Role of per-oral pancreatoscopy in the evaluation of suspected pancreatic duct neoplasia: a 13-year U.S. single-center experience

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ABSTRACT

Background and Aims: The role of peroral pancreatoscopy (POP) in the evaluation of occult pancreatic duct (PD) lesions remains limited to case series. The aim of this study was to evaluate the ability of POP to differentiate malignant from benign diseases of the PD.

Methods: Patients who underwent POP between 2000 and 2013 for the evaluation of indeterminate PD strictures, dilatations, or with suspected or known main duct IPMN were identified. Main outcome measurements were the visual impression accuracy, POP tissue sampling, efficacy, and safety of POP.

Results: During the study period, a total of 79 patients who underwent POP for the evaluation of pancreatic stricture or dilatation were identified. Technical success was achieved in 78 (97%). In the PD neoplasia group (n=33), final diagnosis was based on index confirmatory POP-guided tissue sampling in 29 (88%). For the detection of PD neoplasia, POP visual impression had a sensitivity, specificity, PPV, NPV, and accuracy of 87%, 86%, 83%, 91%, and 87% respectively. When combined with POP-guided tissue sampling, these were 91%, 95%, 94%, 93%, and 94% respectively. Out of 102 POPs performed, AEs were noted in 12 (12%) cases.

Conclusions: This study demonstrates a high technical success rate, visual impression accuracy, and tissue sampling capability of POP. Exams were performed by endoscopists with expertise in pancreatoscopy interpretation and results may not be generalizable.

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INTRODUCTION

Peroral pancreatoscopy (POP) permits direct visualization of the pancreatic duct (PD). The role of POP in guiding treatment of pancreatic stones using electrohydraulic lithotripsy (EHL) or laser lithotripsy (LL) has been well established.[1,2] Its role in the identification, evaluation, and sampling of occult PD lesions that may not be visible by non-invasive imaging, transluminal endoscopic ultrasound (EUS), or pancreatography remains limited to case series.[3-12] The aims of this study are to: 1) evaluate the safety, efficacy, technical success, and adverse events of POP; and 2) determine the usefulness of POP for the differentiation of malignant from benign diseases of the pancreatic duct.

METHODS

Study Design and Study Population

This retrospective single-center study was approved by the University of Colorado School of Medicine Institutional Review Board. The University of Colorado Hospital endoscopic database was queried for all patients (age ≥18 year old) who had attempted peroral pancreaotoscopy (POP) between January 2000 and August 2013. Patients who underwent POP for the evaluation of indeterminate main pancreatic duct (PD) strictures, dilatation, or with suspected or known main duct IPMN were included. Non-invasive pancreatic imaging with CT and/or MRCP were performed in all study patients. POP procedures performed primarily for stone disease were excluded.

We abstracted the following information from each patient's medical records: patient demographics, number and findings of endoscopic ultrasound (EUS) and endoscopic retrograde cholangiopancreatography (ERCP), pre-POP imaging, indication(s) for POP, type of pancreatoscopes used, location of target lesions, POP findings, any additional interventions performed (CT-guided biopsy, EUS-FNA, ERCP), cytology and pathology findings, clinical outcomes, adverse events, and follow-up. When multiple lesions were identified within the PD, we abstracted the POP findings most concerning for neoplasia.

Peroral pancreatoscopy equipment and technique

Peroral pancreatoscopy was performed using small diameter pancreatoscopes or catheters (passed through the 4.2-mm working channel of a therapeutic duodenoscope). The devices used included CHF BP 30, CHF BP 160, prototype CHF-Y0002 NBI pancreatoscope (Olympus America Inc., Center Valley, PA) and SpyGlass Direct Visualization SystemTM (Boston Scientific Corp, Natick, MA). All procedures were performed by one of four endoscopists with annual volumes of greater than 250 ERCP's (Y.C., R.S., N.F., B.B.).

