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Transabdominal ultrasonography to reduce the burden of X-ray imaging in prophylactic pancreatic stent localization after ERCP—A prospective trial

Florian Alexander Michael[1] | Ludmilla Gerber[1] | Nina Weiler[1] | Peter Marton Hunyady[1] | Nada Abedin[1] | Anna-Lena Laguna de la Vera[1] | Philipp Stoffers[1] | Natalie Filmann[2] | Stefan Zeuzem[1] | Jörg Bojunga[1] | Mireen Friedrich-Rust[1] | Georg Dultz[1]

[1]Department of Internal Medicine 1, University Hospital Frankfurt, Frankfurt, Germany

[2]Institute of Biostatistics and Mathematical Modeling, Frankfurt, Germany

Correspondence
Florian Alexander Michael, Department of Internal Medicine 1, University Hospital Frankfurt, Theodor-Stern-Kai 7, Frankfurt 60590, Germany.
Email: Florian-Alexander.Michael@kgu.de

Abstract

Background: Before performing endoscopy to remove prophylactic pancreatic stents placed in patients with high risk of post-endoscopic retrograde cholangiopancreatography pancreatitis (PEP), X-ray imaging is recommended to confirm the stents position in the pancreatic duct.

Objectives: The aim of the present study was to investigate the feasibility of prophylactic pancreatic stent detection by transabdominal ultrasonography, to reduce the burden of X-ray imaging, which is currently the golden standard.

Methods: All patients who received a pancreatic stent for PEP prophylaxis were included in the present prospective trial. First, stent position was determined by transabdominal ultrasonography. Afterwards, it was verified by X-ray imaging. Retained stents were removed by esophagogastroduodenoscopy. Dislocated stents needed no further intervention.

Results: Fourty-one patients were enrolled in this study. All prophylactic pancreatic stents were straight 6 cm long 5 Fr stents with external flap. All stents were removed between day 1 and 10 (median: 3 days) in all cases. In 34 of 41 cases (83.0%), the pancreatic stent was still in place on the day of examination. Twenty-nine of 34 (85.3%) stents were detected correctly by transabdominal ultrasonography. Overlying gas prevented visualization of the pancreas in 3/41 (7.3%) cases. Sensitivity of sonographic detection of the stent was 93.5% (29/31). Six of seven stents were determined correctly as dislocated by ultrasonography. Here, specificity was 85.7%. A positive predictive value of 96.7% (29/30) was examined. The negative predictive value was 75.0% (6/8).

The study was approved by the institutional review board of the Frankfurt University Hospital (#419/17) and registered at clinical.trials.gov (NCT03649399).

Conclusion: Transabdominal ultrasonography detects the majority of prophylactic pancreatic stents. Thereby, it helps to identify patients with an indication for endoscopy sufficiently. X-ray imaging could subsequently be omitted in about 70% of examinations, reducing the radiation exposure for the patient and the endoscopy staff.

KEYWORDS
endoscopic retrograde cholangiopancreatography, endoscopy, pancreatitis, prophylactic pancreatic stent, transabdominal, X-ray imaging

INTRODUCTION

Endoscopic retrograde cholangiopancreatography (ERCP) is a globally implemented standard procedure in gastroenterology for the treatment of biliary tract diseases.[1] The most common and relevant complication is post-ERCP pancreatitis (PEP) occurring in 3.5%–9.7% of all ERCPs with a mortality of 0.1%–0.7%.[2,3]

Accordingly, the prophylaxis of PEP is of high clinical relevance and consists of several pharmacologic and procedure-related measurements, one being the placement of pancreatic duct stents in patients at high risk for PEP.[1,4–6] The high relevance of pancreatic stents for prophylaxis of PEP has been demonstrated by several large metanalyses (Odds ratio 0.22–0.29)[7–14] and is recommended by national and international guidelines.[1,4–6] Straight 5 Fr polyethylene stents are recommended as they are easier to place and superior in the prevention of PEP than 3 Fr stents.[15–17] Although the stents have a potential of self-dislodgment, the removal of retained stents is recommended within 5–10 days after placement[1,4–6] since stent-associated pancreatic duct injury and pancreatitis have been reported.[18,19] Stents should remain at least 12–24 h to be effective.[20] Before retained stents are removed by esophagogastroduodenoscopy (EGD), they are visualized by abdominal X-ray to avoid an unnecessary EGD in patients with spontaneous stent dislodgement. This procedure is established worldwide and recommended by national and international guidelines.[1,4–6] The European Society of Gastrointestinal Endoscopy guideline suggests that X-ray imaging can be avoided in patients who require a follow-up endoscopic procedure shortly after stent insertion.[6] The necessity of an X-ray examination results in (i) radiation exposure to the patient and staff and (ii) the use of pivotal resources in the endoscopy department, that is, use of the "ERCP-room" with an X-ray device or even the need of transferring the patient to the radiology department before stent removal.

