer
691x pre-operative
EUS+TA (40%)
Results overall:
Sample adequacy 95%
Sensitivity for malignancy
65% (53-90%)
9/17 DPCG centers meet
performance targets
Conclusion:
multidisciplinary reduction
of practice variation and
improved performance of
EUS + TA is needed

Nationwide analysis of diagnostic accuracy of EUS-guided tissue acquisition prior to resection of pancreatic carcinoma

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Submitted for publication

Abstract

Introduction

Endoscopic ultrasonography guided tissue acquisition (EUS+TA) plays a central role in establishing a tissue diagnosis in patients with suspected pancreatic ductal adenocarcinoma (pancreatic carcinoma). The American Society of Gastrointestinal Endoscopy (ASGE) defined rate of adequate sample (RAS) and sensitivity for malignancy (SFM) as key performance indicators (KPI) of EUS+TA of these lesions. The existence of practice variation regarding KPI may indicate that improvement is required. This study aimed to assess practice variation regarding KPI of first EUS+TA procedures in patients who underwent a resection for pancreatic carcinoma in the Netherlands.

Patients and Methods

Data from all pancreatic resections for pancreatic carcinoma from 2014-2018, including results of all EUS+TA prior to surgery, were extracted from the national Dutch Pathology Registry (PALGA). Cyto-and histopathology reports were classified as: insufficient for analysis (b1), benign (b2), atypia (b3), neoplastic other (b4), suspected malignant (b5), and malignant (b6). RAS was defined as the proportion of EUS procedures yielding specimen sufficient for analysis. SFM was calculated using a strict definition (malignant only, SFM-b6), and a broader definition (SFM-b5+6).

Results

Of 1638 patients who had a resection for pancreatic carcinoma, 691 patients (42%) underwent preoperative EUS+TA. For the first EUS procedure, the RAS was 95% (range 89-100%), SFM-b6 was 44% (20-77%), and SFM-b5+6 was 65% (53-90%). All centres met the performance target RAS>85%. Only 9/17 centres met the performance target SFM-b5+6>85%.

Conclusion

This nationwide study detected significant practice variation regarding KPI of first EUS+TA procedures prior to surgical resection of pancreatic carcinoma. Therefore, multidisciplinary quality improvement of EUS+TA in these patients is indicated.

Key words: practice variation; EUS; diagnostic accuracy; pancreatic cancer.

Introduction

Pancreatic cancer is the most lethal malignancy of the gastrointestinal tract. Approximately 2500 patients are newly diagnosed with pancreatic cancer in the Netherlands annually, of whom 78% die within the first year following diagnosis [1]. Pancreatic ductal adenocarcinoma (pancreatic carcinoma) is the most common malignancy of the pancreas and periampullary region [2 3].

EUS-guided tissue acquisition (EUS+TA) plays a central role in establishing a tissue diagnosis in suspected solid pancreatic malignancies [4]. EUS+TA is a complex multistep procedure, involving endosonographers, pathologists and their teams. Multiple equipment and operator variables may influence the outcome of these procedures [5] .

The current national Dutch guideline on diagnosis and treatment of pancreatic malignancies recommends EUS+TA only in cases without a clear mass detected on cross sectional imaging to differentiate malignant from benign lesions [6]. Emerging neoadjuvant treatment protocols for pancreatic carcinoma however, demand a tissue diagnosis prior to the start of therapy [7 8]. Future developments regarding targeted therapy are expected to increase the demand for both a "first-time right" tissue diagnosis and for procurement of sufficient amounts of tissue to facilitate molecular analysis [9-11].

In 2015, the American Society of Gastrointestinal Endoscopy (ASGE) defined key performance indicators (KPI) of EUS+TA of solid pancreatic lesions [4]. These include rate of adequate sample (RAS), diagnostic yield of malignancy (DYM) and sensitivity for malignancy (SFM). The performance targets for these KPIs are RAS>85%, DYM>70%, and SFM>85%. These are based on a meta-analysis by Hewitt et al., in which EUS-guided fine needle aspiration (FNA) of solid pancreatic lesions of 4984 patients from 34 studies were analyzed [12]. Although recent controlled trials from tertiary care facilities have indicated a benefit of a subtype of Fine Needle Biopsy (FNB) needles over FNA techniques, this has not led to changes in the performance targets as defined[13-15].

In Hewitt's meta-analysis a wide range of SFM from 50-100% across studies is described. In our prospective study of EUS+TA of solid pancreatic lesions conducted in 4 community hospitals in the Netherlands, RAS ranged from 83-100% and SFM ranged from 62-92% [16]. It is unknown whether these observations can be extrapolated to the nationwide practice of EUS+TA procedures in patients with suspected solid pancreatic malignancies.

Retrospective data collection nationwide is impracticable due to current privacy legislation. Moreover, collecting data from case records is very time consuming and notorious for "missing data", potentially limiting the generalizability of the data collected.

The Dutch Pathology Registry (PALGA) is a nationwide network and automated registry of histo- and cytopathology in the Netherlands [17]. It contains all consecutive reports of cyto- and histopathology evaluations performed in the Netherlands since 1991. Pancreatic surgery in the Netherlands is performed in 17 designated pancreatic surgery centres, collaborating in the Dutch Pancreatic Cancer Group (DPCG). EUS+TA procedures are performed in at least 34 hospitals, designated pancreatic surgery centres included.

Feedback on KPI measurements allows clinicians to calibrate their perception of the quality delivered to their actual performance, and is a necessary first step for quality improvement. Practice variation regarding KPI may indicate that improvement is required [18 19].

The aim of the present study is to assess practice variation regarding performance (KPI) of EUS+TA in resected pancreatic carcinoma in the Netherlands.

Patients and methods

This is a retrospective observational study evaluating KPI of first EUS+TA procedures in all consecutive patients who underwent a surgical resection for pancreatic carcinoma from 2014-2018 in the Netherlands. The study protocol was approved by the local medical ethics committee (METC Leiden, Den Haag, and Delft. G20.066). This manuscript was prepared using the "strengthening the reporting of observational studies" (STROBE) and "the reporting of studies conducted using observational routinely-collected health data" (RECORD) checklists. All authors had access to the study data and have reviewed and approved the final manuscript.

Selection of study population

Data on all surgical resections of pancreatic tissue, including results of all cytology and histology acquired prior to surgery, were extracted from the Dutch Pathology Registry (PALGA) in March 2020. Patients with pancreatic resections performed in centres with less than 20 pancreatic resections annually, were all without any preoperative tissue analysis and were excluded from analysis (Figure 1).

Cases were categorized according to the pathology report of the resected specimen. Patients with distal cholangiocarcinoma, periampullary carcinoma, other malignancies, as well as benign diagnoses were excluded aiming to eliminate selection-bias due to case-mix differences across centres (Supplemental figure 1).

Reports of cyto- and histopathological specimen acquired by EUS+TA prior to resection were selected. Reports of other tissue acquisition procedures were excluded. Based on

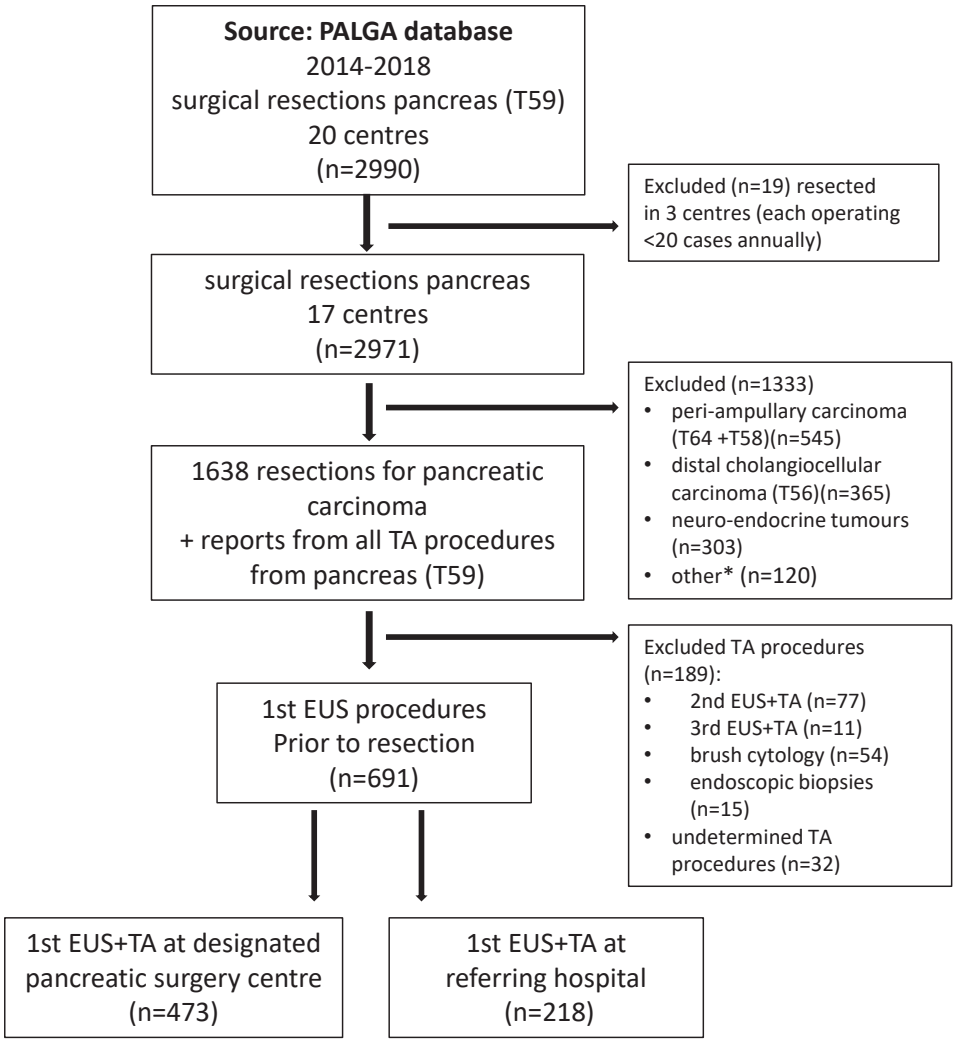

Figure 1. Selection of study population.

dates of the performed EUS+TA procedures, these were classified as 1st, 2nd and 3rd EUS+TA procedures. Only 1st EUS+TA procedures were assessed.

Cyto-and histopathology reports of EUS+TA procedures were evaluated and categorized into one of six categories as follows: insufficient for analysis (b1), benign (b2), atypia (b3), neoplastic other (b4), suspicious for malignancy (b5), and malignant (b6) based on the proposed standard for evaluating pancreatic cytology by the Papanicolaou Society of Cytopathology (Supplementary figure 1) [20]. In case of mixed terminology in a cyto-, and histopathology report, cases were categorized using the description closest to malignancy.

For example, if a report mentioned "atypical cells suspected for adenocarcinoma", the case would be classified as "suspicious for malignancy (b5)" instead of "atypia (b3)".

Outcome parameters

Primary outcome parameters were: 1. RAS, defined as proportion of procedures yielding specimen sufficient for cyto-and/or histopathological analysis, and 2. SFM, defined as proportion of patients with a malignant diagnosis at EUS+TA. Since the dataset did not contain any false positives or true negatives, SFM is equal to both the proportion of malignant diagnoses established at EUS+TA, and the proportion of correct diagnoses. Therefore SFM in this study is equal to both diagnostic yield of malignancy and diagnostic accuracy.

Secondary outcome parameters were: 1. rate of atypia (ROA) defined as the proportion of EUS+TA procedures yielding atypia at pathological evaluation, and 2. proportion of patients who underwent EUS+TA prior to surgical resection of pancreatic carcinoma.

RAS, SFM, and ROA were calculated overall and per designated pancreatic surgery centre. SFM was calculated using a strict definition, based on definite malignant only (b6), as well as a broader definition also including suspicious for malignancy (b5+6).

First EUS+TA procedures were classified as either performed at a referring hospital or at a designated pancreatic surgery centre. Second and third EUS+TA procedures were not included in the analysis of KPI. Data on specific referring hospitals were not available for analysis.

Statistical analysis

Baseline characteristics of the patient population, use and outcome of EUS+TA (RAS, SFM, and ROA) are presented as median and range for continuous variables, and as counts with percentages for categorical variables. Point estimates are presented with 95% confidence intervals (CIs). To investigate differences in performance and associations with patient and hospital characteristics, while taking into account that observations from the same centre may not be independent, we fitted a number of logistic mixed models with a centre-specific (random) intercept.

The between-centre variation of performance of procedures, and proportion of EUS+TA performed, were analyzed using likelihood ratio tests to test if the estimated variance of the random intercept (from models without covariates) was larger than zero. This was repeated in the two subsets containing patients with their first EUS+TA procedure at a designated centre and those with their first EUS+TA procedure in a referring hospital. Additionally, a

comparison of performance between these subsets was made, by including an indicator variable identifying the two groups (as only covariate) in the model.

