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Review Article

Role of Endoscopy in Managing Complications Associated with Pancreaticoduodenectomy: Concise Review of Literature

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Abstract

Pancreaticoduodenectomy (PD) is a complex surgery for the management of periampullary tumors. It is associated with significant morbidity and mortality of 20% and 3 to 5% respectively. While early complications like delayed gastric emptying, hemorrhage, and collections are common, late complications like biliary and pancreatic anastomotic stenosis are also known to occur. With the increase in cases of pancreatic and periampullary cancers, there is an upward trend seen even in the rates of surgery. Endoscopy has emerged over the years as a tool for both evaluation and management of various complications. In this narrative review, we aim to provide a primer for gastroenterologists who are likely to be called upon for endoscopic management of post-PD complications.

Keywords
- complications
- endoscopy
- pancreaticoduodenectomy

Introduction

Pancreaticoduodenectomy (PD) is a complex surgery, performed for tumors of the pancreatic head, distal common bile duct (CBD), ampulla of Vater, and rarely for chronic pancreatitis. Classic Whipple's surgeries described initially by Allen Oldfather Whipple, included resection of the head of the pancreas, gallbladder, CBD, and duodenum, distal gastrectomy with resection of the pylorus and triple anastomosis, i.e., gastrojejunostomy (GJ), hepaticojejunostomy (HJ), and pancreaticojejunostomy (PJ). Pylorus-preserving PD is a modification of classic Whipple's where the stomach and first portion of duodenum are spared described by Traverso and Longmire in 1978.[1] Mortality and morbidity were very high during the initial period when PD was described. Crist et al compared morbidity, mortality, and survival after Whipple's procedure during two time periods.[2] Among the 41 patients operated during 1969 to 1980, hospital morbidity and mortality rates were 59 and 24%, respectively. In 47 patients operated during 1981 to 1986 morbidity and mortality rates were 36 and 2%, respectively. During the 1981 and 1986 period, there were fewer total pancreatectomies (9 vs. 39%), fewer vagotomies (26 vs. 76%), and more pyloric-preserving procedures (30 vs. 0) performed compared with the earlier period. During the second period, fewer operating surgeons (3.4 cases per surgeon vs. 1.9 cases per surgeon) were performing more procedures per year (7.8 vs. 3.4). This led to an era of specialization in this complex surgery with better results. However, despite specialization over the years, morbidity after PD is seen in up to 20% of cases and mortality in up to 3 to 5%.[3] Complications of PD can be early or delayed (►**Table 1**). In this narrative review, we explore the role of endoscopy in managing complications associated with PD.

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Table 1 Complications associated with pancreaticoduodenectomy[3,5]

Early complications	Delayed complications
Delayed gastric emptying	Gastric outlet obstruction
Surgical site infections	Biliary stricture
Pancreatic fistula	Pancreaticojejunostomy stricture
Hemorrhage	
Bile leak	

Challenges in Endoscopy in Postpancreaticoduodenectomy Anatomy

An understanding of variations in surgical anatomy is paramount in performing endoscopy after PD[4] (►**Fig. 1**). Discussion with the surgical team and also review of the surgical notes are necessary before undertaking any interventions in these patients. There are three sites of anastomoses and occasionally an additional Braun-type jejuno-jejunostomy may be done. A standard gastroscope can access the GJ site with ease. Accessing the HJ and PJ is often difficult, however possible in some patients with a standard gastroscope. In patients who undergo a Roux-en-Y anastomosis, the alimentary and biliopancreatic limbs may be long, and accessing the same may often be difficult. One has to traverse 75 to 150 cm to reach papilla in Roux-en-Y gastric bypass and 40 to 60 cm in PD. In these patients, a standard colonoscope or single- or double-balloon enteroscope can be used. In addition, a short-length double-balloon enteroscope is also available for use in these situations to ensure ease of manipulation. Identifying loops may sometimes be difficult in patients with long jejunal limbs. The use of fluoroscopy can assist in such situations.