Hence, the current prospective study analyzed the feasibility of visualizing a prophylactic pancreatic stent with sonography. Therefore, X-ray could be replaced by a simple ultrasound examination to visualize or exclude pancreatic stents to overcome the mentioned disadvantages of the radiologic examination.

METHODS

The present study is a prospective single-center study conducted at the University Hospital Frankfurt, Germany, to evaluate whether sonography is feasible to visualize a prophylactic pancreatic stent. Thereby, sonography could replace X-ray in the detection of pancreatic stents placed for the prophylaxis of PEP. Patients who underwent ERCP and received a 5 Fr 6 cm pancreatic stent with external flap (Optimed) for prophylaxis of PEP were included. All included patients gave written informed consent prior to study participation. Exclusion criteria were therapeutic stent placement for chronic pancreatitis or inability to give written informed consent.

All included patients received an ERCP by experienced examiners in endoscopy (>5 years of experience). In accordance with the European guideline of prophylaxis of PEP, pancreatic stents were placed if one of the following procedure-related risk factors occurred: (i) Cannulation attempts duration >10 min, (ii) pancreatic guidewire passages >1, or (iii) pancreatic injection.[20] Abdominal ultrasound was performed between day 1 and 10 after the ERCP procedure by experienced examiners (>5 years of experience). The result of the ultrasound was either pancreatic stent being visualized in the pancreatic duct (stent in situ), stent not being visualized (stent dislodged) or undefined (pancreas not visible).

Immediately after the ultrasound examination, an abdominal X-ray was performed to evaluate if the pancreatic stent was still in place. Retained stents were removed by EGD. If stent dislodgement was confirmed by abdominal X-ray, no further intervention was needed. The patients' gender, age, weight, presence of liver cirrhosis and pancreas lipomatosis, the date of ERCP and sonography as well as X-ray and EGD, the indication of the ERCP, the number of examiners in ERCP and sonography, the placement of a biliary stent, and the size of the pancreatic stent were documented. In this single-armed study, neither randomization nor blinding were needed. In Figure 1, the algorithm of the study protocol is shown.

The primary outcome of the study was to calculate the positive predictive value of sonography for detection of pancreatic stents. As a reference method, the current gold standard abdominal X-ray was used, followed by the removal of the pancreatic stent by EGD. Secondary outcomes were to calculate the negative predictive value,

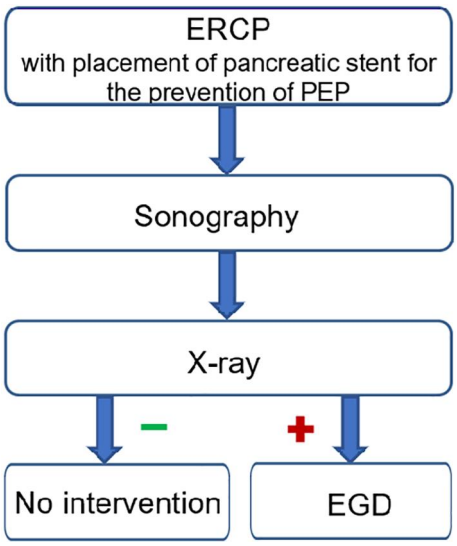

FIGURE 1 Algorithm based on the study protocol. Pancreatic stents being placed by ERCP underwent at first sonography. Afterwards, X-ray as gold standard verified sonographic findings. In cases where the stents are not detected in the pancreatic duct, no further intervention is needed. Retained stents need to be removed by EGD. EGD, esophagogastroduodenoscopy; ERCP, endoscopic retrograde cholangiopancreatography; PEP, post-ERCP pancreatitis

sensitivity, specificity as well as analyzing false-positive and false-negative values. Statistical analyses were performed to investigate associations between baseline characteristics and success of sonographic stent detection.

Ultrasound devices

A total of three different ultrasound devices were used. All examiners were experienced with all three devices and the device was chosen by availability. The used ultrasound devices were either Aplio 500 (Toshiba), Ascendus Hi Vision (Hitachi), or Acuson S2000 (Siemens). In all devices a convex transducer was used. Aplio 500 used PVT-375SC transducer (frequency: 5.0 MHz, range: 1.5–6.0 MHz, field of view: approximately 70°). Ascendus Hi Vision used EUP C715 transducer (frequency: 5.0 MHz, range: 1.0–5.0 MHz, field of view: approximately 70°). Acuson S2000 used 4C1 transducer (frequency: 4.5 MHz, range: 1.0–5.0 MHz, field of view: 66°).