The performance of procedures performed at designated pancreatic surgery centres was visualized by plotting the centre-specific measures and corresponding 95% CIs (Wilson score intervals). A funnel plot was created to visualize the centres' performance with regards to SFM-b5+6 in comparison to the ASGE-defined performance target: SFM>85%.

To gain insight into differences between designated pancreatic surgery centres meeting the performance target SFM>85% ("best practices") and centres who did not ("other practices"), we fitted logistic mixed models for the other performance measures (proportion of EUS+TA performed, RAS, SFM-b6, ROA) with an indicator for "other practices" as covariate.

Results

A total of 1638 consecutive patients underwent a surgical resection for pancreatic carcinoma from 2014-2018. Median age was 67 (19-87) years and 741 (45%) patients were female. Median number of resections per centre for pancreatic carcinoma during the study episode was 94, ranging from 56 to 168. A total of 779 EUS+TA procedures were performed prior to resection in 691 patients, of whom 77 (11%) underwent a second, and 11(1.5%) underwent a third EUS procedure (Figure 1, Table 1).

The proportion of patients who underwent EUS+TA prior to surgery was 42%, varying from 17% to 66% across the designated pancreatic surgery centres. Overall, RAS was 95% (89-100%), SFM-b6 was 44% (20-77%), SFM-b5+6 was 65% (53-90%), and ROA was 11% (3-27%). Practice variation for both SFM-b6, and SFM-b5+6 was statistically significant ($p<0.01$) (Table 2).

EUS+TA at designated pancreatic surgery centres versus referring hospitals

Out of all patients, 1393 (85%) underwent their diagnostic work-up at one of the 17 designated pancreatic surgery centres, and 244 patients (15%) were referred from other hospitals.

A first EUS+TA procedure was performed in 473 (34%) of the patients diagnosed at a designated pancreatic surgery centre, and prior to transfer in a referral hospital in 218 (89%) of patients (OR 15.7, 95%CI [10, 24], $p<0.001$).

Table 1. Baseline characteristics, EUS+TA procedures prior to surgical resection for pancreatic carcinoma 2014-2018.

Resections nationwide	n	1638
Resections per centre	median[range]	94 [56-168]
Age, years	median[range]	67 [19-87]
Female	n (%)	741 (45)
1st EUS+TA procedure	n (%)	691 (42)
2nd EUS+TA procedures	n (%)	77 (11)
3rd EUS+TA procedures	n (%)	11 (1.5)
Total EUS+TA procedures	n	779

EUS+TA: endoscopic ultrasonography guided tissue acquisition

Table 2. Performance indicators of all first EUS+TA procedures (n=691).

Variable	**Median %**	**[range %]**	**Variance**	**p-value**
RAS	95	89- 100	0.05	0.40
SFM-b6	44	20- 77	0.16	<0.01
SFM-b5+6	65	53- 90	0.15	<0.01
ROA	11	3- 27	0.08	0.18
Proportion EUS*	40	17- 66	0.23	<0.01

* in contrast to median proportion presented here, the mean proportion EUS of 42% was presented in the text.
RAS: Rate of adequate sample
SFM-b6: sensitivity for malignancy definite malignancies only (strict definition)
SFM-b5+6: sensitivity for malignancy including suspected malignancy (broad definition)
ROA: Rate of atypia
Proportion EUS: the proportion of patients that underwent EUS+TA prior to surgery

RAS was 100% (80-100%) in referring hospitals, and 97% (89-100%) in designated centres. ROA was 9% (0-27%) in referring hospitals and 11% (0-27%) in designated centres. RAS and ROA are similar between referring hospitals and designated centres, whereas SFM-b5+6 was lower in referring hospitals (OR 0.7, 95%CI [0.50, 0.97], p=0.03) (Table 3).

Practice variation amongst designated pancreatic surgery centres

RAS of EUS+TA performed in the 17 designated centres was 97%, ranging from 89-100% (Figure 2a). SFM-b6 was 50% ranging from 23-92% (Figure 2b). SFM-b5+6 was 75% ranging from 46-100% (Figure 2c), and ROA was 11% ranging from 0-27% (Figure 2d).

The performance target RAS>85% was met in all centres, whereas, the performance target SFM>85% was only met in nine out of 17 centres (53%), when the broad definition for SFM (SFM-b5+6) was used (Figure 3). These nine centres were therefore qualified as best-practices. This did not seem to be related to number of EUS+TA procedures performed per centre (Figure 3).

Table 3: Comparison of performance indicators of EUS+TA in designated pancreatic surgery centres versus referring hospitals.

	1st EUS+TA in designated centre (n=1394)		1st EUS+TA in referring hospital (n=244)*				
Variable	median %	[range %]	median %	[range %]	OR	95% CI	p-value
RAS	97	89- 100	100	80- 100	0.9	[0.43, 1.79]	0.71
SFM-b6	50	23- 92	47	0- 71	0.8	[0.59, 1.09]	0.16
SFM-b5+6	75	46- 100	65	30- 91	0.7	[0.50, 0.97]	0.03
ROA	11	0- 27	9	0- 27	0.9	[0.57, 1.54]	0.81
Proportion EUS**	33	9- 66	91	67- 100	15.7	[10, 24]	<0.001

* presented data reflect all patients referred to a designated pancreatic surgery centre following an EUS+TA procedure at one of the referring centres in the region of a specific designated pancreatic surgery centre.
** in contrast to median proportion presented here, the mean proportions EUS+TA were presented in the text.
RAS: Rate of adequate sample
SFM-b6: sensitivity for malignancy definite malignancies only (strict definition)
SFM-b5+6: sensitivity for malignancy including suspected malignancy (broad definition)
ROA: Rate of atypia
Proportion EUS: the proportion of patients that underwent EUS+TA prior to surgery

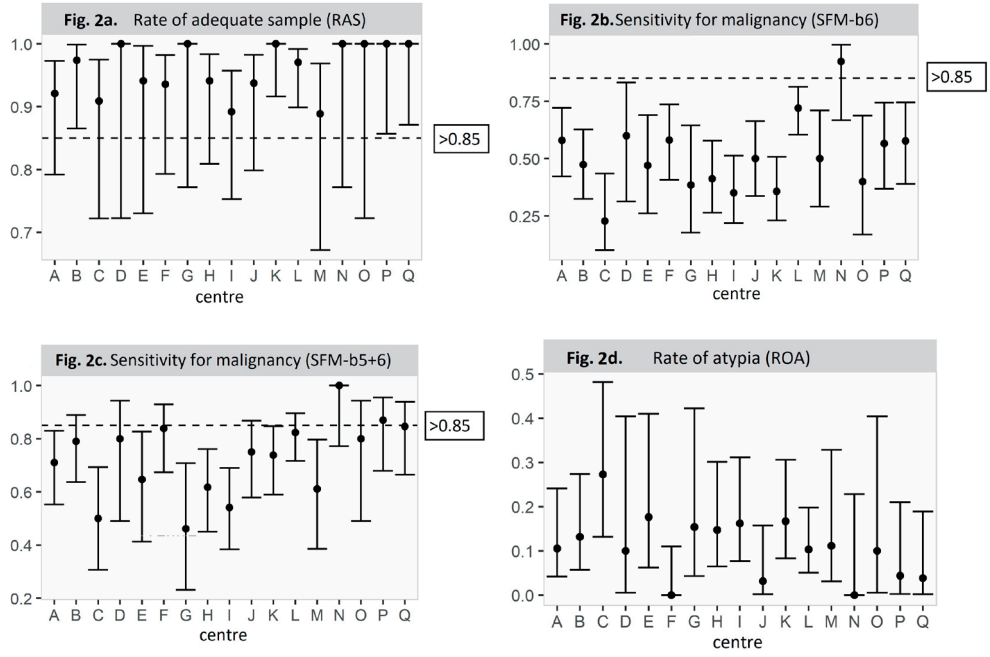

Figure 2. Performance indicators of EUS+TA per centre.
X-axis: Centres A-Q.
Y-axis: value and 95% confidence intervals of rate of adequate sample (RAS) per designated pancreatic surgery centre.
------: ASGE-defined performance target: RAS>85% (in figure 2a) or SFM>85% (in figures 2b and c).

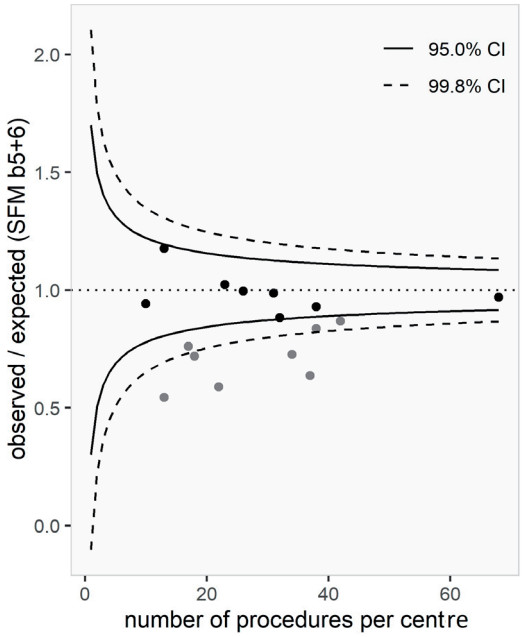

Figure 3. Funnel plot of SFM-b5+6 and number of EUS+TA procedures per centre.
Black dots: best practices, meeting performance target SFM-b5+6 >85%.
Centres D and O are projected as one black dot with both 10 EUS+TA procedures and SFM-b5+6 80%.
Grey-dots: other centres, not meeting performance target.

Table 4. Comparison of performance indicators for first EUS between best practices* with the other designated pancreatic surgery centres.

	Best practices* (B,D,F,J,L,N,O,P,Q)		**Other centres** (A,C,E,G,H,I,K,M)		**Comparison**		
Variable	median %	[range %]	median %	[range %]	OR	95% CI	p-value
RAS	100	94- 100	93	89- 100	0.87	[0.43, 1.79]	0.71
SFM-b6	58	40- 92	40	23- 58	2.10	[1.37, 3.23]	<0.01
ROA	4	0- 13	16	11- 27	0.38	[0.21, 0.70]	<0.01
Proportion EUS**	33	9- 66	35	17- 45	1.06	[0.66, 1.69]	0.83

* Best practices: pancreatic surgery centres with SFMb5+6 meeting the ASGE-defined quality benchmark SFM>85% as demonstrated in figure 2c (black dots).
RAS: Rate of adequate sample
SFM-b6: sensitivity for malignancy definite malignancies only (strict definition)
ROA: Rate of atypia
Proportion EUS: the proportion of patients that underwent EUS+TA prior to surgery

Characteristics of best-practice designated pancreatic surgery centres

In the nine best-practices, RAS was 100% (94-100%), SFM-b6 was 58% (40-92%), and ROA was 4% (0-13%). In the other centres RAS was 93% (89-100%), SFM-b6 was 40% (23-58%), and ROA was 16% (11-27%). When comparing the nine best practices to the remaining eight centres, SFM-b6 was higher (OR 2.10, 95% CI [1.36, 3.23], p<0.01), and ROA was lower (OR 0.38, 95%CI [0.21, 0.70], p<0.01) (Table 4). Both the volume of pancreatic resections, the volume of EUS+TA procedures, and the proportion of EUS+TA procedures performed per centre were unrelated to RAS, SFM-b6, SFM-b5+6, or ROA, with ORs ranging from 0.99 to 1.00 and p>0.1 (Supplementary Table 1).

Discussion

This retrospective observational study of nationwide performance of EUS+TA prior to resection of pancreatic carcinoma in the Netherlands 2014-2018, showed significant practice variation regarding key performance indicators amongst the centres. While the predefined performance target of RAS > 85% was met in all centres, the predefined performance target of SFM > 85% was met in only nine out of 17 designated pancreatic surgery centres. Secondary outcome parameters ROA and proportion of patients undergoing EUS+TA prior to resection of pancreatic carcinoma also varied considerably between the centres. Performance of EUS+TA across designated pancreatic surgery centres appears unrelated to volume of pancreatic resections, volume of EUS+TA procedures performed, and proportion of EUS+TA performed.

The overall proportion of patients in which EUS+TA was performed was 42%, and ranged from 17% to 66% across designated pancreatic surgery centres. Comparing designated centres to referring hospitals EUS+TA procedures were performed in 34% vs 89% of patients. This practice variation regarding use of EUS+TA may reflect differences in perception regarding the necessity of establishing a tissue diagnosis prior to treatment, in local protocols and in trial participation.

Practice variation is a common phenomenon when analyzing results of pancreatic cancer care delivered in different hospitals across nations[1 21 22]. Significant practice variation regarding performance of EUS+TA was described in several previous publications[12 16 23]. Practice variation regarding key performance indicators of EUS+TA is the most important finding of this study, since these performance indicators are inversely related to patient burden. The overall SFM (b5+6) of 65% ranging from 53% to 90% means that for an individual patient in some centres there is a chance of almost 50% that an EUS+TA procedure will not lead to a diagnosis, meaning a 50% chance of the additional burden of an extra procedure, potentially delaying the start of treatment.