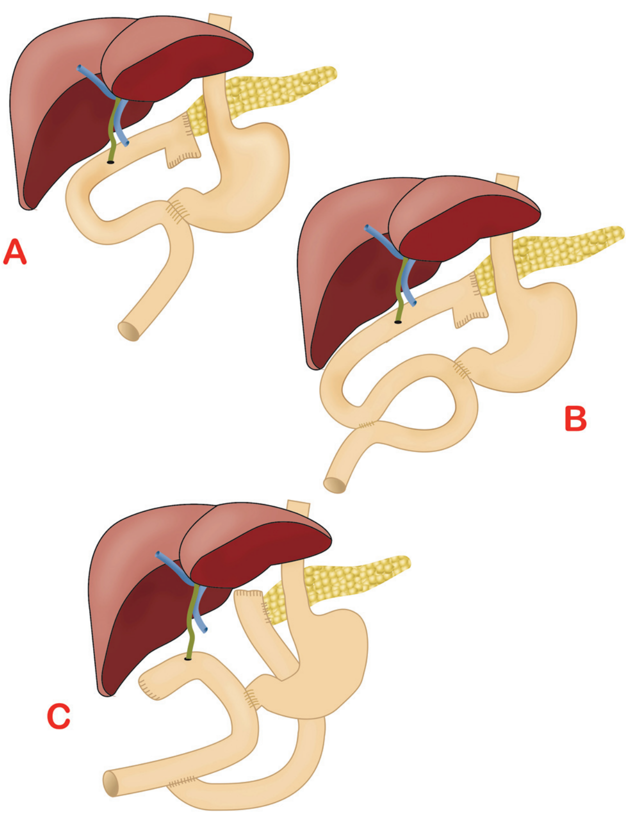

Fig. 1 Anatomical variants after pancreaticoduodenectomy. (**A**) Standard child reconstruction. (**B**) Child reconstruction with Braun enteroenterostomy. (**C**) Isolated Roux-en-Y reconstruction with pancreatic duct draining via the Roux limb.

Endoscopy in the Management of Complications

Hemorrhage

Postsurgical bleeding complications range from 5 to 16%.[5–10] Post-PD hemorrhage can occur early (within 24 hours) and late (after 24 hours).

Early Hemorrhage

Early hemorrhage is mainly due to poor intraoperative hemostasis or coagulopathy. In pancreatic anastomotic site bleeding, Gastroduodenal artery (GDA) is usually the main source. Potential sites of intraluminal and extraluminal early hemorrhage are described in ►**Table 2**.

Delayed Hemorrhage

Delayed hemorrhage is commonly associated with pancreatic leak or uncommonly due to stress gastric ulcer, erosion of ligated vessels due to intra-abdominal infection, and sepsis in the pancreatic anastomotic region or development of a pseudoaneurysm.

Post-PD bleeding is suspected when there is a clinical sign of hypovolemia (i.e., persistent hypotension, tachycardia), peritonitis, or fresh blood in Ryle's tube (RT) aspirate or abdominal drain output. Routine radiological investigations have a limited role in the management of post-PD hemorrhage. Bedside portable ultrasonography may have a role in evaluating free intra-abdominal fluid.[11] In a patient with hemodynamic instability, imaging investigations may delay definitive management in the form of surgical reexploration. Computed tomography scan has a role in identifying anastomotic site dehiscence presenting with bleeding after PD in hemodynamically stable patients. Identifying potential sources of bleeding is often difficult with negative angiography seen in 31% of cases.[12,13]

The role of endoscopy is limited to detecting and helping in the management of luminal source of bleeding. All potential bleeding sites: GJ, HJ, and PJ should be identified if

Table 2 Potential sites of intraluminal and extraluminal bleeding following pancreaticoduodenectomy[8,9,12]

Intraluminal bleeding	Extraluminal bleeding
Pancreatic anastomosis	Gastroduodenal artery
Pancreaticojejunostomy (PJ)	Hepatic artery
Pancreaticogastrostomy (PG)	Splenic artery
Gastrojejunostomy (GJ)/duodenojejunostomy (DJ)	Inferior pancreaticoduodenal artery
Gastric erosion/stress ulcer	Margin of uncinate process of pancreas
Choledochojejunostomy/hepaticojejunostomy	Superior mesenteric vein/portal vein/colic veins

possible. Technical challenges occur during endoscopy due to altered anatomy often making it difficult to negotiate the scope across angulations. In addition, endoscopy has to be attempted with minimal insufflation due to the risk of worsening of anastomotic dehiscence if present. Using a distal attachment cap is often useful to help visualize behind folds in the small bowel and also identify bleeding points with ease. After identifying any active bleeding source, hemostasis can be attempted by mechanical therapy (Clips) (►**Fig. 2**), injection therapy (adrenaline or sclerosant), thermal therapy (gold probe or argon plasma coagulation), or topical therapy (hemospray). Caution should be exercised while using contact probes for hemostasis, due to the risk of inadvertent bowel perforation. Endoscopy is more useful in delayed bleed when compared with early bleed having a higher yield of up to 85.7%.[14] ►**Fig. 3** provides the algorithmic approach to post-PD bleeding.