Statistical analysis

Power and sample size as well as data collection, data management, and statistical analyses were performed with SPSS software package, release 21 (IBM) and BiAS. for Windows version 11.10 (Epsilon Verlag).

Data are lacking as a reference for the calculation of power and sample size. The positive predictive value was the primary outcome of the study and statistic power should be sufficient to support a value of 95%. If three or less stents were labeled false positive (=sonography describes stent being retained but X-ray displays the stent being dislodged), a trial with $n = 38$ would have a power of at least 85% for a positive predictive value of approximately 95%.

Descriptive statistics were computed to provide frequencies and percentages for categorical variables as well as median and range for continuous values. Positive predictive value, negative predictive value, sensitivity, and specificity were calculated from the contingency table. An intention-to-treat analysis was performed with all enrolled patients who underwent sonography and X-ray/EGD. Patients with overlaying gas were excluded in a per-protocol analysis. Univariate analysis was performed to detect a correlation between baseline characteristics and the success of sonographic stent detection (Mann–Whitney-U-test in ordinal scale, $\chi 2$ in nominal scale (respectively Fisher's exact test when $n < 5$ in at least one subgroup) and Cochran–Mantel–Haenszel test in ordinal scale with $5 > n > 2$ strata size. All p-values reported are two-sided p values. A p-value of less than 0.05 was considered to be statistically significant.

RESULTS

Patient population

Figure 2 demonstrates a flow chart of enrollment and analysis of the present trial. Two thousand and fifty-one ERCPs in total and 621 ERCPs with endoscopic papillotomy were performed during enrollment period. A total of 50 patients were assessed for eligibility. All patients received one pancreatic stent to prevent PEP. Nine patients had to be excluded of which five patients did not receive a sonography prior to endoscopy before they were transferred to the endoscopy department before being transferred to sonography department, three patients were transferred to another hospital with the pancreatic stent in situ, and one patient met an exclusion criterion (chronic pancreatitis with the need of therapeutic pancreatic stenting). Therefore, 41 patients underwent the intended study protocol and were analyzed for the primary outcome. Three patients had overlaying gas. Sonography was not able to state the stents position. Those patients were excluded for a per-protocol analysis. Patients were recruited from 10 July 2017 to 20 April 2020 where the predefined number of cases was reached. Characteristics of the study cohort are summarized in Table 1.

All placed pancreatic stents were 6 cm long 5 Fr polyethylene stents with a single external flap and no internal flange. The study protocol with ultrasound, X-ray, and EGD was performed between day 1 and 10 in all cases (median: 3 days). Simultaneous stenting of the common bile duct during ERCP was performed in 24 (58.5%) patients. Four patients (9.8%) developed a mild PEP. No patient had any further complications or died.