To our knowledge, this is the first nationwide analysis of the use and quality of EUS+TA of pancreatic carcinoma or of any other specific target lesion. A limited number of previous publications on outcome of EUS+TA have used histology of resected pancreatic tissue as a gold standard. In a meta-analysis published by Hebert-Magee et al., these studies had a lower SFM in comparison to studies with combined gold standards for a malignant diagnosed (i.e. histology and/or follow-up), 72.7% versus 89.1% respectively [23]. However, these studies were performed up to 20 years ago, had relatively small sample size, and did not report on pancreatic carcinoma only [24-26].

Comparing studies with combined endpoints including follow-up, to studies with histology as gold standard for a malignant diagnosis, it can be assumed that the latter group comprises smaller masses. SFM of EUS+TA is known to be lower when smaller masses are sampled [27-29]. This may partially explain the relatively low SFM described in this study.

The current Dutch guideline, advising to perform EUS+TA only in cases without a discernable mass on cross sectional imaging, may have additionally led to a selection of smaller tumors in which EUS+TA was performed in this study. This may have had a negative impact on the SFM perceived as well.

The comparison of "best-practice" pancreatic surgery centres to the other pancreatic surgery centres clearly indicates that efforts are needed in both endoscopy suites and the histo-, and cytopathology laboratories. The RAS of first EUS-TA procedures in ''best-practice" pancreatic surgery centres ranged from 97%-100%. In comparison, the RAS in the other pancreatic surgery centres had a wider range of 89%-100%. Although these differences were not statistically significant, they do suggest that improving sample adequacy should be the focus of attention of endosonographers and their teams. Similarly, the ROA in the "best practices" was 4% (range 0-13%) in comparison to 16% (range 11-27%) in the other centres, highlighting significant practice variation amongst pathology laboratories of these expert centres, deserving attention.

A meta-analysis of atypical cytology cases of EUS-FNA of solid pancreatic lesions reported on 3566 patients from 23 studies, in which the mean rate of atypia was 5.3%, ranging from 1-14%, with a 95%CI from 4.1-6.9% [30]. The authors suggest consensus on diagnostic categories of pancreatic cytology and feedback on performance of pathology laboratories for future directions, since previous studies have proven to reduce the proportion of atypia diagnosis in thyroid cytology with 70% [31]. Considering the increased use of FNB needles in EUS+TA, of which the outcome is usually considered as histology, there is a demand for standardization and guidelines for EUS+TA (both FNA and FNB) including subsequent tissue analysis of solid pancreatic lesions.

Performing EUS+TA comes with the responsibility to measure KPIs. Feedback on performance is key in order to improve quality [5 18 19 32 33]. Without feedback it is impossible to know whether action is required to improve outcome, or whether a certain change has influenced quality. Examples of such changes are: the implementation of a new type of needle, or the retirement of the local expert cytopathologist. The first step should be to measure performance (KPI). If this is not up to the desired level, scrutinize your protocols regarding patient selection, guideline adherence, and number and experience of practitioners involved. Next, plan and adapt protocols, and keep monitoring. The implementation of this simple concept (plan-do-check-act) amongst collaborating Dutch community hospitals in the Rotterdam region, proved improvement of RAS from 80% to 95%, and of SFM from 63% to 84%[16].

Strengths of this study are that it comprises a national dataset of consecutive patients that underwent resection for pancreatic carcinoma in the years 2014-2018, and therefore likely includes all operators and centres in which EUS+TA procedures in these patients are performed.

Limitations of this study are the lack of clinical data, including the specific indication for performing EUS+TA procedures in these patients, and whether or not patients participated in trials. The indication for EUS+TA is important, since it may have led to variation in dedication and perseverance of endosonographers involved. For example, in a resectable case with biliary obstruction due to a non-discernable mass on CT, EUS+TA is performed as advised in the current Dutch guideline. In such a case resection is likely to be performed anyway, since the chance that outcome of EUS+TA will lead to alternative treatment is limited. When compared to a case in which a tissue diagnosis is mandatory prior to start of neoadjuvant treatment, one can imagine why endosonographers in the latter situation may have been more motivated to perform an extra pass, use a more expensive FNB needle, or invite ROSE. Whether or not a centre participated in trials studying benefits of neoadjuvant treatment may have contributed to the practice variation detected across centres.

Ideally, this study would have included patient characteristics as well as equipment and procedural variables allowing the search for potential explanations for the practice variation observed. Clinical variables can easily be incorporated into national or regional audits on EUS+TA of solid pancreatic lesions, similar to our regional quality in endosonography initiative [16 34].

Naturally, conclusions drawn from routinely collected data can only be as good as the system used to for data collection. However, considering the track record of the PALGA-database the chance of missing cases due to misclassification was considered negligible[17].

Because of the selected study population of patients with resected pancreatic carcinoma only, this study does not provide data on false positive results of EUS+TA since patients with benign histopathology of resected pancreas were excluded. It also does not provide a complete picture on false negative results of EUS+TA procedures, since only resected cases were analyzed, and follow-up of non-resected cases was not available. However, although relevant and interesting, studying these characteristics of EUS+TA was not the main topic of this study.

The limitations discussed should not distract practitioners from detected practice variation regarding outcome of EUS+TA, the main finding of this study.

In conclusion, in this nationwide study of patients who underwent a resection of pancreatic carcinoma, we found significant practice variation regarding performance of first EUS+TA procedures, and an overall SFM for (suspected) malignancy of only 65% indicating ample room for improvement. Considering the increasing body of evidence supporting neo-adjuvant treatment in patients with resectable and borderline resectable pancreatic carcinoma, in which establishing a tissue diagnosis is considered mandatory, this practice variation is unwanted[35 36]. The significant chance of an inconclusive EUS+TA procedure of 35%, its wide range of 10-47% across centres, and the associated additional patient burden should prompt to unfold initiatives aiming to reduce practice variation and improve quality.

We hope the current study will serve as a first step towards the establishment of a multidisciplinary audit aiming for continuous improvement of quality of care in these patients. We would encourage all practitioners involved in EUS+TA procedures, not to wait for such an audit to "come their way", but to proactively start to measure, compare and improve their individual performance instead.

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Supplementary Table 1. Results from logistic mixed models to analyze possible associations between performance indicators of first EUS and centre characteristics (designated centres only).

covariate		OR	2.5 %	97.5 %	p-value
RAS	**characteristics of centre**				
	Cases (n)	1.003	0.985	1.021	0.751
	EUS (n)	1.001	0.973	1.031	0.921
	% EUS	0.997	0.960	1.036	0.880
SFM-b6					
	Cases (n)	1.001	0.990	1.013	0.826
	EUS (n)	1.007	0.989	1.027	0.445
	% EUS	1.003	0.981	1.026	0.776
ROA					
	Cases (n)	1.001	0.989	1.012	0.909
	EUS (n)	1.002	0.982	1.023	0.827
	% EUS	1.003	0.978	1.028	0.841

Cases(n): number of resections performed per centre
EUS (n): number of EUS+TA procedures per centre
% EUS: proportion of EUS+TA procedures performed per centre
RAS: Rate of adequate sample
SFM-b6: sensitivity for malignancy definite malignancies only (strict definition)
ROA: Rate of atypia
OR: Odds Ratio

Categorized and entered into study database:

Categories for resected specimen diagnosis:
1. Pancreatic carcinoma
2. Ampullary carcinoma
3. Duodenal carcinoma
4. Distal cholangiocellular carcinoma
5. Neuro-endocrine tumours
6. Metastasis
7. Benign/IPMN
8. Other

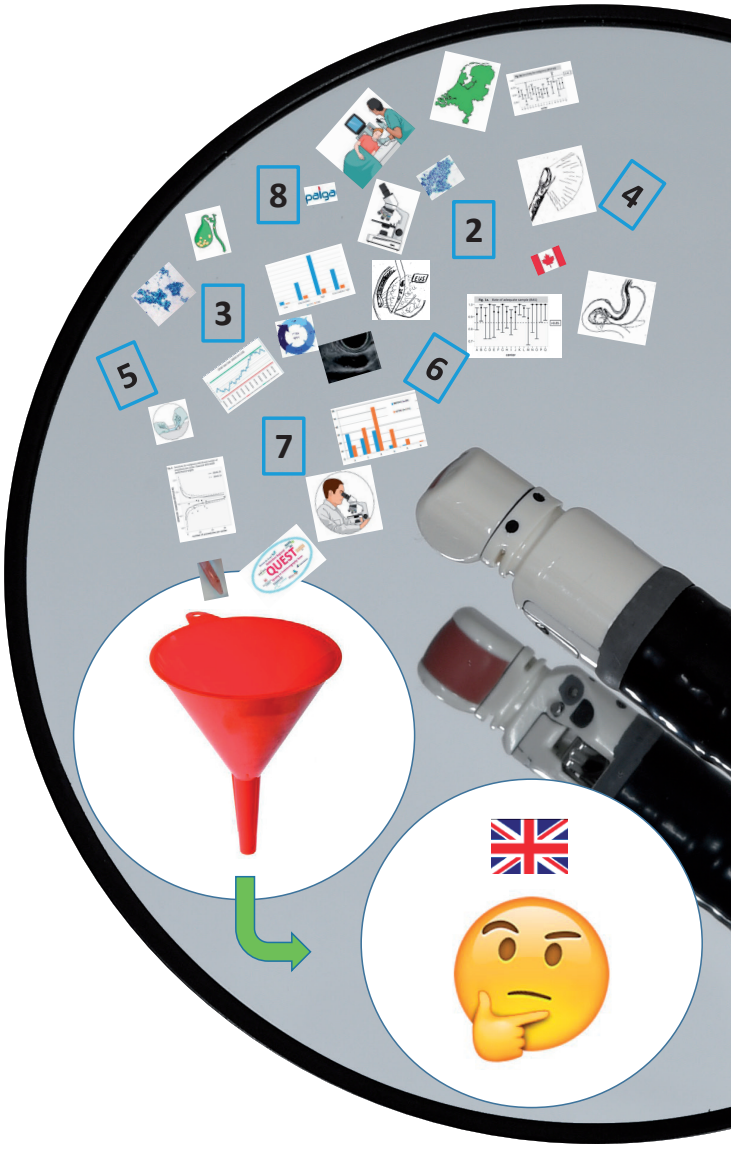
Catergories for pre-op tissue acquisition technique used:
1. EUS + TA
2. Other (including brush cytology during ERCP and endoscopic biopsies)

Categories for EUS+ TA diagnosis:
1. non-diagnostic (inadequate)
2. Benign
3. Atypical
4. Neoplastic (benign and other)
5. Suspected malignancy
6. Malignant

Supplementary Figure 1. Categories used for database construction.

9

CHAPTER 9



Summary and discussion

The aim of this thesis is **to explore the use and quality of care delivered by endoscopic ultrasonography in clinical practice**.

In **Chapter 1** the introduction of endoscopic ultrasound (EUS), dissemination of the technique and developments in the use of EUS over the past 40 years are described. The field of endoscopic ultrasonography has grown tremendously over the 4 decades of its existence. Concerns about interobserver-variability, practice variation, and quality of training in EUS have been raised in several publications [1-5]. To date these topics have received little attention in the framework of scientific studies. As a matter of fact, until recently, quality in EUS was not clearly defined. In recent years, quality improvement programs have been initiated by national and international endoscopy societies [5-8]. These have provided practitioners with key performance indicators (KPI), and performance targets. In this thesis, we explored the use of performance indicators to measure performance in both EUS-guided tissue acquisition (TA) of solid pancreatic lesions, and EUS in patients suspected to have bile duct stones in clinical practice.

Chapter 2 describes the use and yield of linear endosonography in patients with suspected bile duct stones in community hospital practice. In line with previous publications, EUS serves as an excellent tool to select patients for endoscopic therapy. EUS rules out bile duct stones in up to 63% of cases, thereby preventing unnecessary endoscopic retrograde cholangiography and endoscopic sphincterotomy (ERC+ES), and avoiding its complications. However, in some patients, EUS detects bile duct sludge, or microlithiasis, i.e. stones <3 mm. Both sludge and microlithiasis may spontaneously pass into the small bowel, but might also lead to complications such as pancreatitis. The clinical relevance of microlithiasis and bile duct sludge remains to be elucidated. This might lead to a further reduction of the need for endoscopic therapy and its related complications.

In **Chapter 3,** we investigate the interobserver variability among 41 endosonographers evaluating EUS videos of bile duct stones, microlithiasis (i.e. stones < 3mm), and bile duct sludge. We also reported whether the EUS diagnosis would prompt the endosonographer to advise to perform endoscopic therapy (ERC + ES) or refrain from it. Furthermore, we investigated whether the degree of experience of the endosonographer influences diagnosis and treatment decisions. For bile duct stones and a "clean" bile duct, the interobserver agreement was moderate. For both microlithiasis and bile duct sludge, there was only slight agreement. There was an almost perfect agreement regarding the need for endoscopic therapy in cases with bile duct stones or cases with a normal "clean" bile duct. In cases with sludge or microlithiasis, there was no consensus regarding the need for endoscopic therapy. Practitioners' experience appeared not to influence neither EUS diagnoses nor treatment decisions. The only moderate and slight interobserver agreements on stones and sludge

likely reflect both the limited but variable definitions of bile duct sludge in literature, and variations in education and training of contributing endosonographers.

