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Same-session endoscopic diagnosis and symptoms' palliation in pancreato-biliary malignancies: clinical impact of Rapid-on-Site Evaluation

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Conflict of Interest: The authors declare that they have no conflict of interest.

Abstract:
Introduction: Besides increasing adequacy, Rapid-on-Site Evaluation (ROSE) during Endoscopic Ultrasound (EUS) or Endoscopic Retrograde Cholangiopancreatography (ERCP) may impact on choices and timing of subsequent therapeutic procedures, yet unexplored.

Methods: This was a retrospective evaluation of a prospectively maintained database of a tertiary, academic centre with availability of ROSE and hybrid EUS-ERCP suites. All consecutive patients referred for pathological confirmation of suspected malignancy and Jaundice or Gastric Outlet Obstruction (GOO) between Jan-2020 and Sep-2022 were included.

Results: Of 541 patients with underlying malignancy, 323 (59.7%) required same-session pathological diagnosis (male: 54.8%; age 70 [Interquartile Range 63-78]; pancreatic cancer: 76.8%, biliary tract adenocarcinoma 16.1%). ROSE adequacy was 96.6%, higher for EUS versus ERCP. Amongst 302 patients with Jaundice, ERCP-guided stenting was successful in 83.1%, but final drainage was completed in 97.4% thanks to 43 EUS-guided Biliary Drainages. 21 patients with GOO were treated with 15 EUS-Gastro-Enterostomies and 6 duo-denal stenting. All 58 therapeutic EUS procedures occurred after adequate ROSE. Amongst ERCP-guided placement of stents, the use of plastic stents was significantly higher amongst patients with inadequate ROSE (10/11 [90.9%] versus adequate sampling (14/240 [5.8%], p <0.0001, OR=161 [95%CI 19-1352]). Median hospital stay for diagnosis and palliation was 3 [2-7] days and median time to chemotherapy was 33 [24-47] days.

Conclusions: Nearly two-thirds of oncological candidates to endoscopic palliation require contemporary pathological diagnosis. ROSE adequacy allows, since the index procedure, state-of-the-art therapeutics standardly restricted to pathologically confirmed malignancies (e.g. uncovered SEMS or therapeutic EUS), potentially reducing hospitalization and time to oncological treatments.

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Same-session endoscopic diagnosis and symptoms’ palliation in pancreato-biliary malignancies: clinical impact of Rapid-on-Site Evaluation
1. Introduction

Pancreato-biliary malignancies represent an increasing burden, especially in terms of cancer-related mortality.[1,2] A prompt and accurate diagnosis is crucial for timely access to curative surgery or chemotherapy and might impact on disease-specific survival.[3-5]

Endoscopic Ultrasound (EUS) is a fundamental investigation in this setting, being the gold standard for pathological diagnosis of most pancreato-biliary diseases,[6] and it is increasingly acquiring a therapeutic relevance for symptoms palliation.[7]

Rapid-on-Site Evaluation (ROSE) by cytopathologists has been extensively evaluated as an additional tool to reduce false-negative results of EUS-guided Fine Needle Aspiration (FNA) sampling in pancreato-biliary malignancies,[8] despite the need for specific expertise and additional management costs.

Despite EUS-FNA + ROSE might be unnecessary when endoscopists use needles specifically designed for obtaining histological cores, the so-called Fine Needle Biopsy (FNB)[9], false-negative samples might be encountered even after EUS-FNB, and it is necessary to wait for the histopathological report to eventually assess the adequacy of the material.

Notably, most evidence belongs to the setting of pancreatic solid lesions, whereas sampling of non-mass forming biliary strictures remains more challenging,[10] and ROSE has been suggested to increase adequacy of sampling obtained through Endoscopic Retrograde Cholangiopancreatography (ERCP).[11]

Moreover, besides an adequate pathological confirmation of a disease, a fraction of patients with pancreato-biliary diseases requires prompt treatment of symptoms such as Jaundice or Gastric outlet obstruction (GOO) that are frequent at disease onset. As their treatment strictly depends on their aetiology, the absence of a confirmed malignancy might preclude some therapeutic manoeuvres, such as the placement of uncovered [UC] self-expandable metal stents (SEMS) or the performance of some EUS-guided interventions, due to difficult, dangerous, or impossible removability. Indeed, EUS-guided Choledocho-Duodenostomy [EUS-CDS], Hepatico-Gastrostomy [EUS-HGS] or Gastro-Enterostomy (EUS-GE) are standardly restricted to malignant diseases.[13]

For all these reasons, the absence of a malignancy confirmation might determine delay on symptoms' palliation, whilst the availability of ROSE-confirmed malignancy might conversely
lead to same-session diagnosis and definitive palliation of cancer-related symptoms potentially resulting in fewer interventions, shorter hospital stay and time to anti-cancer treatment. Notwithstanding, no study has to date evaluated the role of ROSE in impacting such therapeutic decisions.