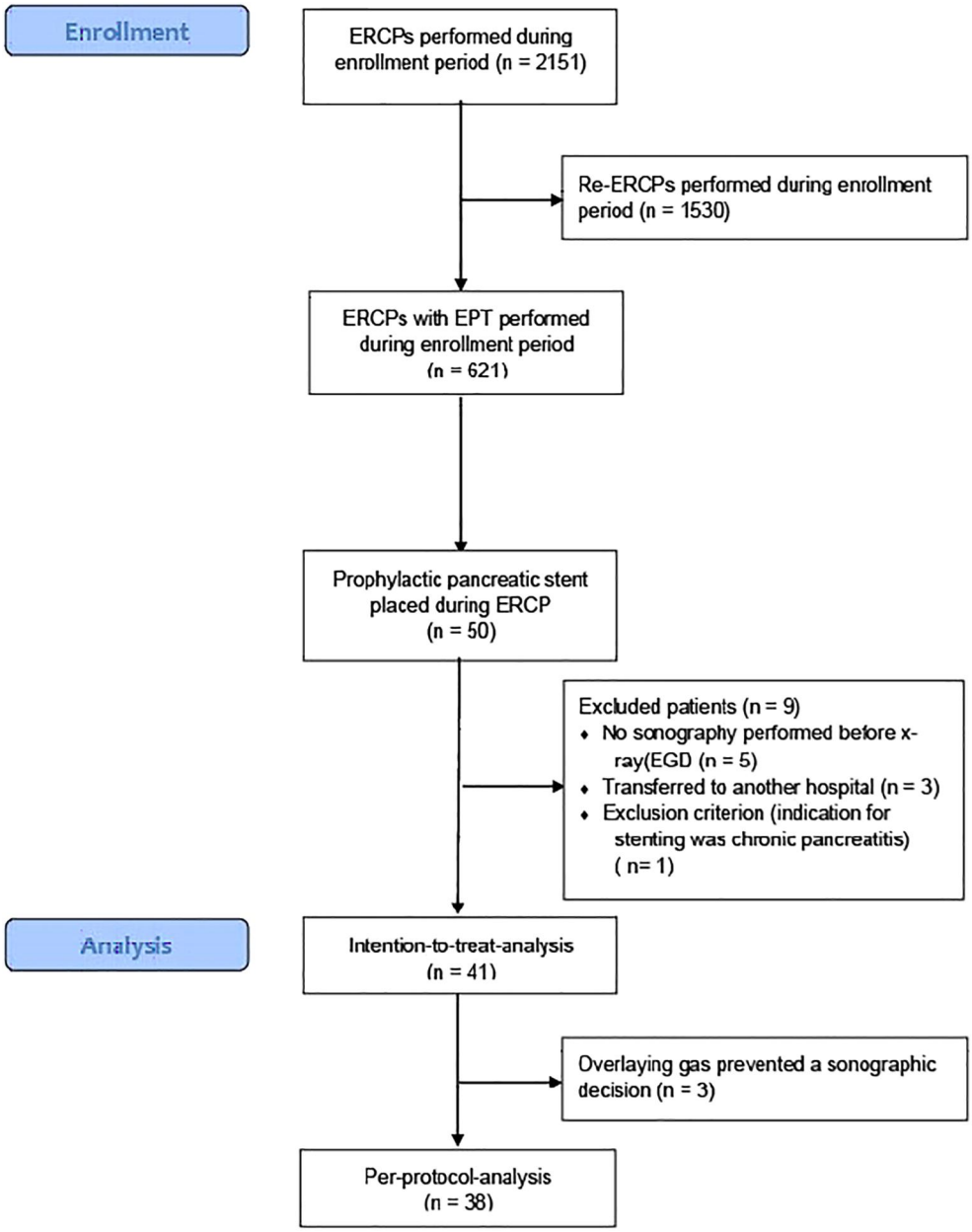

FIGURE 2 Flow diagram of enrollment and analysis. A total of 41 patients were included in intention-to-treat analysis; 38 patients were analyzed per-protocol. EGD, esophagogastroduodenoscopy; EPT, endoscopic papillotomy; ERCP, endoscopic retrograde cholangiopancreatography

Feasibility and recommendations for sonographic evaluation of pancreatic stents

In three (7.3%) of 41 examinations, overlying gas prevented sonographic visualization of the pancreas. Accordingly, the technical success rate of the sonographic procedure was 92.7%.

Our recommendations for the evaluation of pancreatic duct stents are based on the experience prior and during the study: To perform a sonographic examination of the pancreatic duct, the patients are in supine position or in left oblique position in case of overlying gas. Convex transducers with a frequency between 3.0 and 5.5 MHz were used to detect pancreatic stents in a B-scan. The pancreatic stents used for prophylaxis of PEP are thin 5 Fr stents and should carefully be distinguished from biliary stents that are usually 7 Fr or 10 Fr (Figure 3a). A confusion of biliary stents with pancreatic stents could lead to false-positive results. Still, biliary stents can be used as a landmark for identification of pancreatic stents.

The angle of the pancreatic duct in the pancreatic head is very steep and almost parallel to the spine as shown in Figure 4. To visualize the duct and pancreatic stents in the pancreatic head a subxiphoid position slightly to the right of the midline with the

TABLE 1 Baseline characteristics and complications

Characteristic	
Gender: Male	28 (68.3%)
Age (years)	60.0 ± 17.3 (20–92)
Weight (kg)	75.9 ± 18.7 (59–85)
ERCP-indication	
Tumor	21 (51.2%)
Choledocholithiasis	9 (22.0%)
Inflammatory stenosis after intervention/ surgery	4 (9.8%)
PSC/SSC	3 (7.3%)
Anastomosis stenosis after LTx	3 (7.3%)
Undefined common bile duct stenosis	1 (2.4%)
Liver cirrhosis	4 (9.8%)
Pancreatic lipomatosis	10 (24.4%)
Size of pancreatic stent: 5 Fr 6 cm	41 (100%)
Common bile duct stenting	
0 stents	8 (20%)
1 stent	27 (65%)
2 stents	6 (15%)
Plastic stent	31 (93.9%)
cSEMS	2 (6.1%)
Days between ERCP and EGD	
1–3 days	12 (29.3%)
3–5 days	23 (56.1%)
5–10 days	6 (14.6%)
Sonography device	
Tochiba[a]	22 (53.7%)
Hitachi[b]	13 (31.7%)
Siemens[c]	2 (4.9%)
Missing documentation	4 (9.8%)
PEP	4 (9.8%)

Note: Continuous parameters are expressed as means with standard deviation and minimum to maximum, nominal parameters as number of patients with percentage of occurrence.