In order to get more insight in the clinical relevance of bile duct sludge, we studied a large prospective database including over 40.000 EUS procedures recorded in a time-frame of 20 years from a tertiary referral center, in Montreal, Canada. In **Chapter 4**, the prevalence of bile duct sludge is described in patients from this database who had intermediate or high probability of bile duct stones, according to the clinical prediction tool of the American Society of Gastro-Enterology (ASGE). In approximately one out of 25 EUS procedures (4%) performed for this indication, bile duct sludge is diagnosed. The clinical relevance of this finding warrants further study.

In the second section of this thesis, the use and performance of EUS-guided tissue acquisition (EUS-guided TA) of solid pancreatic lesions is investigated. **Chapter 5**, starts with a retrospective study of the yield of 20 EUS-guided TA procedures from four community hospitals, followed by the initiation of a prospective registry of these procedures, and the founding of a regional EUS collaborative aiming to improve the outcome of these procedures. From 2015 onwards, this collaborative quality in endosonography team (QUEST) organized three meetings annually. Topics discussed at these meetings are: guidelines and relevant literature, challenging cases, and feedback on KPI of EUS-guided TA of solid pancreatic lesions per center. Prior to meetings, feedback regarding KPI of EUS+TA is provided to each collaborating practitioner. At meetings, performance data are discussed in an anonymized fashion, in order to create and maintain a safe learning environment for quality improvement. This deliberately leaves the responsibility for the quality delivered with the practitioners from the individual hospitals. Initial retrospective data revealed significant practice variation regarding KPI among contributing hospitals. The first report on the proceedings of QUEST, describes prospectively collected data from January 2015 to September 2016. It concludes that in relatively low-volume community hospitals, regular meetings with feedback on KPI leads to a reduction of practice variation and an improvement of quality up to the desired level.

In **Chapter 6**, the diagnostic yield and agreement on fine needle specimens (FNA) from solid pancreatic lesions were assessed, and a comparison of the traditional "smear technique", and two separate liquid based cytology (LBC) techniques was made. The diagnostic value of two LBC techniques combined (Cellblock and Thinprep), proved superior to traditional "smears" when assessing the yield of a single pass EUS-guided FNA of solid pancreatic lesions. This indicates that LBC adds to the diagnostic value of the traditional "smear technique", and should be considered especially when rapid on-site evaluation of samples is unavailable to ensure sample adequacy. Since LBC also allows for additional testing, such

as immunohistochemistry or next generation sequencing (NGS) we recommend the use of LBC in all cases of EUS-guided FNA of solid pancreatic lesions.

In **Chapter 7**, the proceedings of the regional EUS collaborative QUEST, concerning EUS-guided TA of solid pancreatic lesions from 2015-2018, are reported. This chapter introduces close collaboration with the pathology departments in the contributing hospitals, as well as the use of cumulative sum (CUSUM) analysis, a graphical method to plot learning curves. This study used CUSUM curves to assess trends in quality over time, and explored potential benefits of CUSUM curves as a feedback-tool. Throughout the 4 years of this study, all KPI improved. However, not all ASGE-defined KPI are consistently met in each center yet. Therefore, feedback on performance as well as feedback on potential ways to improve the yield of EUS-guided TA should be an ongoing process. Learning curves were proven a valuable adjunct to tables with numbers for providing such feedback. They allow determination of best practices and comparison amongst peers at a glance and provide additional learning opportunities. Previous studies using learning curves for monitoring development and training of advanced endoscopy trainees, already taught us that numbers of procedures performed are a poor measure of competency [4,9-13]. Similarly, our study shows that numbers of procedures performed are a poor measure of quality. Our study results also indicate that performance of EUS-guided TA differs considerably amongst centers and even individual operators. It therefore is the responsibility of each operator to be informed about the quality of his/her own performance and CUSUM curves are an excellent tool to facilitate this.

Chapter 8 summarizes quality and practice variation regarding EUS+TA of solid pancreatic lesions nationwide in the Netherlands. For this purpose, we retrospectively analyzed all resected pancreatic ductal adenocarcinoma cases from the national pathology database (PALGA), and all pathology reports describing the evaluation of tissue samples from EUS+TA procedures performed in these patients. Again, significant practice variation regarding KPI of EUS+TA was seen. Although the sample adequacy rate (RAS) meets the predefined performance target of 85% in all dedicated pancreatic surgery centers, the performance target 'sensitivity for malignancy >85%', was met in only 9 out of 17 of these centers. This study demonstrates opportunities for improvement in quality of each stage of these multi-step procedures. Consorted action from endosonographers and pathologists should be prioritized , especially since the emergence of neo-adjuvant therapies and future "targeted therapy", are expected to further increase the importance of a "first-time right" diagnosis in these patients. The data from the current study may serve as a reference for a future multidisciplinary audit aiming for continuous improvement of quality of care in patients with suspected pancreatic malignancies.

Discussion and future perspectives

Quality is doing the right thing in the right way [14]. This means a procedure is performed for the right indication, by a trained operator using the appropriate methodology aiming for the best possible outcome: "first time right", including the lowest possible chance of adverse events, and a decreased need for additional care.

Quality of EUS is important to patients since it can limit the burden of being submitted to additional care, including the management of complications, (repeated) endoscopic procedures and/or prolonged hospitalization. This was illustrated in chapter 2, where EUS prevented the unnecessary performance of endoscopic retrograde cholangiography and endoscopic sphincterotomy (ERC+ES) and it's complications in 63%. Another example is the improved quality of EUS guided TA in patients with suspected pancreatic cancer reducing the need for second procedures to establish a pathological diagnosis from 18% to 7% in Chapter 5.

What is EUS performed in "the right way"? How can we measure performance in EUS?

Quality measurements

Volume (number of procedures performed annually) has long been the only measure of quality for many procedures, first because it's easily measured, and second because other (real) quality measures were unavailable. Many publications have highlighted the correlation between outcomes of surgical or endoscopic procedures and case volumes of centers and individual practitioners. The inverse relation between center volume and mortality, established for a multitude of surgical procedures in the United States in 2002, is an example of this [15]. For ERCP it was confirmed that low-volume providers (performing less than 25 ERCPs annually) have a significantly higher failure rates [16].

Although volume is obviously related to outcome, it is at best, a surrogate marker of performance with significant limitations. Main limitation of volume as a performance indicator is the fact that changes in volume will not directly lead to changes in outcome. Therefore, volume is unfit for repeated or continuous quality measures through time. Ideally, performance indicators connect specific procedural characteristics to procedural outcome and related patient burden. Examples of more adequate performance indicators are the adenoma detection rate (ADR) for quality in colonoscopy, and bile duct cannulation rate at ERCP. The rate of adenomas detected by a single endoscopist at colonoscopy (adenoma detection rate: ADR), was proven an independent predictor for a patient's risk of developing colorectal carcinoma 6-36 months after colonoscopy [17]. A low bile duct cannulation rate at ERCP will likely to lead to an increased need for repeated procedures.

The American Society of Gastrointestinal Endoscopy (ASGE) divided quality indicators for EUS into three categories: 1. structural measures, 2. process measures, and 3. outcome measures. Structural measures mainly relate to the environment in which the procedures are performed. Process measures assess performance during the procedure (for example training and experience of the endoscopists involved, or rate of EUS procedures performed for proper indications). Outcome measures assess the results of care provided and are therefore truly relevant for patients. The ASGE proposed nine specific quality indicators for EUS, of which three outcome measures were designated priority performance indicators: diagnostic yield of malignancy (DYM>70%), and sensitivity for malignancy (SFM>85%), as well as incidence of adverse events after EUS guided TA [8].

The European Society of Gastrointestinal Endoscopy defined two key performance measures for EUS: 1. Proportion of antibiotic prophylaxis prior to EUS guided TA of cystic pancreatic lesions, with target >95%, 2. Proportion of adequate tissue samples obtained by EUS guided TA, target >85%. Adequate documentation of EUS landmarks was designated a minor performance measure [6].

The quality measures/performance indicators reported on in this thesis (in chapters 5, 7 and 8) have in common that they are outcome measures likely to have a direct impact on patient burden. When EUS+TA is performed aiming to diagnose pancreatic cancer prior to the start of neoadjuvant therapy, a low adequate sample rate will likely increase the need for repeated EUS+TA procedures. This will be similar for diagnostic yield of malignancy (DYM) and sensitivity for malignancy (SFM).

Why should quality be measured?

Patients, obviously, deserve the best possible care. Therefore, each EUS practitioner should know the quality of care he/she is providing. This cannot be done without measurements. If you do not measure you cannot properly inform your patient. If you do not measure you will never know whether improvement is necessary. If you do not measure you cannot benchmark your performance with your peers. If you do not measure you cannot improve. If you do not measure you miss out on opportunities for teaching advanced endoscopy trainees. If you do not measure you miss learning opportunities and the satisfaction of improving quality of care.

For these reasons endosonographers in the 21st century, both in high-, and low(er) volume centers, should feel obliged to measure key performance indicators. KPI measurements may serve as the basis for regional quality improvement initiatives, including post-graduate teaching and learning opportunities. Measuring different KPI may also allow to pinpoint 'vulnerabilities' in complex multi-step procedures, such as EUS guided TA, and target quality improvement steps, as was illustrated in chapters 7 and 8.

What is keeping us from measuring KPI?

What is preventing endoscopists throughout the world to start measuring KPI to see how they are doing in comparison to the proposed performance targets and their peers? To answer this question, the ESGE quality improvement committee conducted surveys among its member societies in 2017 and 2019. The first barrier identified concerns motivation of endoscopists. Endoscopists fear additional administrative burden next to their already demanding daily practice. They also fear additional costs and prolonged endoscopy reporting times. Another source fueling resistance to implementation is lack of trust in organizations performing audits and the fear of being punished for underperformance [18].

Auditing quality of endoscopy in the Netherlands

With the implementation of the national colorectal cancer screening program, automated performance indicator measurements for colonoscopies on a national level were introduced in 2011[19]. The Dutch gastrointestinal endoscopy audit (DGEA), was initiated in 2016, and is based on the initial colorectal cancer screening framework. DGEA is currently recording performance measures from colonoscopies for all indications performed nationwide. DGEA uses an automated system integrating data from the national pathology database, and endoscopy reporting systems from individual hospitals. DGEA is started by the Dutch Society of Gastroenterology (NVMDL), governed by the Clinical Audit Board of the NVMDL, and executed by the Dutch Institute of Clinical Auditing (DICA). Ownership of data in DGEA remains with the contributing hospitals. DGEA aims to include a variety of endoscopic procedures in the near future, including ERCP and EUS [20].

The Dutch registration of complications in endoscopy (DRCE) was also initiated in 2016 and comprises all complications of endoscopic procedures performed in the Netherlands. The registration of endoscopic complications in DRCE is performed manually by individual endoscopists, following their institutions local evaluation of complications of endoscopic procedures.

From 2012 onwards, quality metrics of all ERCP procedures performed nationwide are prospectively recorded. Feedback on recorded data is provided to contributing endoscopists. This has led to both a nationwide reduction in the number of gastroenterologists performing ERCPs, as well as improvement in performance compared to initial measurements [21-23].

Future directions

Measuring KPI and improving quality of endoscopic procedures should be incorporated into clinical practice as well as into the training curriculum of future endoscopists. Regardless of the continued focus on volume and "production" in hospitals, endoscopists should feel obliged to start measuring and improving. Moreover, measuring KPI of endoscopy should be integrated in a structured curriculum for lifelong learning [24]. Policy makers

and hospital management may endorse and facilitate such initiatives by stimulating multidisciplinary collaboration in and amongst hospitals, measuring costs (and cost-reductions likely achieved), and by supporting the construction of necessary information technology platforms.

Based on experience with performance indicators of EUS+TA described in this thesis and other publications on this topic, we suggest as a core data set to audit EUS performance: age and sex of the subjects, indication of the EUS procedure, and RAS and DYM in cases of EUS+TA of solid pancreatic lesions, and complications [6,8]. RAS and DYM are both performance indicators reflecting outcome of EUS+TA procedures, having a direct effect on patient burden. They both are available within a week following the procedure, and therefore suitable for "real-time" monitoring of performance. Moreover, they can be extracted automatically from the Dutch national pathology database (PALGA), preventing administrative burden, and can be presented as CUSUM-curves, allowing for instant comparison with benchmarks and performance of peers.

Prior to initializing such an audit standardization of pathology reports is required. We would suggest implementation of the classification suggested for evaluation of cytology of solid pancreatic lesions by the Papanicolaou society for all EUS+TA procedures of solid lesions, regardless of the type of needles (FNA or FNB) used [25]. Implementation and governance of an EUS audit should be organized and led by the Dutch Society of Gastroenterology and Hepatology (Nederlandse Vereniging van Maag-, Darm-, en Leverartsen: NVMDL) in collaboration with the Dutch Society of Pathologists (Nederlandse vereniging voor pathologie, NVVP).