Delayed Gastric Emptying

Delayed gastric emptying (DGE) is one of the most common complications after the Whipple's surgery in various studies with incidence ranging from 5 to 61%.[15–18] Various risk factors for DGE are diabetes mellitus, male sex, smoking, fistulas, intra-abdominal collection, disruption of vagal innervations, and duodenal resection. DGE after PD has two components—early gastric stasis and postprandial delayed emptying. DGE is typically defined by an unusually prolonged need for nasogastric suction. Postprandial DGE is defined as the inability of oral intake of more than half of usual soft meals at 1 month postoperatively. ►**Table 3** shows us the classification for DGE as per the ISGPF (International Study Group on Pancreatic Fistula) into three grades.[19]

Maintenance of electrolyte balance in the immediate postoperative period might prevent the development of DGE after PD. Initial understanding was a higher incidence of DGE in patients with PPPD compared with classic Whipple's's.[20,21] However, various studies show no difference between the two groups. Antecolic reconstruction has reduced chances of DGE in studies (10 vs. 22% retrocolic).[22] In a study by Yeo et al, erythromycin was found to be a safe, inexpensive drug that significantly accelerates gastric emptying after PD and reduces the incidence of DGE by 37%.[23] However, no large-scale studies are available to endorse the routine use of any prokinetics.

There are limited data on the endoscopic management of DGE after PD. DGE should prompt for postoperative collections as it is one of the most common factors associated with DGE. The role of endoscopy in the management of DGE is limited to Grade B and C (►**Fig. 4**). In a single-center retrospective cohort study by Calogero et al, 281 patients who underwent PD between 2017 and 2020 were evaluated. DGE developed in 55 (19.6%) patients. Of these, nine patients with Grade B or C DGE underwent endoscopy and the median time to endoscopic intervention was 15 days. Six patients had angulations or strictures with edema, with anastomotic ulcer seen in two patients. One-third required balloon dilation of stricture or angulation during endoscopy, and seven (77.8%) patients reported immediate improvement in DGE symptoms postendoscopy.[24]

Postoperative Collections

Postoperative collection is a common complication after PD, the frequency of postoperative fluid collection after PD is between 4 and 40%.[25–29] The frequency of peripancreatic

Fig. 2 Nonbleeding visible vessel at gastrojejunostomy anastomotic site tackled by endoscopic clip placement.