Abbreviations: cSEMS, covered self-expandable metal stent; EGD, esophagogastroduodenoscopy; ERCP, endoscopic retrograde cholangiopancreatography; Fr, French; LTx, liver transplantation; PEP, post-ERCP pancreatitis; PSC, primary sclerosing cholangitis, SSC, secondary sclerosing cholangitis.

[a]Aplio 500 (Toshiba).

[b]Ascendus Hi Vision (Hitachi).

[c]Acuson S2000 (Siemens).

transducer placed in a left-angled oblique longitudinal orientation is needed. Accordingly, the pancreatic stent can be visualized in a longitudinal section as shown in Figure 3b.

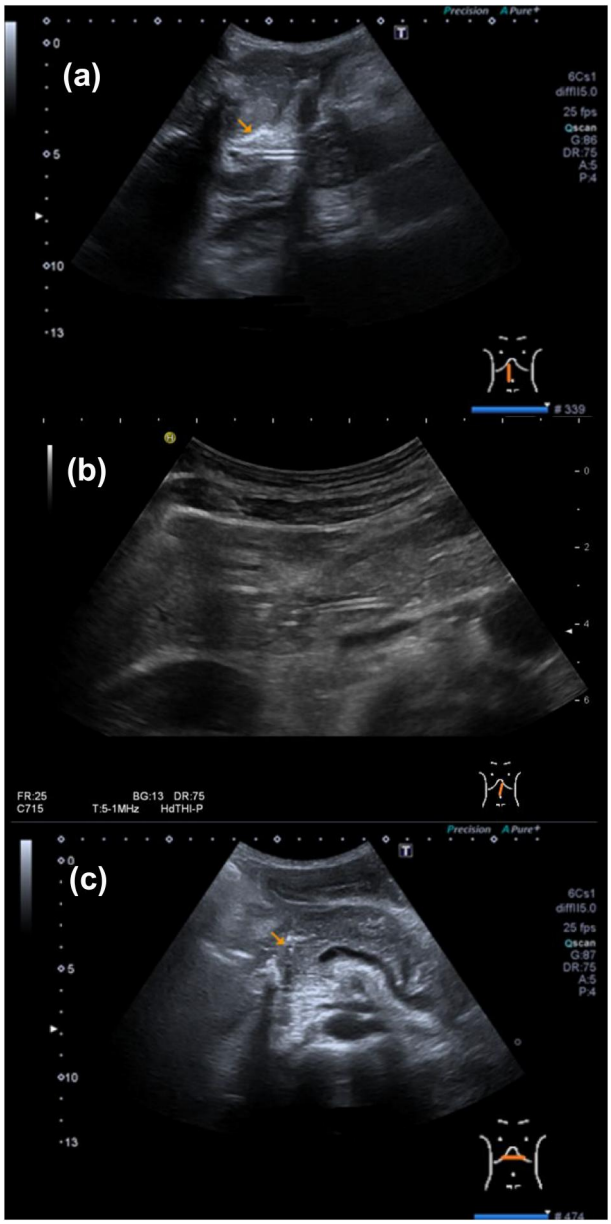

FIGURE 3 Biliary and pancreatic stents in B-mode ultrasound. (a) Biliary stent in B-mode ultrasound. Longitudinal section of the extrahepatic part of a stent in the common bile duct (Toshiba). (b) Pancreatic stent in B-mode ultrasound. Longitudinal section of a pancreatic stent in the pancreatic head. The pancreatic duct has a slightly right-tilted craniocaudal orientation before it turns to have a transverse orientation in the corpus part (Hitachi). (c) Pancreatic stent in B-mode ultrasound. Transversal section of a pancreatic stent in the pancreatic head (Toshiba)

Tilting the transducer by 90° counterclockwise in a transversal position displays the pancreatic stent in a cross section (Figure 3c). As the transducer follows the pancreatic duct to the corpus part, the orientation becomes transverse. The pancreatic duct without a stent has an anechoic to a hypoechoic lumen with two slightly isoechoic to hyperechoic boundaries corresponding to the pancreatic duct wall. If a pancreatic stent is in place, the boundaries appear as bright