With regards to the use of EUS for selecting patients with suspected bile duct stones for ERC+ES, we would suggest to add a performance indicator to the list of ERCP performance indicators. Since MRCP is also used for this purpose, we suggest to introduce the proportion of patients with proven bile duct lithiasis prior to ERCP as a performance indicator. Although this indicator reflects the quality of the diagnostic process leading to ERCP, instead of reflecting actual ERCP performance, creating a separate EUS performance indicator on this topic seems less practical.

In our opinion, the provision of feedback on performance to individual endosonographers should be organized regionally. By introducing regional quality improvement teams with regular meetings amongst a limited number of professionals familiar with one another, a safe environment is created in which feedback data and improvement strategies can be discussed. Presenting feedback data at these meetings in an anonymized fashion, will further add to this feeling of safety, and leaves the responsibility for the quality delivered with the contributors from individual centers. As described in the proceedings of QUEST

(chapters 5 and 7), this will lead to improvement of quality overall and in each individual center, without the need for "top-down" interventions. This method allows practitioners the responsiblity to take their own action in case of underperformance, supervised and guided by their regional peers.

We would encourage all practitioners involved in EUS+TA procedures, not to wait for an audit to "come their way", but to proactively start to measure and improve their individual performance instead. We would advise all endosonographers to review the last 20 EUS+TA procedures of both solid pancreatic lesions, and solid non-pancreatic lesions performed in their endoscopy unit. The proportion of non-diagnostic procedures should be <15% (equal to RAS > 85%) and the diagnostic yield of malignancy in case of suspected pancreatic malignancies should be >70%. If these performance targets are not met, we suggest to re-evaluate the protocols and techniques used, and discuss the subject with your peers and local pathologist, devise a strategy for quality improvement, and continue your measurements.

Endosonographers throughout the world are invited to share the results of their measurements with the Dutch Quality in Endosonography Team (QUEST) by e-mail (r.quispel@rdgg.nl). We intend to provide a sequel of the benchmark for quality performance measurements study performed by Savides et al in 2007 [26].

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CHAPTER 10

Samenvatting en discussie

Het doel van dit proefschrift is het beschrijven van het gebruik en de kwaliteit van endo-echografie in de klinische praktijk. Twee vragen uit de dagelijkse praktijk van een endo-echografist in Nederland hebben geleid tot de studies beschreven in dit proefschrift. De eerste vraag: "Waarom zie ik geen stenen of gruis bij ERCP, nadat deze eerder zijn vastgesteld bij endo-echografie?", is aanleiding geweest voor de studies beschreven in de hoofdstukken twee, drie en vier. De tweede vraag: "Hoe kan het dat de patholoog beweert onvoldoende materiaal voor een diagnose te hebben, terwijl ik de endo-echogeleide punctie van de solide afwijking van de alvleesklier precies zo heb uitgevoerd als ik heb geleerd?", is de basis geweest voor de studies beschreven in de hoofdstukken vijf, zes, zeven en acht.

In **hoofdstuk 1** wordt de geschiedenis van endo-echografie beschreven en het doel van dit proefschrift toegelicht. In 1992 werd endo-echografie slechts in 5-10 ziekenhuizen in Nederland verricht en verscheen de eerste publicatie over endo-echogeleide weefseldiagnostiek [1]. Vandaag de dag wordt endo-echografie in alle grote ziekenhuizen van Nederland verricht en vervult endo-echogeleide weefseldiagnostiek een centrale rol in de diagnostiek van diverse aandoeningen [2,3]. Sinds enkele jaren zijn er, dankzij de internationale beroepsverenigingen ASGE en ESGE (American and European Society of Gastrointestinal Endoscopy) kwaliteitsmaten voor endo-echografie gedefinieerd [4-6]. Tot op heden zijn deze in de algemene praktijk nog nauwelijks toegepast. Het doel van dit proefschrift is om hier verandering in te brengen en inzicht te verkrijgen in het gebruik en de kwaliteit van endo-echografie in de klinische praktijk.

Hoofdstuk 2 beschrijft het gebruik van endo-echografie in een algemeen ziekenhuis om galwegstenen uit te sluiten, zodat het uitvoeren van een endoscopische behandeling (endoscopische retrograde cholangiografie met endoscopische sfincterotomie, ERC+ ES) van galwegstenen achterwege gelaten kan worden. Dit is van belang, omdat de ERC+ES gepaard kan gaan met complicaties in tot 10% van de gevallen [7]. In deze studie leidt de toepassing van endo-echografie om galwegstenen uit te sluiten tot het niet verrichten van een endoscopische behandeling in 63% van de gevallen. Daarnaast wordt aangetoond dat de kans dat bij ERC+ES geen stenen of gruis worden aangetroffen groter is naarmate: 1. het tijdsinterval tussen de endo-echografie en de ERC+ES langer is, en 2. de galweginhoud zoals vastgesteld bij endo-echografie (steen, steentjes of gruis) kleiner is.

In **hoofdstuk 3** worden 30 endo-echografie video's van patiënten verdacht voor galwegstenen, met veelal kleine steentjes of gruis ("sludge") beoordeeld door 41 Nederlandse endo-echografisten. De overeenstemming tussen deze beoordelingen en de hierop volgende keuze voor wel-, of geen endoscopische behandeling (ERC+ES) werd bestudeerd. Daarnaast werd onderzocht of de ervaring van de deelnemende endo-echografisten bij beoordeling en besluitvorming een rol speelt. Voor de diagnosen "galwegsteen" en "normale galweg zonder stenen of gruis" was de overeenstemming redelijk

("moderate"). Voor de diagnosen "microlithiasis" (steentjes < 3mm) en "gruis" (sludge) was de overeenstemming minimaal ("slight"). In geval van "stenen" of "een normale galweg zonder inhoud" was men het eens over het te voeren beleid. In geval van microlithiasis of gruis was er wat betreft het te voeren beleid geen consensus. Ervaring van endo-echografisten in jaren lijkt geen invloed te hebben op de beoordelingen of op de gemaakte beleidskeuzes. De beperkte tot minimale overeenstemming tussen verschillende endo-echografisten is mogelijk gevolg van de wisselende definities van microlithiasis en galweggruis die in de literatuur worden gehanteerd en verschillen in de opleiding en training van endo-echografisten.

De prevalentie van galweggruis werd onderzocht in **hoofdstuk 4.** Voor dit doel werd gebruik gemaakt van een grote prospectief bijgehouden database van alle endo-echografie procedures verricht in Centre Hospitalier de Quebec, in Montreal, Canada. Deze database betreft meer dan 40.000 endo-echografie procedures verricht in een periode van 20 jaar. Bij patiënten die volgens de ASGE-classificatie uit 2010 een gemiddelde of hoge verdenking op galwegstenen hebben, wordt bij circa 1 op de 25 endo-echografie procedures (4%) galweggruis ("sludge") vastgesteld[8]. De klinische relevantie van galweggruis zal door toekomstig onderzoek moeten worden opgehelderd.

In het tweede deel van dit proefschrift werden de toepassing en opbrengst van endo-echografie geleide weefseldiagnostiek bij solide afwijkingen van de alvleesklier onderzocht. In **hoofdstuk 5** wordt gestart met de evaluatie van de laatste 20 endo-echogeleide puncties van solide afwijkingen van de alvleesklier, verricht in 4 algemene ziekenhuizen. Dit werd gevolgd door de start van een prospectieve registratie van deze procedures vanaf januari 2015 en de oprichting van een regionaal samenwerkingsverband tussen deze ziekenhuizen (QUEST) gericht op de verbetering van kwaliteit. Per jaar worden 3 bijeenkomsten georganiseerd waarbij richtlijnen, recente publicaties, uitdagende casuïstiek en de resultaten van de metingen worden besproken. Voorafgaand aan de bijeenkomsten worden de individuele resultaten per endo-echografist en per centrum gedeeld met de deelnemers. Gedurende de bijeenkomsten worden de resultaten van de metingen op geanonimiseerde wijze gepresenteerd en bediscussieerd. Doel van deze werkwijze is het scheppen van een veilige omgeving om te kunnen leren en verbeteren, alsmede de verantwoordelijkheid voor de resultaten te houden bij de eigenaars van de gegevens (de ziekenhuizen en endo-echografisten welke het betreft). De retrospectieve gegevens tonen aanzienlijke praktijkvariatie tussen de 4 deelnemende ziekenhuizen voor wat betreft de prestatie indicatoren van endo-echogeleide weefseldiagnostiek. Het eerste verslag van de prospectief verzamelde gegevens toont dat het in teamverband samenwerken deze praktijkvariatie aanzienlijk kan terugbrengen en kan leiden tot verbetering van de prestatie indicatoren tot op het gewenste niveau.

Hoofdstuk 6 vergelijkt de diagnostische prestaties van de traditionele weefseluitstrijktechniek met de alternatieve verwerkingstechnieken Thinprep en Cellblock van middels endo-echografie verkregen fijne naald aspiraten (FNA) van solide pancreaslesies. Daarnaast wordt de overeenstemming tussen drie verschillende beoordelaars voor de verschillende technieken van verwerking van cytologisch materiaal onderzocht. De diagnostische prestaties van de combinatie van Thinprep en Cellblock blijken superieur ten opzichte van de uitstrijktechniek voor wat betreft de weefselkwaliteit, de diagnostische nauwkeurigheid voor maligniteit en de overeenstemming tussen de drie beoordelaars. Dit toont dat alternatieve verwerkingstechnieken van cytologisch materiaal (de zogenaamde "liquid based cytology" (LBC)-technieken) van toegevoegde waarde zijn naast de uitstrijktechniek, vooral als er geen cytopathologische beoordeling van verkregen materiaal gedurende de endo-echo procedures beschikbaar is. Omdat LBC hiernaast ook aanvullende immunohistochemische kleuringen en aanvullend genetisch onderzoek van het verkregen materiaal mogelijk maakt, wordt het gebruik van LBC bij FNA van solide pancreaslesies geadviseerd.

In **hoofdstuk 7** wordt verslag gedaan van de voortgang van het regionale endo-echografie samenwerkingsverband QUEST, wat betreft endo-echografie geleide weefseldiagnostiek van solide pancreaslesies van 2015 tot 2018. In dit hoofdstuk wordt intensivering van de samenwerking met de pathologen van de deelnemende ziekenhuizen beschreven en wordt de toepassing van cumulatieve summatie curves (CUSUM) als visuele representatie van prestatie in de tijd (leercurves) geintroduceerd. De toegevoegde waarde van leercurves als middel om de ontwikkeling van prestatie indicatoren in de tijd weer te geven voor feedback, werd onderzocht. Gedurende de 4 jaren van prospectieve registratie beschreven in dit hoofdstuk, werd verbetering vastgesteld voor wat betreft alle sleutel prestatie indicatoren. Echter worden nog niet alle door de ASGE gedefinieerde prestatiedoelen in alle centra gehaald. Mede om deze reden blijft feedback over prestaties en mogelijkheden om prestaties te verbeteren als onderdeel van een continu proces van groot belang. Leercurves blijken hierin van waarde omdat vergelijking tussen endo-echografisten en ziekenhuizen onderling in één oogopslag mogelijk wordt gemaakt, en er daarnaast meer inzicht wordt verkregen in kwaliteit en prestaties dan op basis van enkel tabellen met gegevens ooit zou kunnen. Leercurves zijn eerder gebruikt voor het meten van de ontwikkeling van endoscopisten in opleiding [9,10]. Zowel deze eerdere publicaties als onze studie, tonen aan dat volume (het aantal procedures verricht per tijdseenheid) een zeer beperkte kwaliteitsmaat is. Onze studie toont aanmerkelijke verschillen in diagnostische prestatie van endo-echografie geleide weefseldiagnostiek van solide pancreaslesies tussen ziekenhuizen en individuele endo-echografisten. Het is de verantwoordelijkheid van elke endo-echografist om zijn/haar eigen diagnostische prestatie te kennen en te vervolgen. Leercurves zijn hiervoor een geschikt instrument.