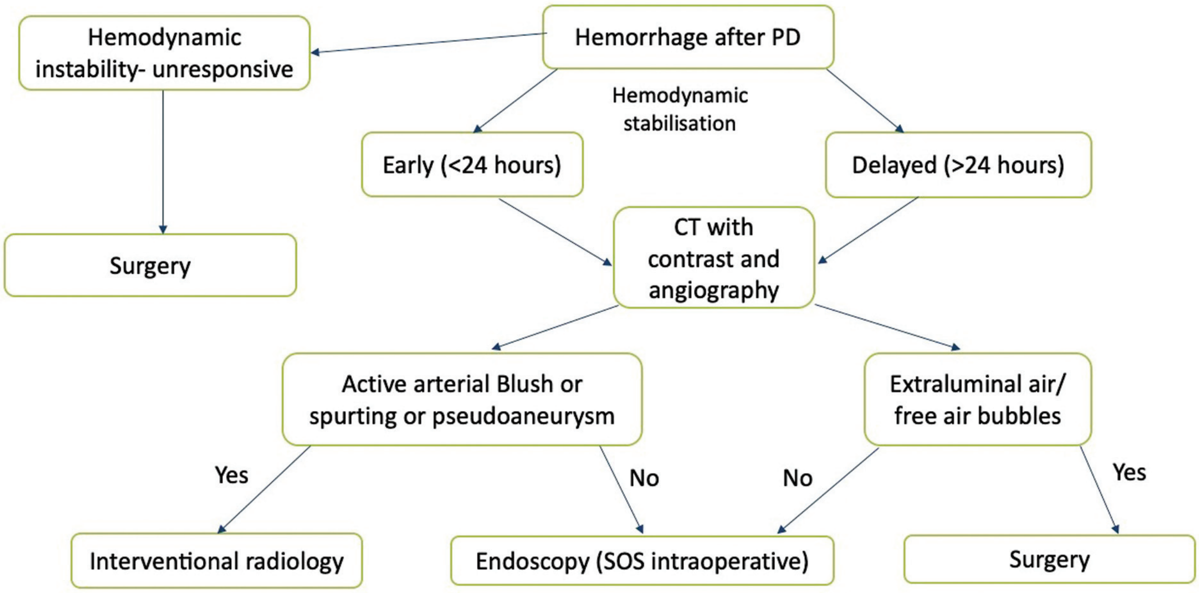

Fig. 3 Algorithm for approach to hemorrhage in a patient with postpancreaticoduodenectomy.

Table 3 International Study Group of Pancreatic Surgery grading of delayed gastric emptying[19]

DGE grade	NGT requirement	Unable to tolerate solid oral intake by POD	Vomiting/gastric distension	Use of prokinetics
A	4–7 d or reinsertion > POD3	7	±	±
B	8–14 d or reinsertion > POD7	14	+	+
C	>14 d or reinsertion > POD14	21	+	+

Abbreviations: DGE, delayed gastric emptying; NGT, nasogastric tube; POD, postoperative day.

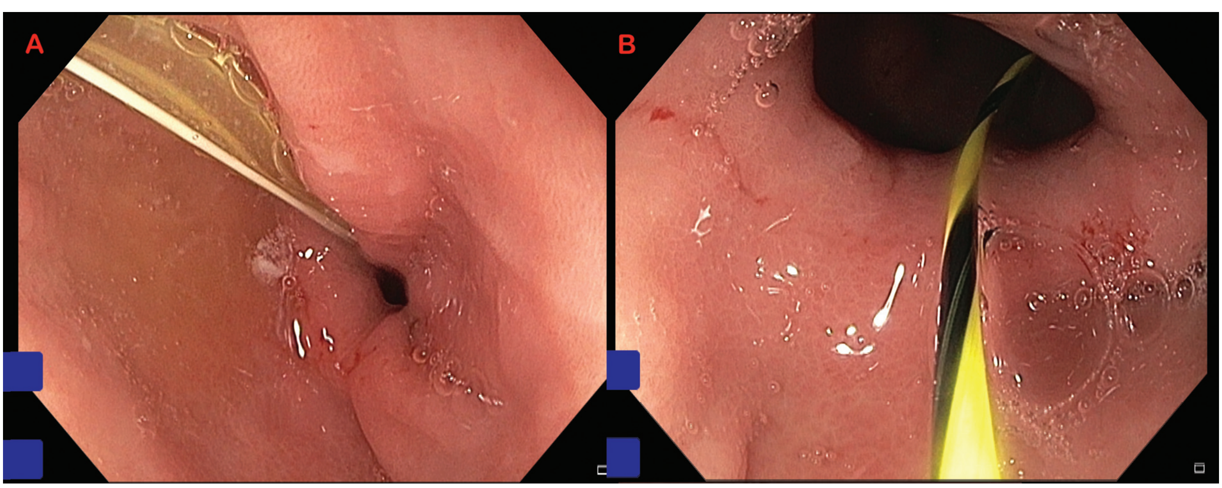

Fig. 4 (**A**) Deviated axis of the pylorus in a patient with delayed gastric emptying. (**B**) Endoscopic dilatation of pylorus done with relief of delayed gastric emptying.