The aim of this study was, therefore, to evaluate all consecutive patients with suspected malignancy requiring both cyto-histological characterization of a suspected pancreato-biliary neoplasia and additional therapeutic manoeuvres for Jaundice or GOO, with the aim to analyse: 1) the prevalence of this scenario; 2) the diagnostic impact of ROSE in terms of adequacy and 3) the clinical impact of ROSE-assessed adequacy in subsequent therapeutic management.
2. Methods

This was a retrospective evaluation of a prospectively maintained endoscopic database of San Raffaele Hospital (Milan, Italy), a tertiary, academic, referral centre with availability of ROSE and hybrid endoscopic suites allowing same-session diagnostic EUS, ERCP and therapeutic EUS. All consecutive patients referred to the endoscopy unit for treatment of either jaundice and/or GOO between January 2020 and September 2022 were queried. Patients with suspected malignancy were screened to evaluate how malignancy confirmation was obtained. Patients with same-session EUS/ERCP with ROSE were finally included.

2.1 Endpoints

The aims of this study were to analyse: 1) the rate (proportion) of therapeutic procedures requiring contemporary EUS-/ERCP-guided sampling of a suspected malignancy; 2) the rate (proportion) of ROSE-assessed adequacy of first endoscopic sampling; 3) the rate (proportion) of technical success of Jaundice or GOO endoscopic palliation, with focus on the need to adopt procedures usually restricted to confirmed malignancies; 4) total length of hospital stay for diagnosis and palliation; 5) time to chemotherapy initiation/resumption.

2.2 Patients

Inclusion Criteria:

- Final confirmation of malignancy. Gold standard for malignancy was a cyto-histological positive sample obtained through any technique (EUS, ERCP, liver biopsy of a metastasis, forceps biopsy during luminal endoscopy, surgical specimen) or by a clear clinico-radiological neoplastic evolution of the disease.
- Need for symptoms’ palliation, either Jaundice (bilirubin ≥2 mg/dl) or GOO (GOO Scoring System [GOOSS[14]] <2, no intake or liquids only) in the presence of a radiologically or endoscopically confirmed biliary or upper gastrointestinal stenosis
- First-time referral for an endoscopic therapeutic procedure
- Clinical Follow-up (FU) of at least 30 days

Exclusion Criteria:

- Benign diseases, either by clear benign indication for the procedures (e.g., choledocholithiasis; treatment of post-surgical biliary fistula) or by exclusion of
malignancy in indeterminate stenoses (either by histological confirmation of resected patients or clear clinico-radiological exclusion of malignancy after at least 12-months FU)

- Need for symptoms’ palliation in patients with malignancies characterized in a previous diagnostic procedure.
- Patients who already received a treatment for the same symptom (e.g. ERCP performed in another hospital)
- FU <30 days

2.3 Definitions

Same-session diagnostic and symptoms’ palliation was defined as a diagnostic EUS being performed before ERCP, enteral stenting or therapeutic EUS, in the same room, under the same sedation.

ROSE Adequacy was defined as confirmation of the presence of enough material to confirm the clinico-radiological suspicion of malignancy.

Technical success (TS) was defined as the completion of the intended procedure. In case therapeutic EUS was used as a rescue of failed ERCP, a separate TS was reported of ERCP alone and of overall biliary drainage, independently from the adopted procedure.

Hospital stay and time to chemotherapy were calculated from the day of the procedure to the day of hospital discharge and initiation of oncological treatment, respectively.

The complete list of collected variables is reported as Supplementary Statement 1

2.4 Endoscopic procedures

All procedures were performed under deep sedation or general anaesthesia, in a fluoroscopy-equipped room.

EUS was performed using linear echoendoscopes (EG38-J10U, Pentax Medical). In our center, EUS-FNA is usually performed starting with a 25G Menghini-type FNA needle, however the use of larger caliber needles or FNB design is adopted at the discretion of the endoscopists.
ERCPs were performed using duodenoscopes (ED3470TK, ED34i10T, Pentax Medical) by expert endoscopists performing >200 procedures per year. Cannulations is usually performed with sphincterotome over the wire, followed by contrast injection, double-guidewire technique, pre-cut or transpancreatic sphincterotomy at the discretion of the endoscopists. ERCP-guided sampling in usually started with over-the-wire brushing catheters, with secondary use of biopsy forceps or cholangioscopy at the discretion of the endoscopists. Retrograde biliary stenting is usually performed through SEMS, with plastic stents restricted to resectable hilar malignancies or inadequate sampling. For distal malignant stenoses, a partially-covered SEMS (PC-SEMS) is usually preferred, whereas uncovered SEMS are usually preferred in unresectable hilar malignancies.