Hoofdstuk 8 geeft een overzicht van de kwaliteit en praktijkvariatie van endo-echogeleide weefseldiagnostiek verricht bij patiënten voorafgaand aan een chirurgische resectie vanwege pancreascarcinoom in Nederland. Er werd een retrospectieve analyse verricht van alle vanwege pancreascarcinoom in Nederland geopereerde patiënten van 2014-2018 en de verrichte pre-operatieve endo-echogeleide weefseldiagnostiek. De verslagen van deze onderzoeken werden verkregen uit PALGA, het nationale geautomatiseerde archief van alle in Nederland verrichte weefseldiagnostiek. Opnieuw werd aanzienlijke praktijkvariatie betreffende de sleutel prestatie-indicatoren van endo-echogeleide weefseldiagnostiek vastgesteld. Hoewel de proportie beoordeelbare weefselpreparaten (rate of adequate sample (RAS)) voldoet aan het geformuleerde prestatie-doel van 85%, wordt het prestatie-doel sensitiviteit voor maligniteit (sensitivity for malignancy (SFM)) slechts gehaald in 9 van de 17 centra waar pancreaschirurgie wordt verricht. Deze studie toont mogelijkheden voor verbetering in alle facetten van endo-echogeleide weefseldiagnostiek en nodigt uit tot verregaande samenwerking en multidisciplinaire inspanning van endo-echografisten en pathologen. Dit dient op korte termijn te worden vormgegeven, aangezien de toenemende toepassing van neo-adjuvante chemotherapie en toekomstige "targeted therapy" het belang van toegankelijke en direct accurate endo-echogeleide weefseldiagnostiek verder zullen doen toenemen. Mogelijk kunnen de resultaten van deze studie dienen als een eerste stap in de richting van een multidisciplinaire audit gericht op continue verbetering van de uitkomsten van zorg voor patiënten met solide pancreaslesies verdacht voor carcinoom.

Discussie en blik op de toekomst

Kwaliteit is het juiste doen op de juiste manier [11]. Dit betekent dat een procedure wordt uitgevoerd vanwege een goede indicatie, door een getrainde specialist die de juiste technieken gebruikt met als doel om in één keer de best mogelijke uitkomst voor de patiënt te bereiken. Deze best mogelijke uitkomst omvat een zo laag mogelijke kans op complicaties en een zo laag mogelijke kans op de noodzaak tot aanvullende medische zorg.

Kwaliteit van endo-echografie is belangrijk voor patiënten omdat het de belasting die elke medische behandeling voor een patiënt vormt, inclusief de kans op complicaties, de noodzaak tot aanvullende (herhaalde) endoscopische diagnostiek of behandeling, en kans op een verlengde opnameduur in ziekenhuis, kan beperken. Dit werd geïllustreerd in hoofdstuk 2, waar endo-echografie het verrichten van endoscopische therapie (ERCP) en de hieraan gerelateerde complicaties overbodig maakte in 63% van de gevallen. Een ander voorbeeld is de verbeterde kwaliteit van endo-echogeleide weefseldiagnostiek bij patiënten met solide pancreaslesies verdacht voor carcinoom. In hoofdstuk 5 werd voor deze patiëntencategorie de noodzaak tot het ondergaan van een 2^{e} procedure teruggebracht van 18% tot 7%.

Wat is endo-echografie "op de juiste manier"? Hoe kunnen we prestaties en kwaliteit van endo-echografie meten??

Kwaliteitsmaten

Volume (het aantal procedures verricht per jaar) is lang de enige kwaliteitsmaat geweest van diverse procedures. Ten eerste, omdat het een makkelijk te meten maat is en ten tweede omdat er geen andere (echte) kwaliteitsmaten beschikbaar waren. Vele publicaties hebben de relatie beschreven tussen de resultaten van chirurgische en endoscopische behandelingen en het volume van deze behandelingen verricht per ziekenhuis of per dokter per jaar. De inverse relatie tussen volume per ziekenhuis en mortaliteit, zoals vastgesteld voor een breed scala aan chirurgische ingrepen verricht in de Verenigde Staten in 2002, is hier een voorbeeld van [12]. Voor ERCPs werd aangetoond dat scopisten die minder dan 25 van deze procedures per jaar uitvoeren, deze procedures minder vaak tot een goed einde brengen [13].

Hoewel volume duidelijk gerelateerd is aan uitkomst, is het hooguit een surrogaat uitkomstmaat met belangrijke beperkingen. De belangrijkste beperking is dat veranderingen in volume niet direct zullen leiden tot veranderende uitkomsten. Dit maakt volume als kwaliteitsmaat ongeschikt voor herhaalde of continue metingen in de tijd. Een ideale uitkomstmaat verbindt specifieke karakteristieken van een procedure aan uitkomst van de procedure en de hieraan gerelateerde belasting voor de patiënt. Voorbeelden van betere kwaliteitsmaten zijn het percentage coloscopieën waarbij tenminste één adenoom wordt vastgesteld, de zogenaamde "adenoma detection rate" (ADR) en het percentage succesvolle canulaties van de galweg of "bile duct cannulation rate" bij ERCP. De ADR is een onafhankelijke risicofactor voor de kans die een patiënt heeft om kanker van de dikke darm te ontwikkelen 6-36 maanden na de colonoscopie [14]. Een laag percentage succesvolle canulaties van de galwegen bij ERCP, brengt een grote kans op een niet succesvolle procedure (die vervolgens herhaald moet worden) met zich mee.

De American Society of Gastrointestinal Endoscopy (ASGE) heeft prestatie-indicatoren voor endoscopie onderverdeeld in 3 categorieen: 1. Structurele indicatoren, 2. Procesindicatoren en 3. Uitkomstindicatoren. Structurele indicatoren hebben vooral te maken met de omgeving waarin procedures worden uitgevoerd. Procesindicatoren zeggen iets over prestatie gedurende een procedure. Voorbeelden hiervan zijn de training en ervaring van de endoscopist die een procedure uitvoert of het percentage procedures uitgevoerd voor een juiste indicatie. Uitkomstindicatoren of uitkomstmaten meten de resultaten van de aan de patiënt geleverde zorg, en zijn daarom voor de patiënt van het grootste belang. De ASGE heeft negen specifieke prestatie-indicatoren voor endo-echografie gedefinieerd, waarvan 3 uitkomstindicatoren aangewezen zijn als prioriteits prestatie-indicatoren: het percentage endo-echogeleide puncties op basis waarvan een maligne diagnose wordt

gesteld (Diagnostic Yield of Malignancy, DYM>70%), sensitiviteit voor maligniteit (Sensitivity For Malignancy, SFM>85%) en het percentage complicaties volgend op een procedure waarbij middels endo-echografie weefsel is verkregen[6].

De European Society of Gastrointestinal Endoscopy (ESGE) heeft 2 zogenaamde sleutel prestatie-indicatoren vastgesteld: 1. Het percentage patiënten dat voorafgaand aan een endo-echogeleide punctie van cysteuze pancreaslesies antibiotica krijgt toegediend, met als prestatiedoel >95% en 2. Het percentage waarin middels endo-echografie geleide punctie voor de patholoog beoordeelbaar materiaal is verkregen, met als prestatiedoel >85%. Het adequaat in het scopieverslag vastleggen van endo-echo-oriëntatiepunten (landmarks), werd als reguliere prestatie-indicator voorgesteld [4].

De prestatie-indicatoren of kwaliteitsmaten gebruikt in dit proefschrift (in de hoofdstukken vijf, zeven en acht) hebben gemeen dat het uitkomstmaten zijn die direct gevolgen hebben voor de belasting van de patiënt. Als endo-echogeleide punctie wordt verricht van een solide pancreasafwijking met als doel om een diagnose te stellen, in een ziekenhuis met een laag percentage beoordeelbaar materiaal (Rate of adequate sample, RAS), dan de kans dat een 2^{e} procedure moet volgen om een diagnose te stellen groter zijn. Voor een laag percentage maligne diagnosen (Diagnostic yield of malignancy, DYM) of een lage sensitiviteit voor maligniteit (Sensitivity for malignancy, SFM) geldt hetzelfde.

Waarom zou kwaliteit gemeten moeten worden?

Het spreekt vanzelf dat patiënten de best mogelijke zorg verdienen. Daarom zou elke endo-echografist de kwaliteit moeten kennen van de zorg die hij/zij levert. Dat kan niet zonder metingen. Als je niet meet kun je je patiënt niet goed voorlichten. Als je niet meet heb je geen idee of er een reden is om te verbeteren. Als je niet meet weet je niet of je het beter of slechter doet dan je collega's. Als je niet meet kun je je ook niet verbeteren. Als je niet meet mis je kansen om endoscopisten in opleiding iets te leren. Als je niet meet mis je zelf kansen om te leren en om het succes van het verbeteren van de kwaliteit van zorg te ervaren.

Dit maakt dat endo-echografisten in de 21ste eeuw, werkzaam in grote en in kleine(re) ziekenhuizen, zich verplicht zouden moeten voelen om de zogenaamde sleutel kwaliteitsindicatoren (key performance indicators, KPI) te meten. Deze metingen kunnen dienen als basis voor regionale kwaliteitsinitiatieven, in combinatie met postdoctoraal onderwijs. Het meten van verschillende kwaliteitsindicatoren biedt de mogelijkheid om kwetsbare onderdelen van het proces van endo-echogeleide weefseldiagnostiek, dat uit meerdere stappen bestaat, te herleiden, zodat deze specifieke aandacht kunnen krijgen.

Wat houdt ons tegen om te gaan meten?

Welke belemmeringen ervaren endoscopisten om te starten met het meten van prestatie-indicatoren? Om deze vraag te beantwoorden heeft de kwaliteitscommissie van de ESGE in 2017 en 2019 een enquête doen uitgaan naar de deelnemende nationale endoscopieverenigingen. De eerste barrière betreft de motivatie van endoscopisten. Endoscopisten zijn bang voor een verdere toename van de bestaande administratieve taken in de al veeleisende dagelijkse praktijk. Daarnaast vreest men een toename van kosten en van de tijd nodig voor verslaglegging. Een volgende bron van weerstand is het gebrek aan vertrouwen in instanties die kwaliteitsmetingen (audits) uitvoeren en de hieruit volgende angst om gestraft te worden voor prestaties die niet aan de norm voldoen [15].

Auditeren van de kwaliteit van endoscopie in Nederland

Met de invoering van het nationale darmkanker screeningsprogramma in Nederland in 2011, werd ook gestart met de invoering van geautomatiseerde metingen van kwaliteitsindicatoren voor coloscopieën [16]. De Nederlandse gastrointestinale endoscopie audit (the Dutch gastrointestinal endoscopy audit, DGEA) werd opgestart op 2016 en is gebaseerd op de geautomatiseerde metingen van KPI zoals deze sinds 2011 in het kader van het bevolkingsonderzoek worden uitgevoerd. DGEA registreert kwaliteisindicatoren van coloscopieen voor alle indicaties in Nederland. Hiervoor wordt een geautomatiseerd systeem gebruikt dat gegevens van de landelijke pathologie database (PALGA) en de gegevens van de verschillende endoscopieverslagsystemen uit de ziekenhuizen integreert. DGEA is opgericht door de Nederlandse Vereniging voor Maag-, Darm-, en Leverartsen en wordt beheerd door de zogenaamde "Clinical Audit Board" van deze vereniging, en uitgevoerd door het Nederlands instituut voor klinisch auditeren (Dutch Institute of Clinical Auditing, DICA). De in DGEA geregistreerde gegevens blijven eigendom van de deelnemende ziekenhuizen. DGEA heeft als doel om in de toekomst meerdere endoscopische procedures, zoals ERCP en endo-echografie te gaan includeren [17].

De Nederlandse complicatieregistratie van endoscopische procedures (The Dutch Registration of Complications in Endoscopy, DRCE) werd eveneens gestart in 2016 en omvat de registratie van complicaties van alle endoscopische diagnostiek van het maagdarmkanaal verricht in Nederland. Deze registratie wordt handmatig verricht door de betrokken endoscopisten, nadat de complicatie op de wekelijkse complicatiebespreking in het betrokken ziekenhuis is besproken.

Vanaf 2012 worden in Nederland prospectief prestatie-indicatoren van ERCP-procedures geregistreerd. Jaarlijks worden de alle endoscopisten die ERCPs verrichten van feedback voorzien betreffende de door hen behaalde resultaten. De invoering van deze registratie heeft geleid tot een verbetering van de uitkomsten van ERCP procedures en tot afname van het aantal endoscopisten dat deze procedures verricht [18-20].

Een blik op de toekomst

Het meten van KPI en verbeteren van kwaliteit van endoscopische procedures zou een integraal onderdeel moeten worden de klinische praktijk en van het opleidingscurriculum van de endoscopisten van de toekomst. Tegen de stroom van de aanhoudende focus op volume en "productie" in de ziekenhuizen in, zouden endoscopisten zich verplicht moeten voelen om te starten met meten en verbeteren. Daarnaast zou het meten en verbeteren geïntegreerd moeten worden in een gestructureerd postdoctoraal curriculum voor "lifelong learning" [21]. Beleidsmakers en ziekenhuisbestuurders zouden deze initiatieven kunnen faciliteren door multidisciplinaire samenwerking in en tussen ziekenhuizen onderling te stimuleren, de kosten (en vooral de besparing hiervan) te meten, en de bouw van de noodzakelijke technologie-platforms te organiseren.