leak and fluid collection is higher with distal pancreatectomy and central pancreatectomy.[30] Pancreatic fistula was classified into three grades by International Study Group of Pancreatic Surgery (ISGPS) in 2005: Grade A, spontaneous resolution; Grade B, management with a drain in situ, and Grade C, additional intervention requirement.[31] In an update of postoperative pancreatic fistula (POPF) by ISGPS in 2016,[32] the original "Grade A" POPF is no longer considered a true pancreatic fistula. Percutaneous drainage and endoscopic ultrasound (EUS)-guided drainage are options for drainage of post-PD collections that occur as a sequel to POPF. Surgery is usually considered a last resort in these situations. Percutaneous drainage often leads to a lower quality of life due to the external drain[33,34] and the risk of permanent pancreatic-cutaneous fistula in 25% of cases.[35,36] Hence, in situations where technically feasible, endoscopy should be considered as a primary modality for drainage. As is the case with peripancreatic fluid collections that occur as a consequence of pancreatitis, EUS drainage is preferred over direct endoscopic drainage due to better visualization of the collection with optimal access even without a luminal bulge.[37,38]

In a study by Al Efishat et al comparing Endoscopic versus percutaneous drainage of postoperative peripancreatic fluid collections following pancreatic resection, 39 patients were included each in the endoscopic drainage and percutaneous drainage groups. Technical success was achieved in almost all patients in both endoscopic and percutaneous groups (100 and 97%, p = not significant); clinical success was achieved in 67 and 59%, respectively ($p = 0.63$). They concluded that endoscopic drainage of postoperative pancreatic fluid collection (PFC) is as safe and effective with comparable success rates and outcomes to percutaneous drainage.[37] In another study by Woo et al comparing EUS-guided drainage and percutaneous catheter drainage of the postoperative fluid collection after PD, 53 patients were retrospectively analyzed. A total of 32 patients underwent EUS-guided drainage and 21 patients underwent percutaneous drainage. The two groups showed no statistically significant difference in technical or clinical success rate, reintervention rate, or adverse event (AE) rate; however, the EUS group had a shorter postprocedural hospital stay.[39] In a systematic review and meta-analysis of 25 studies with 477 patients, the technical and clinical success rates of EUS drainage were 94 and 87%, respectively, with postprocedural complications of 14% and recurrence rates of 9%. EUS drainage showed a significantly shorter duration of hospital stay compared with that of patients treated with Percutaneous drainage (PCD).[40]

Technical challenges in endoscopy are the need for wall formation for EUS intervention. Hence, in patients with immature collections with ill-formed walls, percutaneous drainage may be preferred. While no comparative data between plastic stents and lumen-apposing metal stents (LAMS) in the postoperative setting is available, LAMS or biflanged metal stent (BFMS) are preferred due to ease of placement and to ensure optimal drainage of necrotic or infection contents with debris.[41,42] Cautery-enhanced LAMS make placement much easier considering the single-step delivery process. On the other hand, the multistep process of stent placement makes it cumbersome to place cold LAMS or BFMS. However, there is a paucity of data in postoperative collections. Coaxial plastic stents are placed through metal stents to avoid blockage with reduced need for reintervention.[43] Removal of metal stents is done at 3 to 4 weeks as done in patients with pseudocysts or walled-off pancreatic necrosis to avoid the risk of a buried metal stent.[44] In patients with large collections, tracking into the paracolic gutter, there may be a preference for percutaneous or surgical intervention.

Pancreaticobiliary Complications

Stenosis of biliary and pancreatic anastomosis typically occurs as a delayed complication. In rare cases, biliary or pancreatic calculi may develop. The incidence of biliary stricture after PD ranges from 2.6 to 5%. It is associated with pain with cholangitis. Factors associated with biliary anastomotic strictures (BAS) include laparoscopic approach, POPF, postoperative bile leak (BL), and administration of adjuvant radiation therapy. Malignant pathology was associated with lower rates of BAS.[45,46] The PJ anastomosis stenosis varies from 1.9 to 11% in different studies.[45] Possible etiological factors, such as pancreatic stump texture, ischemia, or anastomotic suturing technique. PJ stenosis was predominantly seen in patients with low-grade malignancy or benign tumors. The main clinical manifestations of Pancreaticojejunostomy stenosis (PJS) include abdominal pain, distension, and recurrent pancreatitis.[47–49] Diagnosis is based on clinical manifestations and imaging findings. Endoscopy can be useful in both biliary and pancreatic ductal stenoses. Alternatively for biliary obstruction, percutaneous transhepatic biliary drainage (PTBD) can be done. However, PTBD has issues with persistent external drainage tube, occlusion, dislocation, and risk of infections.[50]