In case of ERCP failure (either biliary access, or stenting of a desired biliary segment), EUS-guided biliary drainage is usually performed in the same session (typically EUS-CDS for distal stenoses and EUS-HGS for proximal stenoses). EUS-CDS is performed through free-hand placement of an 8x8mm or a 6x8mm Lumen-Apposing Metal Stent (LAMS, Hot Axios, Boston Scientific) between the common bile duct and the duodenum[16] EUS-HGS is performed by EUS-guided access of a left intrahepatic duct through a 19G needle, followed by contrast injection, guidewire cannulation, tract creation through a 6Fr cystotome (Endo-flex GmbH) and placement of a partially covered stent (Giobor, Taewoong).[17]

As for GOO, Enteral Stenting was performed by through-the-scope placement of an uncovered 22mm wide SEMS across the stenosis.[18] EUS-GE was performed using the Wireless Simplified EUS-GE Technique (WEST)[19], involving an oro-jejunal tube for jejunal distension and free-hand placement of an electrocautery-enhanced 20mm LAMS (Hot Axios, Boston Scientific).[18]

### 1.1 ROSE technique

EUS-FNA or ERCP-guided samples are given to the onsite cytologist for ROSE, and the endoscopist would wait for the response regarding the adequacy to either perform additional passes or move on to additional diagnostic modalities or therapeutic procedures. The smears are prepared immediately after obtaining the specimen. Smears were fixed in absolute alcohol and stained with a rapid 2-minute haematoxylin-eosin stain (see Figure 1). Once the slides were prepared, they were examined by an onsite cytologist and real-
time evaluation of the sample adequacy was performed. A sample was considered adequate based on whether there was enough material representative of the site of sampling and compatible with the clinical suspicion of malignancy. The diagnosis was based on classic cytologic criteria, i.e nuclear shape and dimension, such as nuclei enlargement with irregularities and grooves, high nuclear-cytoplasmic ratio, pleomorphism, eventual necrotic background and the architectural crowding with formation of 3D structures. The onsite cytologist was not blinded to patient clinical and radiological history.

1.2 Ethics

This study was conducted in compliance with the Declaration of Helsinki and Good Clinical Practice. This retrospective study was approved by the Ethics Committee (Id: 178/INT/2020).

1.3 Statistics

Descriptive statistics is reported as frequencies (proportions) and medians (interquartile ranges). Comparisons were performed through the Chi-Squared or Fisher’s test for qualitative data. A p value <0.05 was considered significant. All analyses were performed using Medcalc (Ostende, Belgium).
2. Results

Between Jan-2020 and Sep-2022, 541 patients with underlying malignancy were referred to San Raffaele Pancreatobiliary Endoscopy Unit for Jaundice or GOO palliation. Of those, 218 had already received a pathological diagnosis of their malignancy, whilst 323 (59.7%) required same-session pathological confirmation before a therapeutic procedure, and represent the cohort under analysis.

Characteristics of included patients are reported in Table 1. Men were 54.8%; median age was 70 [63-78]; primary disease was pancreatic cancer in 76.8% and cholangiocarcinoma in 16.1%; The neoplasm was resectable / borderline resectable in 33.1% of cases and locally advanced 47.7%, while a higher rate of metastatic patients was seen amongst patients treated for GOO versus Jaundice (38.1% versus 17.9%, p= 0.02).

2.1 Diagnostic adequacy

EUS was chosen as the upfront modality to obtain pathological diagnosis in 318 (98.5%) cases (see Table 2). ERCP-guided sampling was used in 16 (4.9%) cases, but only in 5 (1.5%) cases it was used without any prior EUS attempt, whereas in 11 cases it followed an inadequate EUS sampling.

Total adequacy of first round of sampling (see Table 2) was 96.6%.

This rate was significantly higher for EUS versus ERCP (95.6% versus 50%, p <0.0001).

Amongst the 11 (3.4%) patients with inadequate sampling, in 5 cases pathological confirmation was obtained at subsequent EUS or ERCP (in 1 case by cholangioscopy-guided biopsies), whilst it was obtained through surgical resection and clinical and radiological follow-up in 2 and 4 cases, respectively.

Sampling adequacy was significantly higher in distal versus proximal biliary stenosis (see Supplementary Table 1), both overall (97.1% versus 90%, p=0.05), and when attempted via EUS (96.3% versus 85%, p=0.01).