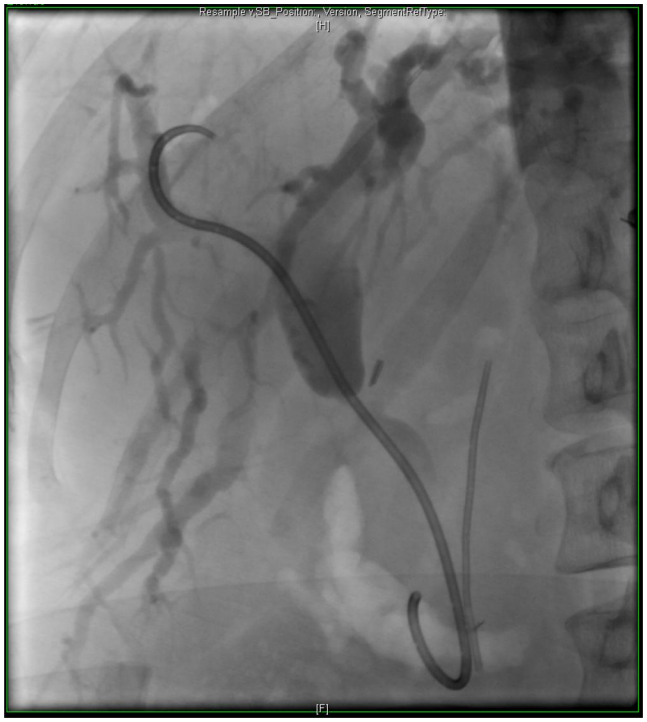

FIGURE 4 Pancreatic stent in X-ray imaging. X-ray of a short 5 Fr 6 cm pancreatic stent with an external flap and a 10 Fr double pigtail stent in the common bile duct as well as cholestasis in the biliary system

hyperechoic reflexes. The end of the stent in the pancreatic caput is displayed by a transition of the bright hyperechoic boundary to a poorer hyperechoic or isoechoic signal in the further parts of the duct.

Outcome of sonographic evaluation

A retained pancreatic stent was confirmed by abdominal X-ray in 34 of the remaining 41 cases (82.9%) and was removed endoscopically. Seven (18.4%) pancreatic stents had been dislodged spontaneously and no further intervention was needed.

Figure 5 is the contingency table of sonographic and radiologic stent detection. An intention-to-treat analysis was performed with all enrolled patients who received both sonographic and radiologic/endoscopic work up. In a per-protocol analysis all patients with overlaying gas in the pancreatic region were excluded because in those patients no statement of the stents position was feasible.

Intention-to-treat analysis

The ultrasound examination visualized the pancreatic stent correctly in 29 of 34 cases (sensitivity: 85.3%, 95% CI: 68–95) with five false-negative results (14.7%).

Stent dislodgment was assessed correctly by sonography in six of seven cases (specificity: 85.7%, 95% CI: 42–100) with one false-positive result (14.3%).

(a) Intention-to treat analysis

		Stent verified by x-ray/EGD		
		yes	no	
Stent visualized by sonography	yes	29	1	96.7%[1]
	no	5	6	54.5%[2]
		85.3%[3]	85.7%[4]	41

(b) Per-protocol analysis

		Stent verified by x-ray/EGD		
		yes	no	
Stent visualized by sonography	yes	29	1	96.7%[1]
	no	2	6	75.0%[2]
		93.5%[3]	85.7%[4]	38

FIGURE 5 Contingency table of the study outcome. (a) Intention-to-treat analysis of all patients who underwent sonography and X-ray or EGD. (b) Per-protocol analysis without those patients with overlaying gas that prevented a sonographic result. All three patients with overlaying gas had a pancreatic stent in the pancreatic duct. 1: positive predictive value; 2: negative predictive value; 3: sensitivity; 4: specificity. EGD, esophagogastroduodenoscopy

The positive predictive value of sonography to detect retained stents was 96.7% (95% CI 83–100) with 29 correct sonographic detections of a total of 30 retained stents.

The negative predictive value of sonography to exclude dislodged stents was 54.5% (95% CI: 23–83) with six of 11 pancreatic stents being correctly labeled as dislodged by ultrasound.

When decision for stent removal had been based only on the ultrasound examination in cases where the stent was detected by ultrasound, X-ray could have been omitted in 29 of 41 cases (70.7%) while one unnecessary EGD would have been performed.

In the cases where sonography assumed stent dislodgement, five of 11 stents (54.5%) would have remained in the pancreatic duct had the decision been made relying on the ultrasound examination only. In three of those five cases overlaying gas prevented a sonographic decision of the stents' position. In all three cases the pancreatic stent was detected in situ by x-ray and removed by EGD.