Endoscopic Retrograde Cholangiopancreatography in Postpancreaticoduodenectomy Anatomy

Endoscopic retrograde cholangiopancreatography (ERCP) in post-PD anatomy is challenging considering the difficulty in accessing afferent limbs, finding the HJ or PJ site, and subsequently achieving cannulation. The HJ site is proximal to the PJ site and can be accessed first. Cannulation can be attempted using a pediatric colonoscope or single or double-balloon enteroscope. ERCP cannula can be used to achieve cannulation. The success rate of intubating the afferent limb is 95 to 100%. Successful cannulation rate is 85% for biliary indications and much lower for pancreatic indications <60 to 70%.[51] A prospective study by Pal et al evaluated the safety and efficacy of single-balloon enteroscopy-assisted ERCP (SBE-ERCP) in surgically altered anatomy in patients who failed ERCP with a colonoscope/duodenoscope. Diagnostic success was 91.3% of patients with Roux-en-Y anatomy and 100% with Billroth II anatomy. Therapeutic success was achieved in 86.95 and 94.1% of patients with Roux-en-Y and Billroth II anatomy with an immediate complication rate of 7.5% in the form of perforation.[52] In another study by Garcés-Durán, feasibility and safety of SBE-ERCP in post-PD anatomy were assessed; 34 patients underwent 106 SBE-ERCP, 76 procedures performed for biliary indication had a 90% technical success and 88% clinical success rate, whereas among 30 procedures performed for pancreatic intervention technical success rate was 80% and the clinical success rate was 65%.[53] While either side-view or forward-viewing scopes can be used, passage of a side-view scope into the afferent limb is often tricky. Cannulation is trickier with end-on scopes rather than side-view scopes.[54] Pancreatic ductal interventions are more complex as compared with biliary interventions as the PJ orifice is usually distal to the HJ orifice in the afferent limb. Also, standard maneuvers for stone extraction are often difficult. Stabilizing scope in a loop that is angulated is often an issue and requires expertise.

Endoscopic Ultrasound Biliary Intervention

EUS-guided biliary drainage (EUS-BD) can be through transpapillary intervention or transmural procedure.[55] These procedures are performed under conscious sedation or general anesthesia. EUS-guided puncture to the biliary tract can be achieved through segment 2 or 3 biliary radicles through gastric remnant.[56–58] EUS transhepatic rendezvous can be attempted when the papilla is accessible using duodenoscope or enteroscopy. Transhepatic rendezvous is associated with higher technical failure and more complications as compared with transduodenal rendezvous.[59] However, this is the only route for rendezvous with post-PD anatomy. Guidewire once passed across the biliary tree through papilla is grasped by duodenoscope or enteroscope. In EUS-guided antegrade drainage, after puncturing segment 2 or 3, the guidewire is negotiated across stricture or anastomotic site and the stent can be placed through an antegrade route (►**Fig. 5**). In the case of benign stricture, dilatation is feasible. In choledocholithiasis, balloon dilatation can be performed in an antegrade fashion and stones can be pushed into the bowel. Direct stent placement is also feasible if indicated.[56–58,60,61] Transmural procedures (EUS-hepaticogastrostomy [EUS-HGS]) involve the creation of a fistulous tract by taking a puncture from the stomach or gastric remnant into the biliary tree segment 2 or 3. Guidewire is passed deep inside the biliary tree. Cystotome is subsequently passed over the guidewire to create tract and a self-expandable metal stent is placed. Staged procedures with HGS followed by subsequent antegrade intervention through the HGS tract or stent can be done in patients with large stones where extraction was not feasible. Cholangioscopy can also be undertaken through the antegrade route for stone fragmentation and extraction.[62]