Sampling adequacy was significantly higher in pancreatic cancer versus biliary tract cancer (see Supplementary Table 2), both overall (98.4% versus 90.4%, p=0.002), and when attempted via EUS (97.9% versus 87.2%, p <0.001).
2.2 Symptoms palliation

2.2.1 Jaundice

Amongst 302 patients with Jaundice (see Table 2), ERCP-guided stenting was successful in 83.1%, but final endoscopic drainage was completed in 97.4%, through 37 EUS-Choledocho-Duodenostomies (see Figure 2, A-C), 5 EUS-Hepatico-Gastrostomies (see Figure 2, D-F) and 1 EUS-Gallbladder Drainage. Only 7 (2.3%) patients required Percutaneous Transhepatic Biliary Drainage, whereas 1 patient underwent surgical bypass.

AEs were 12.6%, including a 5.6% rate of post-ERCP pancreatitis.

Median hospital stay for diagnosis and symptoms’ palliation was 3 [2-7] days and median time to chemotherapy was 34 [25-49] days.

Amongst ERCP-guided stenting (see Supplementary Table 2 and Supplementary Table 3), the use of plastic stenting and uncovered stenting was significantly higher in proximal stenoses and amongst cholangiocarcinomas, whereas most distal stenoses and pancreatic cancer-related strictures were treated with PC-SEMS.

The rate of plastic stenting was significantly higher amongst patients with inadequate ROSE (10/11 [90.9%]) than amongst those with adequate sampling (14/240 [5.8%], p <0.001, OR=161 [95% Confidence Interval 19-1352]), whereas most remaining plastic stenting was due to a resectable hilar malignancy.

2.2.2 GOO

Amongst the 21 patients requiring GOO palliation (see Table 2), EUS-Gastro-Enterostomy was performed in 15 (see Figure 3) and endoscopic placement of uncovered duodenal SEMS in 6, with a technical success of 95.2% at first procedure, and an AEs rate of 14.3%.

Median hospital stay for diagnosis and symptoms’ palliation was 6.5 [4.5-11] days and median time to chemotherapy was 26.5 [22-30] days.

All 58 therapeutic EUS procedures occurred after adequate ROSE.
3. Discussion

Rapid On-Site Evaluation has been extensively evaluated as an add-on to increase diagnostic accuracy of EUS-guided FNA sampling. Despite conflicting results of studies and meta-analysis, ROSE seems associated to an increased diagnostic yield and decreased need for repeated sampling.[8,20,21]. However, the need for specific cytopathological expertise, additional costs and procedural time, have restricted the use of ROSE to a limited number of centres.[8]

Furthermore, the advantage of ROSE is increasingly debated to be trivial in light of the introduction of needles with “core” design (EUS-FNB). However, most evidence belongs to pancreatic solid lesions, and does not account for some additional theoretical advantages of ROSE in clinical practice, which have been poorly investigated in the available literature. Specifically, no paper has analysed a potential impact on timing and choices of subsequent therapeutic procedures.

In our series, almost 60% of patients needing palliation of jaundice or GOO required same-session pathological confirmation of the suspected malignancy, thus suggesting that a large majority of patients referred for endoscopic palliation would benefit of same-session diagnostics and therapeutics, where available.

Second, as expected, ROSE availability has resulted in an extremely high (97%) rate of sampling adequacy in this series. Moreover, our data provide some additional insights on variables affecting sampling adequacy, as this was higher in EUS versus ERCP sampling (95.6% versus 50%, p <0.0001), in proximal versus distal biliary stenoses (97.1% versus 90%, p=0.05), and in pancreatic cancer versus cholangiocarcinoma (98.4% versus 90.4%, p=0.002).

The relatively low yield of ERCP-guided sampling in this series is likely due to the selection of patients, being mostly used after inadequate EUS-guided sampling, which was a relatively rare event in this series. These data support the previously reported evidence that EUS-FNA has higher accuracy than ERCP-guided brushing in biliary stenoses, especially those extrahepatic, extrinsic and mass-forming.[6,23] This might endorse EUS as the primary sampling modality independently on the level of the stenosis, especially since the mostly reported drawback is needle-tract seeding. Nonetheless, pancreatic cancer needle-tract seeding is extremely rare, [24] reported mostly as seeding nodules arising in the gastric wall that can be easily removed surgically[25], and it has been proved that EUS-FNA does not increase the rate of peritoneal...
spread\cite{26}, and does not impact overall and recurrence-free survival\cite{27-29}. As for proximal cholangiocarcinoma, needle-tract seeding was initially suggested by anecdotal cases (N=5) in small series of transperitoneal FNA sampling, the majority of which was performed via a percutaneous rather than EUS-guided route\cite{30}, whilst subsequent larger experiences demonstrated no influence of preoperative sampling on overall and progression-free survival.\cite{26,31} Furthermore, optimisation of intraductal (ERCP-guided) sampling would require the more expensive use of cholangioscopy,\cite{6} which we usually restrict to cases with inadequate first-round sampling.