Per-protocol analysis

As mentioned above, in three (7.3%) of 41 examinations, overlying gas prevented sonographic visualization of the pancreas leading to a false-negative result. Those patients were excluded from the per-protocol calculations of sensitivity, specificity, and predictive values.

The ultrasound examination visualized the pancreatic stent correctly in 29 of 31 cases (sensitivity: 93.5% (95% CI: 79–99) with two false-negative results (6.5%).

The negative predictive value of sonography to exclude dislodged stents was 75% (95% CI: 35–97) with six of eight pancreatic stents being correctly labeled as dislodged by ultrasound.

Results of positive predictive value and specificity are the same in the intention-to-treat analysis and per-protocol analysis.

Association of parameters with stent dislodgement and outcome

No significant association was observed between stent dislodgement and the time from ERCP to stent visualization ($p > 0.2$). Four stents were found to be dislodged on Day 3, two stents on Day 4, and one stent on Day 5. Furthermore, there was no significant association between stent dislodgement and simultaneous placement of a biliary stent ($p = 0.2$).

Univariate analysis showed no significant association between baseline characteristics and success of the sonographic stent detection (age ($p > 0.2$), weight ($p > 0.2$), indication ($p > 0.2$), used sonography device ($p > 0.2$), type of biliary stentic (metal/plastic, $p > 0.2$) pancreas lipomatosis ($p > 0.2$), liver cirrhosis ($p > 0.2$), and pancreatitis ($p > 0.2$)).

Furthermore, no association between biliary stenting and the baseline characteristics was found (age [$p > 0.2$], weight [$p > 0.2$], indication [$p > 0.2$], used sonography device [$p > 0.2$], pancreas lipomatosis [$p > 0.2$], liver cirrhosis [$p > 0.2$], pancreatitis [$p > 0.2$]).

DISCUSSION

Visualizing pancreatic stents by experienced examiners using high-quality ultrasound devices was first described as feasible in 2005.[21] However, data on its longitudinal use are widely lacking. To our knowledge, this is the first study which prospectively evaluates the detection of prophylactic pancreatic stents in the pancreatic duct compared to X-ray in a well-characterized cohort of consecutive patients.

Visualization of at least parts of the pancreatic duct was shown to be feasible in up to 85% by studies performed in the 1980s.[22–24] As the image resolution of ultrasound devices has improved enormously by technical enhancements such as harmonic imaging, fields of application have been expanded and the sensitivity of visualization of the pancreatic duct has increased. Accordingly, the present study reports a technical success rate of 92.7% to display the pancreatic duct in the head and corpus region by experienced sonographers.

Regarding the success of the sonographic detection of retained pancreatic stents the present study reports an excellent sensitivity of 85.3% and a positive predictive value of 96.7%. If patients with overlaying gas are excluded, who need to undergo X-ray anyways, sensitivity is 93.5% for sonographic detection of a pancreatic stent in the duct. Comparable data are lacking, still there are publications on the detection of pancreatic lesions and biliary stents. A recent trial investigated the detection rate of pancreatic cystic lesions following an elaborated ultrasound protocol. The sensitivity of detecting pancreatic cysts was 88.7% for the uncinate process and inferior head, 97.5% for the head, 97.1% for the body, 89.0% for the body-tail, 66.7% for the tail, and 92.2% for all cystic lesions in the pancreas.[25] Another trial by Titare et al. evaluated the accuracy and utility of ultrasound in the assessment of biliary stents in 221 patients. Results revealed a sensitivity of 77.3%, positive predictive value of 93.4%, specificity of 94.6%, and negative predictive value of 80.8%. To our agreement, the authors came to the conclusion that sonography is a reliable, noninvasive imaging modality to evaluate the presence of biliary stents.[26] Our study shows a comparable sensitivity and even better positive predictive value for pancreatic stents which might be due to the prospective study protocol and experienced examiners. Specificity of 85.7% and negative predictive value of 75% were slightly below the values reported for biliary stents.[26] Reasons might be the small size of the pancreatic duct with up to 3 mm as well as the small diameter and length of pancreatic stents compared to the larger biliary stents. Additionally, artifacts and parts of the pancreatic duct can be misinterpreted as a pancreatic stent.

Abdominal X-ray is still the recommended modality for the detection of retained pancreatic stents by current international guidelines.[1,4–6] Still, even the current gold standard X-ray can be misleading. A retrospective trial reported a false-negative rate of 4.8% (8 patients) in 167 patients with pancreatic stents examined by abdominal X-ray. In eight cases the radiologic report said “no stent” while the retained pancreatic stent was found in three cases during subsequent procedures for indications unrelated to the initial stent placement and five retained stents were identified on a second review of the imaging by an endoscopist.[27] Accordingly, X-ray is not impeccable in this context. To use EGD directly without confirmation of stent retention is generally not recommended by international guidelines.[6] Though EGD is a fast standard procedure with a very low complication rate,[28] it is nowadays often performed under sedation and as such an avoidable risk if the stent has been dislodged spontaneously.