In a multicenter comparative cohort study at 10 tertiary centers, enteroscopy-assisted ERCP (e-ERCP) and EUS-BD were compared in patients with surgically altered upper gastrointestinal anatomy. Technical success was achieved in a higher number of patients undergoing EUS-BD (98% EUS-BD vs. 65.3% e-ERCP, p = significant) with higher clinical success (88% EUS-BD group vs. 59.1% e-ERCP, p = significant) and shorter procedure time (55-minute EUS-BD vs. 95-minute e-ERCP). Adverse effects occurred more commonly in the EUS-BD group (20 vs. 4%). However, most of the adverse effects (90%) were mild or moderate. Length of stay was significantly longer in the EUS-BD group (6.6 vs. 2.4 days).[63] In a retrospective study, comparing biliary drainage in postsurgical anatomy using single-balloon e-ERCP and EUS-BD including 48 patients who underwent single-balloon e-ERCP and EUS-HGS, technical success rate comparable (93.5% in SBE drainage and 85% in EUS-HGS group).[64] Another systematic review and meta-analysis showed technical success, clinical success, and complication

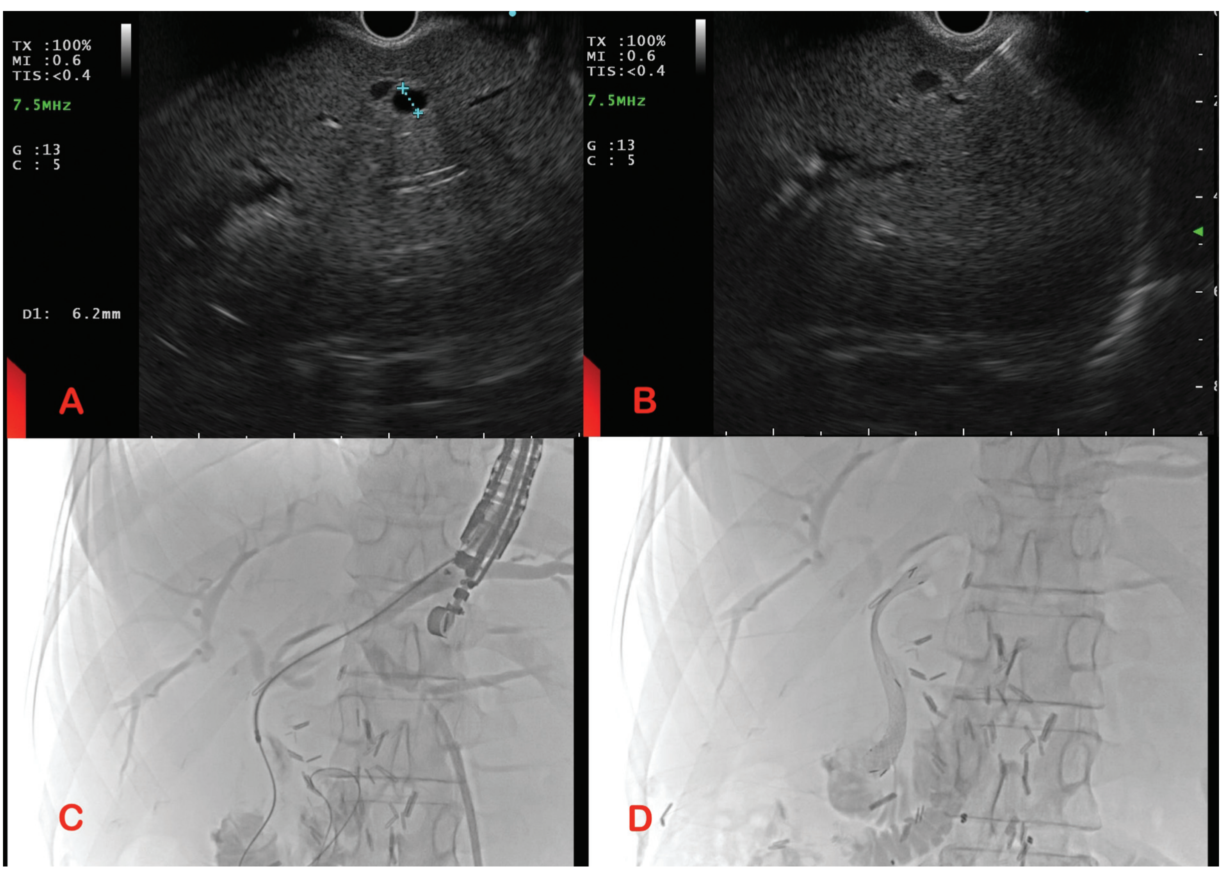

Fig. 5 (A) Dilated intrahepatic radicle in segment II in a patient with recurrence postpancreaticoduodenectomy at hepaticojejunostomy (HJ) anastomotic site. (B) Puncture into segment II dilated radicle with 19-G fine-needle aspiration needle. (C) Guidewire negotiated into the afferent limb. (D) Stent placement was done across the HJ site.