Unless a patulous pancreatic orifice was encountered, endoscopic sphincterotomy of the major or minor papilla, as applicable, was routinely performed in preparation for pancreatoscopy. Conventional ERCP techniques such as balloon dilation of downstream strictures were performed as needed to facilitate scope passage across the papilla or stricture. The pancreatoscope was advanced over a guidewire ideally beyond the target lesion. Intermittent irrigation with sterile saline was performed while the pancreatoscope was slowly withdrawn to inspect the PD. Periodic suctioning of duodenal contents and aspiration through the working channel of the control section (using a Y-adapter) was performed. If passage of the biopsy forceps was possible through the accessory channel, POP-directed biopsies (PDB) were obtained. If the target lesion was closer to the pancreatic orifice resulting in a more acute angulation of the pancreatoscope limiting passage of the miniature forceps, POP-assisted biopsies (PAB) were obtained (see Study definitions below).

Patients who underwent the index ERCP at our institution and/or pancreatic sphincterotomy were routinely admitted to the hospital for 23-hour observation after the procedure. Patients undergoing follow-up ERCP or POP were often discharged after 1 to 2-hour observation. On completion of the POP, the endoscopist provided a presumptive diagnosis based on the POP visual impression consisting of benign or malignant. On review of the cytology and/or histology findings, the diagnosis was updated.

Study definitions

Successful procedure was defined when all 3 of the following criteria were met: (1): successful advancement of the pancreatoscope to the desired target, (2) adequate visualization of the area of interest and (3) successful applications of all diagnostic maneuvers that were deemed necessary based on the endoscopic findings. Lesions' characteristics including appearance, number, and location were determined by review of the endoscopy report. POP diagnosis was based on the visual impression of the endoscopist. The final diagnosis of PD neoplasia or non-neoplasia was based on gold standard and a composite reference standard criteria. Clinical criteria include: neoplastic cytohistopathology by endoscopic, radiologic, or surgical sampling. Composite reference standard criteria include: neoplastic POP impression and a clinical course suggestive of malignancy (i.e. death), non-neoplastic POP impression and a benign clinical course at ≥ 12 months of follow-up. If the lesions were indeterminate on index POP (by visual impression i.e. high clinical suspicion of malignancy though without POP findings suggestive of neoplasia, or by sampling i.e. without cytohistologic confirmation), further work-up and/or management were performed as indicated. These included repeat POP with sampling, or use of other conventional ERCP techniques, EUS-FNA, CT-guided biopsies, or surgery. Based on previously published reports[3-12] and our personal experience[13-15], suspected neoplastic and non-neoplastic findings were subcategorized in Table 1.

The IPMNs were classified into main-duct (MD), mixed-type, and branch-duct (BD). Patients with IPMNs were divided into malignant or invasive (IPMN with associated infiltrating carcinoma) and benign or non-invasive (IPMN without associated infiltrating carcinoma) groups based on pathology findings.

POP-directed biopsies (PDB) were defined as biopsies obtained under direct pancreatoscopy visualization. POP-assisted biopsies (PAB) were defined as biopsies using pediatric or biliary forceps obtained after a spot fluoroscopic film of the pancreatoscope at the target lesion was taken in order to guide fluoroscopic sampling.[14] Brushings were obtained with the latter technique. A minimum of 3 passes and bites were attempted with each biopsy method, and the decision to perform both methods of tissue sampling was at the discretion of the endoscopist. Biopsies were performed whenever POP inspection revealed any of the abnormal findings detailed above. Biopsies were not performed if erythematous epithelial changes were not raised or associated with a defined stricture. If fluoroscopic findings were equivocal (eg, PD dilation with suspected PD stricture) but the POP was normal, then biopsies were not obtained.

The capability to make these observations by POP and the frequency with which abnormal findings were identified in each disease were evaluated. The sensitivity and specificity of POP for discrimination between neoplastic and non-neoplastic PD neoplasia were determined.