More important, in our series an adequate ROSE has allowed same-session diagnostics and state-of-the-art therapeutics standardly restricted to pathologically confirmed malignancies, leading to an overall median hospital stay of 3 [2-7] days and a median time to chemotherapy of 33 [24-47] days. Despite the absence of a control group, these results intrinsically suggest that the availability of ROSE and hybrid suites allowing EUS, ERCP and Therapeutic EUS might contribute to reducing the time to obtain pathological confirmation of a neoplasia and a long-lasting symptoms palliation. This time minimization does not intrinsically depend on ROSE, but on the reduced rate of false negative sampling and the reduced need for reinterventions deriving from using state-of-the-art therapeutics. Conversely, in facilities where diagnostic EUS and operative procedures are performed in different rooms, two procedures are required, and they are usually not planned on the same day. In the same setting, in case of failed ERCP, EUS-guided rescue drainage might require rescheduling the procedure in a different session or room. Moreover, the availability of a pathological confirmation of malignancy is considered mandatory for some specific therapeutic modalities. Indeed, to date, EUS-guided biliary drainage is restricted to pathologically confirmed malignancies, as also suggested by the only available guidelines on this topic.\cite{13} In our experience, the possibility to perform same-session EUS-CDS or EUS-HGS has raised the technical success of biliary drainage from 83% (retrograde stenting) to 97% (combined retrograde and EUS-guided drainage); this also means that need for Percutaneous Transhepatic Biliary Drainage (PTBD), with its known morbidity burden,\cite{32,33} might be significantly contained where adequate endoscopic expertise is available, and that definitive biliary drainage might be obtained during the first endoscopic procedure in almost all cases, provided an adequate ROSE is available.
Pathological diagnosis might also impact on choices regarding ERCP stenting: plastic stenting or fully covered SEMS (FC-SEMS) are usually preferred by centres not performing ROSE, as an uncovered design might significantly complicate removability of stents in case of an eventual benign aetiology or when additional sampling is required.[34] However, plastic stenting has demonstrated significantly higher rate of jaundice recurrence, even in the neoadjuvant setting, and this might result in unplanned readmission or chemotherapy interruptions in these patients[12]. Despite FC-SEMS might be a good compromise in distal stenoses, PC-SEMS seems associated with longer patency and might be preferrable in case of confirmed malignancies.[15] Moreover, FC-SEMS are not recommended for hilar strictures, due to the risk of obstructing side biliary branches,[34] and therefore an unconfirmed malignancy would preclude the placement of better performing UC-SEMS. Consistently, the use of plastic stenting in our series was significantly higher in case of inadequate sampling.

The potential advantages of a ROSE-assessed adequacy are even more eloquent when dealing with management of GOO. In this scenario, management of benign versus malignant GOO involve completely different procedures, ranging from medical treatment, balloon dilation or surgical bypass in the former to uncovered SEMS or, more recently, EUS-guided gastroenterostomy in the latter. Therefore in the absence of ROSE, the definitive treatment of GOO must be deferred, usually by temporary placement of a nasogastric decompression tube, while waiting pathological confirmation of malignancy.

For all these reasons, we believe that availability of ROSE and hybrid EUS, ERCP and Therapeutic EUS suites can play a major role in the management of patients with pancreato-biliary malignancies.

This study has several limitations. First, despite an accurate and extensive search, the retrospective nature might have led to exclusion of some patients / events of interest. Second, these results were obtained in a tertiary, academic, multidisciplinary referral centre with cytopathological expertise and high-volume experience in pancreatic pathology, pancreato-biliary endoscopy and therapeutic EUS. The generalizability of the findings outside this setting cannot be assured. Additionally, the absence of a control group calls for caution in the interpretation of the data that should still be considered speculative with need of confirmation; Nevertheless, the authors attempted unsuccessfully to procure a control group of patients treated for similar indications without the use of ROSE from other centers. Finally, while it is
tempting to speculate that shorter hospitalization and time to active treatment may result in lower costs, better quality of life and longer disease-specific survival, these data were not collected in our study.

Notwithstanding, to the best of our knowledge, this is the only available report describing how availability of ROSE might impact on timing and efficacy of symptoms palliation amongst pancreato-biliary malignancies. Whilst awaiting prospective, controlled comparisons on this topic, the present findings suggest that availability of ROSE and hybrid EUS/ERCP/therapeutic EUS expertise could contribute to reducing hospitalization and access time to oncological treatments for patients with newly diagnosed pancreato-biliary malignancies, especially in patients with more challenging scenarios, such as proximal/intrinsic biliary strictures, GOO or double obstruction.
References


Figure Legends

Figure 1: Pathological smears. A) EUS-FNA sampling; haematoxylin-eosin staining (20x): normal ductal epithelium; B) EUS-FNA sampling; haematoxylin-eosin staining (20x): biliary adenocarcinoma; C) ERCP-guided brushing; haematoxylin-eosin staining (20x): normal ductal epithelium close to a fragment of adenocarcinoma; D) EUS-FNA sampling; haematoxylin-eosin staining (40x); cell block from EUS-FNA showing abundant material representing adenocarcinoma.