Gebaseerd op de ervaringen met uitkomstmaten van endo-echogeleide weefseldiagnostiek zoals beschreven in dit proefschrift en in diverse andere publicaties, zou onze suggestie zijn om een beknopte set indicatoren te gaan gebruiken voor een audit van de kwaliteit van endo-echografie: leeftijd en geslacht van de patiënt, indicatie van de endo-echo-procedure, RAS en DYM in geval van punctie van solide pancreaslesies en complicaties [4-6]. RAS en DYM zijn beiden uitkomstmaten van endo-echogeleide puncties die een direct effect hebben op de belasting van de patiënt. Beiden zijn binnen een week na de endo-echo-procedure beschikbaar, hetgeen ze geschikt maakt voor kort cyclisch monitoren van kwaliteit. Daarnaast kunnen beiden automatisch worden geëxtraheerd uit de landelijke pathologie database (PALGA), hetgeen extra administratieve last voor de endoscopist voorkomt. RAS en DYM kunnen beiden gepresenteerd worden als CUSUM-curves welke vergelijking met prestatiedoelen (benchmarks) en de prestaties van collega-endoscopisten in één oogopslag mogelijk maakt.

Voordat een dergelijke audit van start kan gaan dienen echter de verslagen van het weefselonderzoek gestandaardiseerd te worden. De classificatie zoals opgesteld voor de beoordeling van de cytologie van solide pancreaslesies door de Papanicolaou society kan gebruikt worden voor alle endo-echogeleide puncties van deze lesies, los van het type endo-echo-naald (FNA of FNB) dat gebruikt is [22]. De invoering en het beheer van een endo-echografie audit zou in handen moeten zijn van de NVMDL, in samenwerking met de Nederlandse vereniging voor pathologie (NVVP).

Wat betreft het gebruik van endo-echografie voor de selectie van patiënten verdacht voor het hebben galwegstenen voor endoscopische therapie (ERC+ES), stellen we voor om een kwaliteitsindicator toe te voegen aan de lijst van ERCP-prestatie-indicatoren. Aangezien meerdere beeldvormende technieken kunnen worden ingezet om galwegstenen aan te tonen of uit te sluiten, zouden we het percentage ERCPs verricht bij patiënten met bewezen galwegstenen als kwaliteitsindicator willen introduceren. Hoewel deze indicator vooral de

kwaliteit van de diagnostiek en besluitvorming leidend tot endoscopische behandeling (ERC+ES) weergeeft, in plaats van dat de kwaliteit van de procedure wordt weergegeven, lijkt het introduceren van een aparte indicator voor endo-echografie in dit geval minder praktisch.

Naar onze mening dient het voorzien van endoscopisten van feedback op hun prestaties regionaal georganiseerd te worden. Het oprichten van regionale kwaliteitsteams, waarvan het beperkte aantal leden elkaar al kent, draagt bij aan een veilige atmosfeer waarbinnen prestatie-metingen en strategieën voor verbetering van kwaliteit besproken kunnen worden. Bij besprekingen van deze regionale teams zal het presenteren van geanonimiseerde gegevens per ziekenhuis en per endoscopist, verder bijdragen aan deze veilige leer- en verbeteromgeving. Hiermee wordt ook de verantwoordelijkheid voor de geleverde prestaties en eventuele verbeter-acties gelegd bij de deelnemers. Zoals beschreven in de hoofdstukken vijf en zeven van dit proefschrift, zal dit leiden tot verbetering van de algehele kwaliteit en de kwaliteit zoals geleverd in de individuele ziekenhuizen, zonder dat van bovenaf opgelegde maatregelen nodig zijn. Deze methode geeft endoscopisten de verantwoordelijkheid om actie te ondernemen in geval van achterblijvende resultaten onder supervisie en begeleiding van hun collega's binnen het regionale kwaliteitsteam.

We willen alle endo-echografisten, betrokken bij het verrichten van endo-echogeleide weefseldiagnostiek, aanmoedigen om niet te wachten tot er een audit van start gaat, maar in plaats daarvan proactief te starten met het meten en verbeteren van de eigen kwaliteit. Ons advies aan elke endo-echografist is om de laatste 20 endo-echogeleide puncties van zowel solide pancreaslesies, als van diverse andere (non-pancreas) solide lesies in kaart te brengen om een idee te krijgen van de eigen kwaliteit. Het percentage niet-diagnostische procedures dient kleiner te zijn dan 15%. Dit komt overeen met een RAS>85%. Het percentage maligne diagnosen dient in geval van de solide pancreaslesies meer dan 70% te zijn. Als deze prestatiedoelen niet gehaald worden is er een reden om de eigen protocollen nog eens kritisch te bezien, de resultaten te bespreken met collega's en de lokale patholoog, een plan op te stellen om tot verbetering te komen en vooral door te gaan met meten.

Alle endo-echografisten in Nederland zijn van harte uitgenodigd om de resultaten van de verrichte metingen te delen met het QUality in EndoSonography Team (QUEST) per e-mail (r.quispel@rdgg.nl). Het is ons plan om bij voldoende respons een vervolg te maken op de "benchmark for quality performance measurements"-studie van Savides et al uit 2007 [23].

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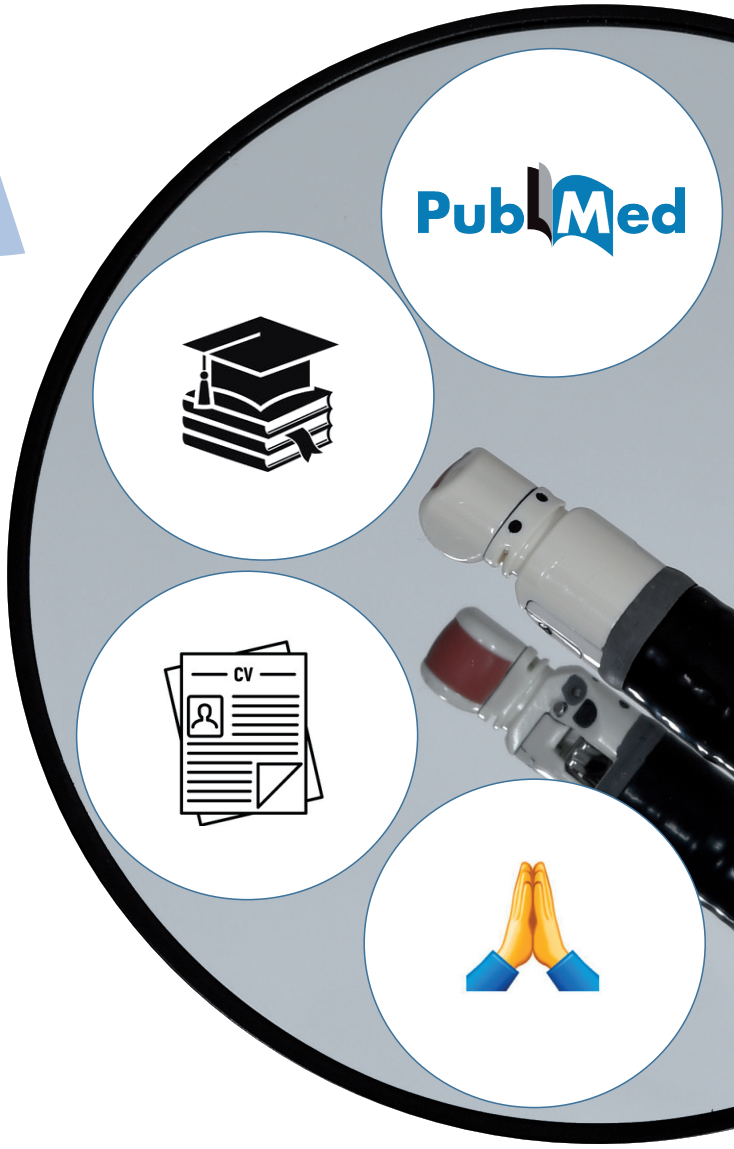
SECTION 3

Appendices

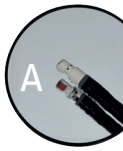
A

APPENDICES



List of abbreviations

ASGE	American society of gastrointestinal endoscopy
CBD	common bile duct
CI	confidence interval
CUSUM	cumulative summation
DA	diagnostic accuracy
DYM	diagnostic yield of malignancy
ERC	endoscopic retrograde cholangiography
ERCP	endoscopic retrograde cholangiopancreaticography
ES	endoscopic sphincterotomy
ESGE	European society of gastrointestinal endoscopy
EUS	endoscopic ultrasonography
FNA	fine needle aspiration
FNA	fine needle aspiration
KPI	key performance indicators
LBC	liquid based cytology
METC	medical ethics committee
NET	neuro-endocrine tumor
NGS	next generation sequencing
NS	not significant
NTR	Dutch trial registry
OR	odds ratio
PDAC	pancreatic ductal adenocarcinoma
PPV	positive predictive value
QUEST	quality in endosonography team
RAS	rate of adequate sample
ROSE	rapid on-site cytopathological evaluation
SD	standard deviation
SFM	sensitivity for malignancy
TA	tissue acquisition
PPV	positive predictive value

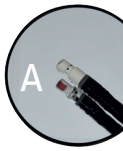


List of publications not included in this thesis

1. Immediate versus Postponed Intervention for Infected Necrotizing Pancreatitis.
   Boxhoorn L, van Dijk SM, van Grinsven J et al.; Dutch Pancreatitis Study Group. N Engl J Med. 2021 Oct 7;385(15):1372-1381.
2. Nationwide practice and outcomes of endoscopic biliary drainage in resectable pancreatic head and periampullary cancer.
   Latenstein AEJ, Mackay TM, van Huijgevoort NCM et al. Dutch Pancreatic Cancer Group. HPB (Oxford). 2021 Feb;23(2):270-278
3. Optimizing cytological specimens of EUS-FNA of solid pancreatic lesions: A pilot study to the effect of a smear preparation training for endoscopy personnel on sample quality and accuracy.
   van Riet PA, **Quispel R**, Cahen DL et al. Diagn Cytopathol. 2021 Feb;49(2):295-302.
4. Role of endoscopic ultrasonography in the diagnostic work-up of idiopathic acute pancreatitis (PICUS): study protocol for a nationwide prospective cohort study.
   Umans DS, Timmerhuis HC, Hallensleben ND et al. BMJ Open. 2020 Aug 20;10(8)
5. Urgent endoscopic retrograde cholangiopancreatography with sphincterotomy versus conservative treatment in predicted severe acute gallstone pancreatitis (APEC): a multicentre randomised controlled trial.
   Schepers NJ, Hallensleben NDL, Besselink MG et al. Dutch Pancreatitis Study Group. Lancet. 2020 Jul 18;396(10245):167-176.
6. Impact of nationwide enhanced implementation of best practices in pancreatic cancer care (PACAP-1): a multicenter stepped-wedge cluster randomized controlled trial.
   Mackay TM, Smits FJ, Latenstein AEJ et al. Dutch Pancreatic Cancer Group. Trials. 2020 Apr 16;21(1):334.
7. Postponed or immediate drainage of infected necrotizing pancreatitis (POINTER trial): study protocol for a randomized controlled trial.
   van Grinsven J, van Dijk SM, Dijkgraaf MG et al. Dutch Pancreatitis Study Group. Trials. 2019 Apr 25;20(1):239.
8. Predictors for choledocholithiasis in patients undergoing endoscopic ultrasound.
   Quispel R, Hallensleben NDL, van Driel LMWJ, Bruno MJ. Scand J Gastroenterol. 2018 Aug; 53(8):984-985.
9. Long-Standing Abdominal Complaints and Hyperamylasemia Due to Foreign Body Ingestion.
   Korteweg L, Veldt BJ, **Quispel R.** Clin Gastroenterol Hepatol. 2018 Sep;16(9): e95-e96.
10. Endoscopic or surgical step-up approach for infected necrotising pancreatitis: a multicentre randomised trial.
    van Brunschot S, van Grinsven J, van Santvoort HC et al. Dutch Pancreatitis Study Group.Lancet. 2018 Jan 6; 391(10115):51-58.
11. Benefit of Earlier Anti-TNF Treatment on IBD Disease Complications?
    Nuij V, Fuhler GM, Edel AJ et al. Dutch Delta IBD Group.J Crohns Colitis. 2015 Nov;9(11):997-1003.
12. Letter: scoring models in alcoholic hepatitis.

Wieten E, Brouwer JT, **Quispel R**, Veldt BJ.Aliment Pharmacol Ther. 2015 Jul;42(1):126.

13. Phenotype of inflammatory bowel disease at diagnosis in the Netherlands: a population-based inception cohort study (the Delta Cohort).
    Nuij VJ, Zelinkova Z, Rijk MC et al. Dutch Delta IBD Group. Inflamm Bowel Dis. 2013 Sep;19(10):2215-22.
14. Image of the month. Tearing of the colon in a patient with collagenous colitis during colonoscopy.
    van Velden R, Snieders I, **Quispel R.** Clin Gastroenterol Hepatol. 2010 Nov;8(11)
15. High prevalence of esophageal involvement in lichen planus: a study using magnification chromoendoscopy.
    Quispel R, van Boxel OS, Schipper ME et al. Endoscopy. 2009 Mar; 41(3):187-93.
16. Re: Gastrointestinal manifestations of dermatologic disorders.
    Quispel R, Schwartz MP, Smout AJ. Clin Gastroenterol Hepatol. 2008 May; 6(5):601; author reply 601.
17. Superselective coil embolization of arterial esophageal hemorrhage.
    Vogten JM, Overtoom TT, Lely RJ, **Quispel R**, de Vries JP. J Vasc Interv Radiol. 2007 Jun;18(6):771-3.
18. Fatal aseptic meningoencephalitis following infliximab treatment for inflammatory bowel disease.
    Quispel R, van der Worp HB, Pruissen M, Schipper ME, Oldenburg B. Gut. 2006 Jul;55(7):1056.
19. Heterotopic gastric tissue mimicking malignant biliary obstruction.
    Quispel R, Schwartz MP, Schipper ME, Samsom M. Gastrointest Endosc. 2005 Jul; 62(1):170-2.
20. Attempted suicide with sustained release diltiazem.
    Quispel R, Baur HJ.Ned Tijdschr Geneeskd. 2001 May 12;145(19):918-22.