The study period was defined as the interval between the index POP and the most recent available clinical follow-up, with an attempt to obtain a minimum of 12-month follow-up for patients with benign POP findings. Other than surgical confirmation that malignancy was not present, a minimum of 12 months follow-up from the index POP was required to define a true negative. Long term follow-up information after index procedure was obtained by review of medical records, patient contact by telephone, contact with the referring physician, or a query of the US Social Security Death Index.[16]

Adverse events

Adverse events were defined and graded by using the Cotton et al. classification.[17] Further, post-procedural abdominal pain that did not meet pancreatitis criteria but required hospitalization beyond a 23 hour observation was considered an adverse event.

Data analysis

All clinical and endoscopic variables were obtained from the database. For purposes of analysis, histocytological specimens acquired were categorized as positive (e.g. suspicious, malignant) or negative (e.g. benign, reactive, and indeterminate). In the absence of surgical confirmation of pancreatic pathology, a composite reference standard that included the results of all available tissue sampling and clinical course at time of follow-up was used to determine the final diagnosis. Sensitivity, specificity, positive predictive value, and negative predictive value were calculated on the basis of this reference standard. Descriptive statistics consisted of means ± standard deviations or medians with ranges for continuous variables and simple proportions for dichotomous variables. Statistical analysis was performed using SPSS version 20 (SPSS Inc, Chicago, IL, USA).

RESULTS

From January 2000 and August 2013, a total of 134 patients who underwent POP were identified (Figure 1). Fifty five patients with isolated stone disease (chronic calcific pancreatitis) were excluded leaving 79 patients that comprised the study cohort. Forty four (56%) were female and the mean age of patients was 60 ± 16.32. Technical failure was noted in one patient thus the overall technical success was achieved in 78 patients (97%). Some patients underwent repeat POPs for different indications. The total number of procedures performed in the studied 78 patients was 102. Baseline characteristics are summarized in Table 2.

Overall, 33 (42%) patients had PD neoplasia, and 45 (58%) patients did not have PD neoplasia. Among the PD neoplasia group, 12 patients were diagnosed with pancreatic duct adenocarcinoma (PDAC) (Figure 2), and 21 patients were diagnosed with MD-IPMN (Figure 3). This latter group of MD-IPMN was subdivided into invasive (6 patients) and non-invasive (15 patients) subgroups. Among the 45 non-PD neoplasia group, 40 patients were diagnosed with benign strictures (Figure 4), and 5 patients were diagnosed with BD-IPMN (Figure 1).

Peroral pancreatoscopy directed and assisted biopsies (PDB and/or PAB) results

At index POP, tissue sampling was deemed necessary in 54 (70%) patients. PDB was performed in 24 (45%) patients, PAB in 12 (22%) patients, PA-brushing in 10 (18%) patients, and combination of techniques in 8 (15%) patients. In the PD neoplasia group (n=33), PDB and/or PAB was performed in 33 (100%) patients. Tissue sampling results included: MD-IPMN in 20 (invasive in 6, non-invasive in 14), adenocarcinoma in 9, indeterminate in 2, and atypical cells in 2. In the Non-PD neoplasia group (n=45), PDB and/or PAB were performed in 21 (47%) patients. Tissue sampling results included: BD-IPMN in 2 (no atypia), benign cells in 13, indeterminate in 2, inadequate sampling in 2, and atypical cells in 2.

Basis for the Final Diagnosis

The mean follow-up of patients was 62 ±12 months. Tissue sampling at index POP provided the basis for the final diagnosis in 29 (88%) patients in the PD neoplasia group, and 21 (47%) in the non-PD neoplasia group. Four other procedures for tissue confirmation were required in the first group (EUS-FNA 2, ERCP 1, CT-guided biopsy 1). In the second group, 6 other procedures (surgery 2, EUS-FNA 2, ERCP-guided biopsy 2) were performed and 18 had clinical follow-up alone (≥ 12 months).