Figure 2: Management of Jaundice. A-C) Patient with Pancreatic Adenocarcinoma. A) EUS-FNA sampling of a pancreatic head lesion, adequate for malignancy; B) Failed ERCP now withstanding pre-cut fistulotomy; C) Biliary drainage achieved through EUS-guided Choledochoduodenostomy, as seen by the fluoroscopic visualization of aerobilia through the LAMS (inlet: endoscopic visualization of the LAMS at the end of the procedure). D-F) Patient with Klatskin tumor and jaundice. A) EUS-FNA of an unresectable hilar lesion with infiltration of the biliary carrefour; FNA was adequate for malignancy; B) ERCP was performed with retrograde stenting of the right lobe (2 uncovered SEMS in the right dorsal and right ventral ducts), whereas access to the left lobe was impossible; C) same-session EUS-guided hepaticogastrostomy was performed to achieve complete biliary drainage.

Figure 3: Management of a double obstruction. Pancreatic with adenocarcinoma and double biliary and gastric outlet obstruction. A) EUS revealed a pancreatic head lesion determining biliary duct and duodenal infiltration; FNA was adequate for malignancy; B) A symptomatic duodenal neoplastic obstruction impeded access to the papillary region; C,D) EUS-guided gastroenterostomy and hepaticogastrostomy were performed in the same session (C: fluoroscopy; D: endoscopy).
# Tables

**Table 1**: Characteristics of included patients, separated according to the presenting symptom

<table>
<thead>
<tr>
<th>Variable</th>
<th>Jaundice (N = 302)</th>
<th>GOO (N = 21)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, median [IR]</td>
<td>70 [68-71]</td>
<td>70 [62-76]</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>165 (54.6%)</td>
<td>11 (52.4%)</td>
</tr>
<tr>
<td>Primary disease, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pancreatic cancer</td>
<td>231 (76.5%)</td>
<td>17 (80.9%)</td>
</tr>
<tr>
<td>Cholangiocarcinoma</td>
<td>52 (17.2%)</td>
<td>1 (4.8%)</td>
</tr>
<tr>
<td>Ampullary / Duodenal cancer</td>
<td>8 (2.6%)</td>
<td>2 (9.5%)</td>
</tr>
<tr>
<td>Metastatic lesion</td>
<td>5 (1.8%)</td>
<td>/</td>
</tr>
<tr>
<td>Other malignancies</td>
<td>6 (1.9%)</td>
<td>1 (4.8%)</td>
</tr>
<tr>
<td>Oncological Staging, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Resectable / Borderline resectable</td>
<td>229 (75.8%)</td>
<td>1 (4.8%)</td>
</tr>
<tr>
<td>Locally advanced</td>
<td>17 (5.6%)</td>
<td>12 (57.2%)</td>
</tr>
<tr>
<td>Metastatic</td>
<td>55 (18.2%)</td>
<td>8 (38.1%)</td>
</tr>
</tbody>
</table>

GOO: Gastric Outlet Obstruction

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### Table 2: Characteristics of sampling procedures

<table>
<thead>
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<th>Variable</th>
<th>n = 323</th>
</tr>
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<tbody>
<tr>
<td>Upfront procedure</td>
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<tr>
<td>EUS, n (%)</td>
<td>318 (98.5)</td>
</tr>
<tr>
<td>ERCP, n (%)</td>
<td>5 (1.5)</td>
</tr>
<tr>
<td>ERCP after inadequate EUS, n (%)</td>
<td>11 (3.4)</td>
</tr>
<tr>
<td>First-session Adequacy, n (%)</td>
<td>312 (96.6)</td>
</tr>
<tr>
<td>EUS Adequacy, n (%)</td>
<td>304/318 (95.6)</td>
</tr>
<tr>
<td>ERCP Adequacy, n (%)</td>
<td>8/16 (50)</td>
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<tr>
<td>Inadequate samples, n (%)</td>
<td>11 (3.4)</td>
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<tr>
<td>Final Diagnosis obtained by:</td>
<td></td>
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<tr>
<td>Subsequent EUS</td>
<td>1</td>
</tr>
<tr>
<td>Subsequent ERCP</td>
<td>4</td>
</tr>
<tr>
<td>Surgical Specimen</td>
<td>2</td>
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<tr>
<td>Clinico-Radiological FU</td>
<td>4</td>
</tr>
<tr>
<td>Adverse events during sampling</td>
<td>1/316 (0.3)</td>
</tr>
<tr>
<td>Duodenal perforation*</td>
<td>1</td>
</tr>
</tbody>
</table>