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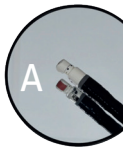

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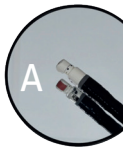

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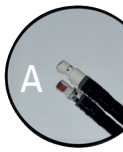
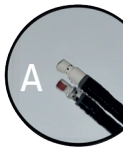


Portfolio

PhD student: Rutger Quispel
PhD period: 2014-2021
Supervisors: Dr. L.M.J.W.van Driel, Dr. B.J.Veldt and Prof.dr. M.J. Bruno

PhD training	Year	Workload (hours)
Courses		
Good Clinical Practice-BROK	2015	12
Good Clinical Practice- BROK refresher course	2019	4
Presentations		
Positive predictive value of endoscopic ultrasound for the detection of intraluminal filling defects in the common bile duct in a large non-academic teaching hospital. – United European Gastroenterology week (poster).	2014	6
Impact of the formation of a regional EUS interest group amongst community hospitals on the yield of EUS-guided tissue acquisition in suspected pancreatic malignancy. – United European Gastroenterology week (poster).	2016	6
EUS for suspected choledocholithiasis. First results of a change in strategy regarding indication and timing of ERCP. – United European Gastroenterology week (poster)	2016	6
EUS for suspected choledocholithiasis. First results of a change in strategy regarding indication and timing of ERCP. – Digestive Disease Days.	2016	12
Impact of the formation of a regional EUS interest group amongst community hospitals on the yield of EUS guided tissue acquisition in suspected pancreatic malignancy. – Digestive Disease Days.	2016	12

PhD training	**Year**	**Workload (hours)**
Improving the yield of EUS guided tissue acquisition from solid pancreatic lesions in community hospital practice. – Reinier de Graaf wetenschapsmiddag.	2016	6
Improving the yield of EUS guided tissue acquisition from pancreatic lesions. – ErasmusMC cytopathology seminar.	2017	6
Endo-echografie in de periferie: Solide pancreaslesies. – Diner Pensant Gastroenterologie, Wassenaar.	2017	6
Endo-echografie geleide weefseldiagnostiek van solide pancreaslesies. – Reinier de Graaf wetenschapsmiddag.	2017	6
Endo-echografie geleide weefseldiagnostiek van solide pancreaslesies. –1st QUEST-endo-echografie symposium 2017.	2017	12
Solide pancreaslesies, EUS-FNA en FNB. – Diner Pensant Twente.	2019	6
Predictors of adequate sampling in EUS guided TA of solid pancreatic lesions in a large prospective cohort of Dutch community hospitals. European-African Hepato-Pancreato-Biliary Association meeting.	2019	12
CUSUM analysis guiding improvement of team performance in EUS guided tissue acquisition of solid pancreatic lesions in community hospitals. – evenement Stichting Toplinische Ziekenhuizen (poster).	2019	6
Predictors of adequate sampling in endoscopic ultrasound guided tissue acquisition of solid pancreatic lesions in a large prospective cohort of Dutch community hospitals. – United European Gastroenterology Week (poster).	2019	6
Cumulative sum analyses guiding improvement of team performance in EUS guided tissue acquisition of solid pancreatic lesions in community hospitals. – United European Gastroenterology Week (poster).	2019	6



PhD training	Year	Workload (hours)
CUSUM analysis guiding multicenter quality improvement of EUS-guided tissue acquisition of solid lesions of the pancreas. – United European Gastroenterology Week.	2020	12
Do endosonographers agree on the presence and subsequent need for treatment of bile duct sludge? – United European Gastroenterology Week (poster).	2020	6
Lessons learned from cusum analysis of EUS-guided tissue acquisition of suspected pancreatic cancer. – United European Gastroenterology Week (poster).	2020	6
CUSUM analysis guiding improvement of team performance in EUS guided tissue acquisition of solid pancreatic lesions in community hospitals. – Reinier de Graaf wetenschapsmiddag.	2020	3
CUSUM analysis is a valuable tool for monitoring quality of EUS guided tissue acquisition of solid pancreatic lesions. – Reinier de Graaf wetenschapsmiddag.	2020	3
Klinische context en voorwaarde bij EUS-FNA/FNB – Veldhuizen cursus cytopathologie.	2020	12
Nationwide practice and yield of EUS guided tissue acquisition prior to resection of pancreatic ductal adenocarcinoma. – QUEST national EUS webinar.	2021	6
Nationwide practice and yield of EUS guided tissue acquisition prior to resection of pancreatic ductal adenocarcinoma. – Dutch Pancreatic Cancer Group webinar.	2021	3
Nationwide practice and yield of EUS guided tissue acquisition prior to resection of pancreatic ductal adenocarcinoma. – National cytopathology webinar.	2021	3
This is how we do it: EUS guided tissue acquisition of solid pancreatic lesions. – Digestive Disease Days virtual.	2021	6

PhD training	Year	Workload (hours)
Spontane passage van kleine galwegsteentjes, afwachten of ERCP? – GE- Zuid West, regional gastroenterology meeting.	2021	3
Nationwide practice and yield of EUS guided tissue acquisition prior to resection of pancreatic ductal adenocarcinoma. – United European Gastroenterology Week virtual.	2021	6

Teaching		
Supervising master thesis of Minke van Mierlo (LUMC)	2015	24
Supervising part-time science project Cecile Vink (RdGG)	2020	12
Smear-training cytopathology department erasmusMC	2019	6

Attendance at conferences and seminars		
Diner Pensant Pancreas	2015	4
Digestive Disease Days	2015-2021	34
Digestive Disease Days-cursorisch onderwijs	2015, 2017	12
Quality in Endosonography Team-meetings	2015-2021	42
United European Gastroenterology Week	2015, 2016, 2017, 2020 and 2021	82
UEG- Postgraduate Training	2015 and 2017	24
National upper GI cancer conference	2015 and 2016	15
Pancreasdag	2016 and 2018	12
EUS-live Amsterdam	2018 and 2021	16
EUS masterclass Utrecht	2018	6
13th Congress of European-African-HPB-association	2019	8
GE-zuidwest regionaal onderwijs	2019-2021	6
Dusseldorf 22th International Endoscopy Symposium	2020	15

Grants

QUality in EndoSonography Team. Multidisciplinary research initiatives NVGE Grant
Team Westland Grant for EUS guided TA of solid pancreatic lesions
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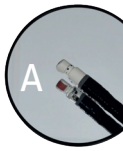
Research Grant. Reinier de Graaf Gasthuis Wetenschapscommissie



Curriculum vitae

De schrijver van dit proefschrift werd geboren op 6 april 1974 in Schiedam, groeide op in Oldenzaal en studeerde Geneeskunde in Groningen. Een keuze co-assistentschap Heelkunde/Intensive Care geneeskunde resulteerde in een eerste baan als arts-assistent op de Intensive Care in het Westeinde ziekenhuis te Den Haag.

Dit werd gevolgd door een functie als onderwijs-, en onderzoeks-arts-assistent in het UMC-Utrecht onder supervisie van Prof. D.W. Erkelens, opleider Interne Geneeskunde. In Utrecht werd vervolgens gestart met de opleiding Interne Geneeskunde. Na geboeid te zijn geraakt door de Maag, -Darm en Leverziekten en met name door de endoscopie, werd de overstap gemaakt naar de opleiding tot MDL-arts (Prof. G.P. van Berge Henegouwen, en later Prof. M. Samsom). Het laatste jaar van de opleiding bestond uit een stage "advanced"-endoscopie, inclusief endo-echografie, in het Antonius Ziekenhuis te Nieuwegein (Dr. R. Timmer).

Sinds september 2006 is hij werkzaam als MDL-arts in het Reinier de Graaf Gasthuis te Delft met als aandachtsgebieden oncologie, interventie-endoscopie en endo-echografie. Van 2011-2015 vervulde hij de rol van Medisch Manager van de vakgroep MDL en bestuurslid van de maatschap Interne, MDL en Reumatologie. Momenteel is hij vice-voorzitter van de netwerktumorgroep Hepato-Pancreatico-Biliaire tumoren in de regio west, welke zich bezig houdt met de kwaliteit van zorg op het gebied van levermetastasen, alvleesklier-, galweg- en galblaastumoren.

In het Reinier de Graaf Gasthuis werd gestart met het verzamelen van gegevens betreffende endo-echografie, hetgeen uiteindelijk geresulteerd heeft in de oprichting van een regionale onderzoeksgroep (QUEST) en dit proefschrift. Dit proefschrift is tot stand gekomen in samenwerking met, en onder begeleiding van Prof M.J. Bruno, Dr. L.M.J.W. van Driel en Dr. B.J. Veldt, van de afdelingen Maag-, Darm-en Leverziekten van het Erasmus Medisch Centrum te Rotterdam en het Reinier de Graaf Gasthuis te Delft. Per september 2021 is de derde QUEST-promovendus van start gegaan.

Sinds 2006 is hij getrouwd met Josine. Ze hebben 3 kinderen: Michiel, Teun en Lola.

Dankwoord

Dit is een woord van dank voor iedereen die op welke manier dan ook heeft bijgedragen aan het tot stand komen van dit proefschrift. Omdat dit simpelweg teveel mensen zijn om allemaal bij naam te noemen, beperk ik mij tot diegenen die mijn bijzondere dank verdienen.

Groot is mijn dank voor alle patiënten die toestemming gaven voor het gebruiken van de gegevens van de procedures die zij ondergingen. Lieve mensen, dankzij jullie staat het meten van kwaliteit van endo-echografie op de kaart en hebben we de eerste stappen kunnen zetten in de verbetering hiervan.

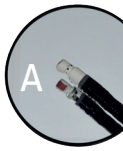
Geachte Professor Bruno, beste Marco, veel dank voor je hulp en het geven van richting aan het onderzoek zoals we dat we de afgelopen jaren hebben uitgevoerd. Ik verwacht nog veel plezier te kunnen beleven aan, en veel te kunnen leren van onze samenwerking in de toekomst.

Geachte leden van de leescommissie: Professor M. Spaander, Professor F. van Kemenade en Professor H. van Santvoort. Ik ben blij dat u zich bereid getoond heeft om tijd te investeren in de beoordeling van dit proefschrift. Dank daarvoor. Uiteraard ook mijn hartelijke dank aan de overige leden van de promotiecommissie: Professor C.J. Hilders, Professor R. Bisschops en Dr B. Groot Koerkamp. Dank voor uw bereidheid om vandaag te willen opponeren.

Beste Lydi en Bart. Ik ben dankbaar en blij dat ik in jullie twee gemotiveerde, onderzoeksminded collega's heb leren kennen. Ik hoop onze plezierige samenwerking nog lang te kunnen voortzetten en kijk uit naar gezamenlijk congresbezoek, inclusief wandelingen door de stad en het bijbehorende museumbezoek als toetje na een dag congres.

Uiteraard gaat mijn dank uit naar alle overige leden van het QUality in EndoSonography Team (QUEST): endo-echografisten en pathologen, zowel de deelnemers van het eerste uur als de meer recente aanwas. Ik denk dat we als groep trots mogen zijn op al hetgeen we tot nu toe bereikt hebben. We zijn nog lang niet klaar! Ik hoop van harte dat we onze samenwerking, zowel op gebied van postdoctoraal onderwijs, als op het gebied van kwaliteit en wetenschap, nog lang kunnen voortzetten.

Beste Hannah, als eerste fulltime QUEST-arts-onderzoeker heb je de voortgang van onze projecten een enorme boost gegeven. Dank daarvoor, en succes met het afronden van je eigen promotietraject.



Beste Guus, zonder jouw "monnikenwerk" had hoofdstuk 8 nooit bestaan. Dank voor je hulp en veel succes met je studie.

Zonder de financiële ondersteuning van de Nederlandse Vereniging voor gastro-enterologie (NVGE), de wetenschaps advies commissie (WAC) van het Reinier de Graaf Gasthuis, de fietsers van Team Westland en Jan Dalsem was dit proefschrift er waarschijnlijk nooit gekomen. Allen veel dank! Ook het wetenschapsbureau van het Reinier de Graaf dank ik voor de ondersteuning in verleden, heden en hopelijk ook de toekomst.

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En natuurlijk: wat zou het leven zijn zonder familie en schoonfamilie?

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