POP findings in relation to the final diagnosis are summarized in Table 3. Exams with discrepancy between POP visual Impression and the final diagnosis included two false positives (FP) and three false

negatives (FN). Interestingly, all 5 patients with diagnostic discrepancy had chronic pancreatitis. The 2 FP impressions included: a nodular protrusion induced by impacted stones and an infiltrative stricture that was stent-associated. The 3 FN impressions included: stricture with erythema, stricture with atrophic mucosa, and stricture with band-like scarring. Diagnosis of PDAC was made by EUS-FNA in 2, and CT guided-biopsy in 1.

The sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy of POP visual impression, PDB and/or PAB, and combined POP visual impression with PDB and/or PAB are summarized in Table 4.

Adverse events

Out of 102 POPs performed, adverse events were noted in 12 (12%) cases: 7 (7%) patients experienced a flare-up of baseline abdominal pain that required admission for more than 24 hours, and 5 (5%) patients had serious adverse events. The latter were distributed as such: 4 (4%) patients had post-procedure acute pancreatitis: mild (n=1), moderate (n=1), and severe (n=1), and 1 (1%) patient had moderate post sphincterotomy bleed requiring hospitalization, endotherapy, and blood transfusion.

DISCUSSION

The role of POP in the identification, evaluation, and sampling of occult PD lesions,[14,15,18] remains limited to case series[3-12] (Table 5). Our study expands the growing literature on this role and summarizes our largest single center study of attempted POP examinations in a heterogonous patient population with advanced or technically difficult to sample or treat pathology. Many of these patients referred to our tertiary referral center have already had a number of ERCPs and EUSs with negative sampling before the index POP. Our technical success was 97 %. Our POP operating characteristics were robust as evident in high sensitivity, specificity, PPV, NPV, and accuracy of combined POP visual impression and PDB and/or

PAB. These were 91%, 95%, 94%, 93%, and 94% respectively. Our adverse events rates were acceptable and noted in 12 (12%) cases with only a minority having enzyme positive post-ERCP pancreatitis.

Our high rate (97%) of technical success required reaching the target region and performing tissue sampling when necessary. It involved patients with chronic pancreatitis, MD- and BD-IPMN, and pancreatic cancer. Prior highly selective series that included primarily MD-IPMN evaluation,[7,9] defined success by visualization alone or in combination with sampling and ranged from 73%-100% (Table 5).

Pancreatoscopy findings in pancreatic cancer may include coarse granular mucosa, erythema, friability, tumor vessels, papillary projections, protrusions, and infiltrative strictures (e.g. near occlusion of the lumen) with irregular margins. The presence of tumor vessels, protrusions, and friability have a sensitivity varying between 23-50%, and a specificity of 100% when compared to benign lesions.[10] In the series of kodama et al.[9], 5 of 8 pancreatic cancer cases were adequately seen: all had stenosis or duct cutoff in the MPD, 4 had friable mucosa with erythema and erosive changes, and 1 had extrinsic compression and normal mucosa. The authors reported 3 FP POP impressions that included a chronic pancreatitis stricture, blood clot obstructing lumen visualization, and an idiopathic benign stricture. In our series, we had 2 FP POP impressions that included a nodular protrusion induced by impacted stones and an infiltrative appearance of a stent-induced stricture.

Because IPMN constitutes a potentially malignant and premalignant condition, an accurate assessment of disease extent and tissue sampling helps to guide management.[18,19] Pancreatoscopy findings in IPMN were well studied by Hara et al.[8] This was a retrospective review of 60 patients with IPMN. The authors assessed tumor type (elevated vs excavated), morphology per POP, maximum tumor height as determined by intraductal ultrasound (IDUS), and tumor extent (head vs body vs tail; MD vs BD). Results obtained with POP and IDUS were correlated and compared with surgical pathology serving as the gold standard. A high proportion (40/60, 67%) had protruding lesions. Most malignant tumors had a POP morphology type III, IV, or V ($p < 0.0001$), with a reported sensitivity, specificity, and accuracy of 68%,