ERCP: Endoscopic Retrograde Cholangiopancreatography; EUS: Endoscopic Ultrasound
\* treated with Over-the-Scope Clip closure
Table 3: Characteristics of Therapeutic Procedures

<table>
<thead>
<tr>
<th>Variable</th>
<th>Jaundice n= 302</th>
<th>GOO n= 21</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Endoscopic Technical Success, n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ERCP</td>
<td>294 (97.4)</td>
<td>20 (95.2)</td>
</tr>
<tr>
<td>EUS-CDS</td>
<td>251 (83.1)</td>
<td>EUS-GE</td>
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<tr>
<td>EUS-HGS</td>
<td>37 (12.3)</td>
<td>Enteral Stenting</td>
</tr>
<tr>
<td>EUS-GBD</td>
<td>5 (1.7)</td>
<td></td>
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<tr>
<td><strong>Rescue of endoscopic failure, n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PTBD</td>
<td>7 (2.3)</td>
<td></td>
</tr>
<tr>
<td>Surgery</td>
<td>1 (0.3)</td>
<td>Surgery</td>
</tr>
<tr>
<td><strong>AEs n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Post ERCP Acute Pancreatitis</td>
<td>17 (5.6)</td>
<td></td>
</tr>
<tr>
<td>Cholecystitis</td>
<td>4 (1.3)</td>
<td></td>
</tr>
<tr>
<td>Cholangitis</td>
<td>5 (1.7)</td>
<td>Bleeding</td>
</tr>
<tr>
<td>LAMS Misdeployment</td>
<td>1 (0.3)</td>
<td>LAMS Misdeployment</td>
</tr>
<tr>
<td><strong>Procedural time</strong> [IQR], minutes</td>
<td>90 [69.3-109.5]</td>
<td>101 [84.3-107.5]</td>
</tr>
<tr>
<td><strong>Hospital Stay</strong> [IQR], days</td>
<td>3 [2-7]</td>
<td>6.5 [4.5-11]</td>
</tr>
<tr>
<td><strong>Time to CHT</strong> [IQR], days</td>
<td>34 [25-49]</td>
<td>26.5 [22-30]</td>
</tr>
</tbody>
</table>

AEs: Adverse events; ERCP: Endoscopic Retrograde Cholangiopancreatography; EUS: Endoscopic Ultrasound; CDS: Choledocho-duodenostomy; GOO: Gastric Outlet Obstruction; GBD: Gallbladder Drainage; GE: Gastro-enterostomy; HGS: Hepatico-gastrostomy; LAMS: Lumen Apposing Metal Stents; PTBD: Percutaneous Transhepatic Biliary Drainage.

\[^{\text{t}}\] Sum of times for the diagnostic part, patient repositioning and instrument exchanging, and the therapeutic part.
Same-session endoscopic diagnosis and symptoms’ palliation in pancreato-biliary malignancies: clinical impact of Rapid-on-Site Evaluation

Supplementary Statement 1: List of collected variables

Characteristics of included patients

- Age, years [IQR]
- Male sex, n (%)
- Primary disease, n (%)
  - Pancreatic cancer
  - Cholangiocarcinoma
  - Ampullary/Duodenal cancer
  - Metastatic lesion
  - Other malignancies
- Oncological Staging, n (%)
  - Resectable/Borderline resectable
  - Locally advanced
  - Metastatic
- Presenting Symptom, n (%)
  - Jaundice
  - GOO

Characteristics of sampling procedures

- Upfront procedure, n (%)
  - EUS
  - ERCP
  - ERCP after inadequate EUS
- First-session Adequacy, n (%)
  - EUS Adequacy
  - ERCP Adequacy
- Inadequate samples, n (%)
  - Final diagnosis obtained by, n
    - Subsequent EUS
    - Subsequent ERCP
    - Surgical specimen
    - Clinico-radiological follow up
- Adverse events during sampling, n (%)

Characteristics of therapeutic procedures

- Endoscopic Technical Success, n (%)
  - ERCP
  - EUS-CDS
  - EUS-HGS
  - EUS-GBD
  - EUS-GE
  - Enteral Stenting
- Rescue of endoscopic failure, n (%)
  - PTBD
  - Surgery
- Adverse events, n (%)
- Procedural time, minutes [IQR]
• Hospital stay, days [IQR]
• Time to chemotherapy, days [IQR]

