

Manuscript No: 43239

Manuscript Title: Role of Pancreatoscopy in Management of Pancreatic Disease

Response to reviewers.

We thank the reviewers for taking the time out to review this manuscript and their insightful comments.

We have made the changes as requested and suggested by the reviewers and hope that the reviewers find them acceptable.

Reviewer 00070310: This manuscript has reviewed the role of pancreatoscopy for pancreatic disease. This paper is well written, interesting, and will be acceptable.

Response: *We thank the reviewer for their encouraging comments and time they took to review the manuscript.*

Reviewer 03727100: Thank you for precise description about pancreatoscopy. I think this paper is well written and well researched, however I have a suggestion. This study has two main parts "Endoscopic pancreatic duct stone therapy" and "Role of POP in Pancreatic duct neoplasia". Each part is too long to understand easily. Would you please make some chapters in each part ? For example, 1. Endoscopic pancreatic duct stone therapy by POP • The method of stone therapy • The results of stone therapy • Adverse events 2. Role of POP in pancreatic duct neoplasia • Image diagnoses (involving NBI, IDUS etc...) • The results of cytology, biopsy • Adverse events

Response: *We thank the reviewer for the efforts and meaningful comments. We have added the appropriate subheadings as suggested. Please see below:*

1. Subheadings added:

a. Pancreatoscopy guided lithotripsy

b. Role of POP visual impression and POP guided biopsy

c. POP with cytology

d. Intra operative POP

e. Intraductal ultrasound (IDUS) with POP

f. POP with imaging enhancing technology

Administrator:

We thank the administrators for suggesting the edits. Please see the highlighted sections below:

1. Comment 2 – Article type confirmed - Systematic review
2. Comment 3- Background added under Abstract section
Per-oral pancreatoscopy (POP) plays a role in the diagnosis and therapy of pancreatic diseases. With recent technological advances, there has been renewed interest in this modality.
3. Comment 4 – Aim added under Abstract section
To evaluate the efficacy and safety of POP in management of pancreatic stone disease and pancreatic duct neoplasia.
4. Abstract updated as per systematic review guidelines
METHODS: To determine the safety and efficacy of POP in management of pancreatic diseases, a systematic search was conducted in Medline, Embase and Ovid. Articles in languages other than English and case reports were excluded. All published case series were eligible. Data specific to POP was extracted from studies, which combined cholangiopancreatography. 10 studies were included in analysis of POP therapy for pancreatic stone disease and 15 case series satisfied the criteria for inclusion for role of POP in management of pancreatic ductal neoplasia. The examined data was sub categorized according to adjunctive modality such as direct tissue sampling, cytology, role of intra operative POP, intra ductal ultrasound (IDUS) and POP combined with image enhancing technology.

RESULTS: The success rate for complete ductal stone clearance ranged from 37.5% to 100%. Factors associated with failure included the presence of strictures, multiple stones and the inability to visualize the target area. Although direct visualization can identify malignant and premalignant conditions, there is significant overlap with benign diseases. Visually directed biopsies provide a high degree of accuracy and represent a unique approach for tissue acquisition in patients with ductal abnormalities. Addition of pancreatic fluid cytology increases diagnostic yield for indeterminate lesions. Protrusions larger than 3 mm noted on intra ductal ultrasound are significantly more likely to be associated with malignancy. The rate of adverse events associated with POP ranged from 0% to 35%.

CONCLUSION: Current evidence supports wider adoption of pancreatoscopy as it is safe and effective. Improved patient selection and utilization of novel technologies may further enhance its role in managing pancreatic disease.
5. Comment 5 – Article highlights added as per Systematic review guidelines
Research background
Pancreatoscopy has been used for over 30 years in diagnosis and management of pancreatic diseases; however, it's use remains limited to

large volume referral centers. Data regarding its efficacy and safety is limited and has been available mainly from single or multi center retrospective case series. Well-designed large randomized controlled trials are lacking and may be difficult to conduct due to heterogenous patient population. With this study we have compiled a systematic review of available data thus highlighting the valuable role of Per oral pancreatoscopy in managing pancreatic diseases.

Research motivation

The main aim of our study was to systematically analyze available data regarding the therapeutic potential of Pancreatoscopy in managing difficult pancreatic stone disease and pancreatic ductal neoplasia. It appears to be safe with rare serious side effects and serves a crucial complementary role to other pancreatic endoscopic modalities.

Research objectives

The main objective of the study was to gather data related to safety and efficacy of pancreatoscopy. We wanted to identify success rates and factors associated with treatment failure for pancreatoscopic management of stone disease. We also aimed to analyze the pancreatoscopic visual findings associated with pancreatic ductal neoplasia and how it can help in differentiating from benign pancreatic duct strictures. The diagnostic potential of adjunctive techniques such as POP guided/assisted biopsy, pancreatic juice cytology and intra ductal ultrasound was evaluated separately.

Research methods

This is a systematic review of available studies published in English. We performed an extensive medical database search to identify relevant publications. Case reports and stand alone abstract publications were excluded from the final analysis. Data regarding safety and efficacy was extracted and presented. Studies addressing role of POP in management of

pancreatic ductal neoplasia with adjunctive modalities were examined separately.

Research results

Pancreatotomy is overall safe with rare reported serious side effects. The success rate ranges between 37.5% to 100% for treating pancreatic stone disease. Factors associated with failure include presence of multiple stones, stones in side branches causing failure of visualization and presence of stricture. Visual impression during pancreatotomy provides important information in patients with indeterminate pancreatic duct strictures. The key finding in our study was the association between villous projections with red color markings, which is associated with high-risk advanced neoplastic lesions across multiple studies. Smooth narrowing with presence of coarse mucosa, protein plugs or stones and blurred mucosal vessels are seen in patients with strictures due to chronic pancreatitis. POP assisted tissue acquisition along with adjunctive techniques such as cytology, narrow band imaging and intra ductal ultrasound greatly enhance the diagnostic potential and help in treatment planning.

Research conclusions

Pancreatotomy is overall safe and effective diagnostic and therapeutic modality. It serves as an important bridge for patients with pancreatolithiasis who fail conventional ERCP or ESWL. Patients with multiple stones in body/tail or those with pancreatic strictures may have risk of decreased success with POP guided therapy, recognition of these factors may help in treatment planning. POP visual impression provides a plethora of information regarding etiology in patients with indeterminate pancreatic ductal strictures, although there is an overlap between benign and malignant conditions. POP guided tissue acquisition has shown to greatly enhance the diagnostic yield but limitations remain due to technical challenges. Addition of newer imaging technology may further augment the potential of POP in managing such scenarios.

Research perspectives

Appropriate future action may involve multi center prospective studies to identify patient characteristics which may make them amenable to POP guided endotherapy for pancreatic diseases. Continued improvement in imaging technology such as narrow band imaging and probe based confocal laser endomicroscopy need to be evaluated extensively before mainstream use is implemented.

6. Comment 6 – All PMID and DOI numbers updated apart from reference number 6 (no DOI recorded)