87%, and 75% for differentiating benign from malignant IPMN. Miura et al.[12] reported their experience of diagnosis of IPMN in 21 patients by means of POP using a small-diameter videoscope and narrow band imaging (NBI). Endoscopically, 7 cases were classified as villous (Type IV) and 2 cases as vegetative (Type V), and 9 cases were diagnosed as adenocarcinoma. Ten cases with "sessile" type or "semi-pedunculated" type were diagnosed as adenoma or hyperplasia. An additional series of patients undergoing POP included 60 patients with surgically confirmed IPMN,[10] POP findings included papillary projections (58%), mucin only (23%), granular mucosa (16%) and coarse mucosa (4%). As in previous series,[10] papillary projections were more prevalent in patients with advanced histology (23% of adenoma, 58% of borderline malignancy, 70% of non-invasive IPMN and 89% of invasive IPMN).

In our subgroup of patients with IPMN, POP findings are in agreement with those reported in the literature. In the invasive group, the predominant findings included: papillary projections, villous, and vegetative appearance. In the non-invasive group, the predominant findings included: papillary projections, granularity, erythema, and mucin.

Pancreatoscopy findings in chronic pancreatitis (CP) were evaluated by Kodama et al.[11] These included: turbid pancreatic juice, protein plug, whitish mucosa, indistinct vascular markings, redness, rough surface, and stenosis. Authors studied the POP findings relative to the Cambridge classification. In the equivocal and mild CP group, predominant POP findings included: turbid pancreatic juice, whitish mucosa, and indistinct vascular markings. In the moderate and marked CP group, predominant POP findings included: protein plug, redness, rough surface, and stenosis. In our series, predominant POP findings included: coarse mucosa, scarring, erythema, and edema. Our 2 FP POP impressions were in chronic pancreatitis patients with infiltrative stricture and protrusions, respectively.

Though our reported AE rate of 12% is comparable to prior series (Table 5), it is important to emphasize the need for non-invasive imaging and consideration for EUS prior to considering POP. Our group compared the rates of complications between 402 ERCPs with cholangiopancreatoscopy (CP) versus

3475 ERCPs alone.[20] The overall AE rate was higher in CP patients (7 % vs 3%), but rates of post-procedure acute pancreatitis were comparable (2.2 % vs 1.3%).

We recognize several limitations to our study, including the intermediate-term follow-up, lack of control arm, retrospective design, and tertiary center referral bias. In addition, the procedures were performed by endoscopists with expertise in pancreatic endotherapy, thus the outcomes may not be generalizable to facilities with less pancreatoscopy experience. Further, endoscopists were aware of the clinical history and this may have influenced the POP "visual impression". Given these limitations, the validity of our findings should be confirmed in a prospective, randomized, controlled, and longitudinal study.

In summary, we provided a large experience of per oral pancreatoscopy in a diverse and challenging patient population. Our study demonstrates a high technical success rate, visual impression accuracy, and tissue sampling capability. POP should be considered when evaluating pancreatic pathology especially when non-invasive imaging or EUS are not diagnostic.

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LEGENDS FOR FIGURES:

Figure 1. Flow chart.

Footnotes:
POP: Peroral pancreatoscopy; *: Excluded patients; PD: pancreatic duct; IPMN: Intraductal Papillary Mucinous Neoplasm; MD: main duct; BD: branch duct.

Figure 2. Adenocarcinoma. (a) Pancreatography showing a stricture in the head of the pancreas. (b & c) Fiberoptic pancreatoscopy showing infiltrative nodular appearing stricture.

Figure 3. IPMN. (a) Pancreatography showing dilated accessory duct. (b) Video pancreatoscopy showing frond-like villous lesion. (c) NBI showing lateral spreading of the tumor.

Figure 4. Benign stricture. (a) Pancreatogram showing multiple segmental strictures of the usptream body. (b) Fiberoptic pancreatoscopy showing a smooth margin with concentric stenosis. (c) Pancreatoscopy with NBI – note the thin caliber vessels.