**Supplementary Table 1: Sampling Adequacy according to Level of the Stenosis**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Gastric Outlet Stenosis (n= 21)</th>
<th>Distal Biliary Stenosis (n= 272)</th>
<th>Proximal Biliary Stenosis (n= 30)</th>
<th>p-value (distal versus proximal)</th>
</tr>
</thead>
<tbody>
<tr>
<td>First attempted sampling modality, n (%)</td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>EUS, n (%)</td>
<td>21 (100)</td>
<td>270 (99.3)</td>
<td>27 (90)</td>
<td>0.007*</td>
</tr>
<tr>
<td>ERCP, n (%)</td>
<td>0 (0)</td>
<td>2 (0.7)</td>
<td>3 (10)</td>
<td></td>
</tr>
<tr>
<td>Total Adequacy, n (%)</td>
<td>21 (100)</td>
<td>264 (97.1)</td>
<td>27 (90)</td>
<td>0.09</td>
</tr>
<tr>
<td>EUS Adequacy, n (%)</td>
<td>21 (100)</td>
<td>260/270 (96.3)</td>
<td>23/27 (85)</td>
<td>0.01*</td>
</tr>
<tr>
<td>ERCP Adequacy, n (%)</td>
<td>4/10 (40)</td>
<td>4/6 (66.7)</td>
<td></td>
<td>0.6</td>
</tr>
</tbody>
</table>

ERCP: Endoscopic Retrograde Cholangiopancreatography; EUS: Endoscopic Ultrasound
* statistically significant
**Supplementary Table 2**: Sampling Adequacy and Stenting according to Pancreatic versus Biliary Cancer

<table>
<thead>
<tr>
<th>Variable</th>
<th>Pancreatic Cancer (n= 248)</th>
<th>Biliary Cancer (n= 52)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>First attempted sampling modality, n (%)</td>
<td></td>
<td></td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>EUS</td>
<td>248 (100)</td>
<td>47 (90.4)</td>
<td></td>
</tr>
<tr>
<td>ERCP</td>
<td>0</td>
<td>5 (9.6)</td>
<td></td>
</tr>
<tr>
<td>Total Adequacy, n (%)</td>
<td>244 (98.4)</td>
<td>47 (90.4)</td>
<td>0.002*</td>
</tr>
<tr>
<td>EUS Adequacy</td>
<td>243/248 (97.9)</td>
<td>41/47 (87.2)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>ERCP Adequacy</td>
<td>1/4 (25)</td>
<td>6/10 (60)</td>
<td>0.6</td>
</tr>
<tr>
<td>Stenting(^{a}) n (%)</td>
<td></td>
<td></td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Plastic</td>
<td>6 (3.1)</td>
<td>16 (34.8)</td>
<td></td>
</tr>
<tr>
<td>PC-SEMS</td>
<td>170 (88.5)</td>
<td>23 (50)</td>
<td></td>
</tr>
<tr>
<td>FC-SEMS</td>
<td>3 (1.6)</td>
<td>1 (2.2)</td>
<td></td>
</tr>
<tr>
<td>UC-SEMS</td>
<td>12 (6.2)</td>
<td>6 (13)</td>
<td></td>
</tr>
</tbody>
</table>


\(^{a}\) Amongst patients with jaundice and retrograde cannulation success

*statistically significant
### Supplementary Table 3: Biliary Stenting according to Level of the stenosis and Adequacy

<table>
<thead>
<tr>
<th>Variable</th>
<th>Distal Biliary Stenosis</th>
<th>Proximal Biliary Stenosis</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Patients (n = 272)</td>
<td>Patients with inadequate sampling (n = 8)</td>
<td>All Patients (n = 30)</td>
</tr>
<tr>
<td>Biliary Stenting, n (%)</td>
<td></td>
<td></td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>ERCP</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Plastic stenting</td>
<td>10 (4.4)</td>
<td>7</td>
<td>14 (51.9)</td>
</tr>
<tr>
<td>Partially Covered SEMS</td>
<td>197 (87.6)</td>
<td>0</td>
<td>7 (25.9%)</td>
</tr>
<tr>
<td>Fully Covered SEMS</td>
<td>5 (2.2)</td>
<td>1</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Uncovered SEMS</td>
<td>12 (5.3)</td>
<td>0</td>
<td>6 (22.2)</td>
</tr>
<tr>
<td>Therapeutic EUS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EUS-Choledochoduodenostomy</td>
<td>37</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>EUS-Hepatico-gastrostomy</td>
<td>4</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>EUS-Gallbladder Drainage</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

ERCP: Endoscopic Retrograde Cholangiopancreatography; EUS: Endoscopic Ultrasound; SEMS: Self-Expandable Metal Stent.
*statistically significant