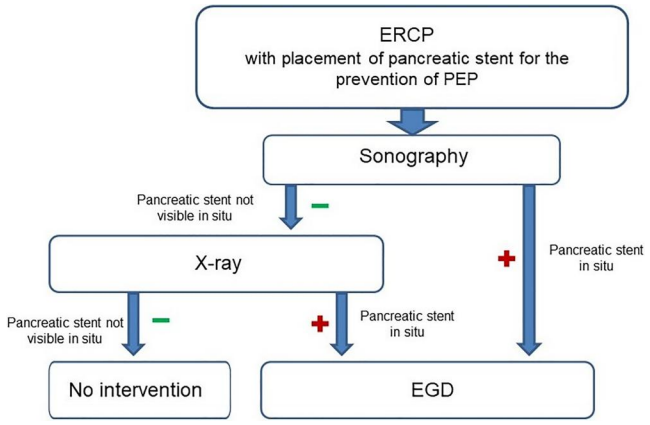

FIGURE 6 Algorithm derived from the trial's outcome. Pancreatic stents being visualized by ultrasound can be removed directly by EGD. In cases were the stents are not detected by ultrasound X-ray has to be used. Subsequently, retained stents need to be removed by EGD. EGD, esophagogastroduodenoscopy; ERCP, endoscopic retrograde cholangiopancreatography; PEP, post-ERCP pancreatitis

The current study demonstrates in a representative population that sonography being ubiquitously available is a fast and sufficient procedure to detect prophylactic pancreatic stents (positive predictive value > 95% and a sensitivity of >85%). A major advantage of sonography compared to X-ray is the lack of radiation exposure to both the patients and the endoscopy staff. Furthermore, pivotal resources in the endoscopy department could be saved since neither a room with an x-ray device has to be blocked nor the patient needs to be transferred to the radiology department.

The strength of the presented study is the novelty of the addressed question concerning a globally used procedure with the potential reduction of radiation and endoscopy resources in a prospective study design. To our knowledge no data is published on this topic so far.

Limitations are the limited number of patients and the single-center design. Furthermore, ultrasound devices of high-quality imaging were utilized by very experienced examiners (>5 years of experience) to identify the pancreatic stents which might be difficult to reproduce in the clinical routine. The results of this trial might not be generalized due to less experienced examiners and sonography devices of fewer quality. Therefore, sensitivity and positive predictive value might decrease in a real world setting.

In conclusion and based on our findings, a novel algorithm for the detection of prophylactic pancreatic stents should be discussed (Figure 6). As a first approach sonography could be used to visualize prophylactic pancreatic stents. Pancreatic stents being in situ could be directly removed by EGD without further diagnostic imaging since positive predictive value was high. If a pancreatic stent cannot be visualized by sonography, complementary x-ray needs to be performed. Pancreatic stents being visualized by X-ray will subsequently be removed by EGD. Dislodged pancreatic stents need no further intervention. The present algorithm would have reduced the need of X-ray by 70.7% in the present study with only 2.4% of the patients receiving an unnecessary EGD. In literature, EGD is being described as a safe procedure.[28] Overall complication rate was described between 0.13% and 0.5% with approximately 60% sedative associated complications and a mortality rate between none and 0.05%.[29–31]

Before this proposed algorithm is used as a standard a larger trial for validation of the current result and using the proposed algorithm is warranted.

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CONFLICT OF INTERESTS

The authors declare that they have no conflict of interests.

AUTHOR CONTRIBUTIONS

Georg Dultz, Mireen Friedrich-Rust, and Ludmilla Gerber developed the study conception and design. Material preparation and data collection were performed by Georg Dultz, Mireen Friedrich-Rust, Ludmilla Gerber, Nina Weiler, Peter Marlon Hunyadi, Nada Abedin, Anna Lena Laguna de la Vera, and Philipp Stoffers. Analysis was performed by Florian Alexander Michael and Natalie Filmann. The first draft of the manuscript was written by Florian Alexander Michael and by Georg Dultz. All authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

DATA AVAILABILITY STATEMENT

Data is available and can be requested by the corresponding author.

ORCID

Florian Alexander Michael https://orcid.org/0000-0002-9305-3691
Georg Dultz https://orcid.org/0000-0003-0775-0907

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