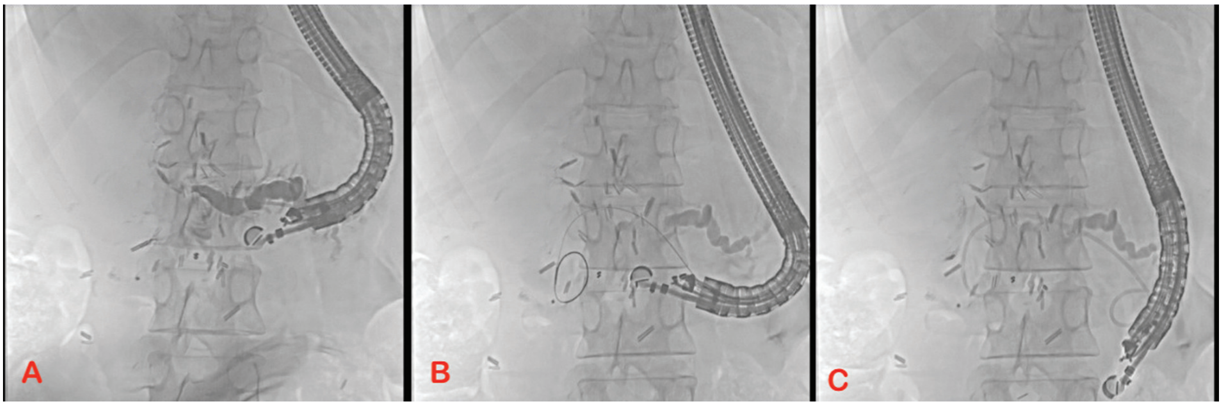

Fig. 6 (**A**) Puncture into dilated Main Pancreatic duct (MPD) in a patient with PJ stenosis. (**B**) Guidewire negotiated into the afferent limb. (**C**) Transmural transpapillary EUS-guided stent placement was done. EUS, endoscopic ultrasound; PJ, pancreaticojejunostomy.

rates were 89.18, 91.07, and 17.5%, respectively, in patients who underwent EUS-BD in patients with surgically altered anatomy.[65] In a multicenter prospective study by Minaga et al assessing the efficacy and safety of EUS-BD in a patient with surgically altered anatomy, technical and clinical success rates were 100 and 95%, respectively, with a complication rate of 8 to 9% and mean procedure time of 36.5 minutes.[66]

Endoscopic Ultrasound Pancreatic Intervention

EUS-guided pancreatic duct drainage (EUS-PDD) is more complex than EUS-BD as the pancreatic duct is usually smaller as compared with biliary ducts making EUS-guided puncture difficult. Dilatation of the pancreatic duct is more difficult with higher chances of pancreatitis in EUS-guided pancreatic intervention. EUS-PDD can be done by EUS pancreatic rendezvous when access to the PJ site is feasible. Else pancreatiogastrostomy can be done through a transmural access.[67,68] In some situations, transmural transpapillary stent placement can also be done (►**Fig. 6**). In a case series of 10 post-PD patients required pancreatic therapeutic ERCP, unassisted pancreatic cannulation was successful in only one patient and EUS rendezvous was successful in five patients.[69]

In a multicenter study by Chen et al comparing EUS-PDD with enteroscopy-assisted endoscopic retrograde pancreatography after Whipple's surgery, 66 patients undergoing 75 procedures were identified (40 EUS-PDD, 35 e-ERP). Technical success was achieved in 92.5% of procedures in the EUS-PDD group compared with 20% of procedures in the e-ERP group. Clinical success was attained in 87.5% of procedures in the EUS-PDD group compared with 23.1% in the e-ERP group. However, AEs occurred more commonly in the EUS-PDD group (35 vs. 2.9%). All AEs were mild or moderate.[70] Another multicenter study by Kogure et al shows higher technical success for EUS-PDD (100%) versus DBE-ERCP (70.7%) with similar clinical success.[71] In a meta-analysis by Chandan et al of 22 studies with 714 patients, the pooled technical success

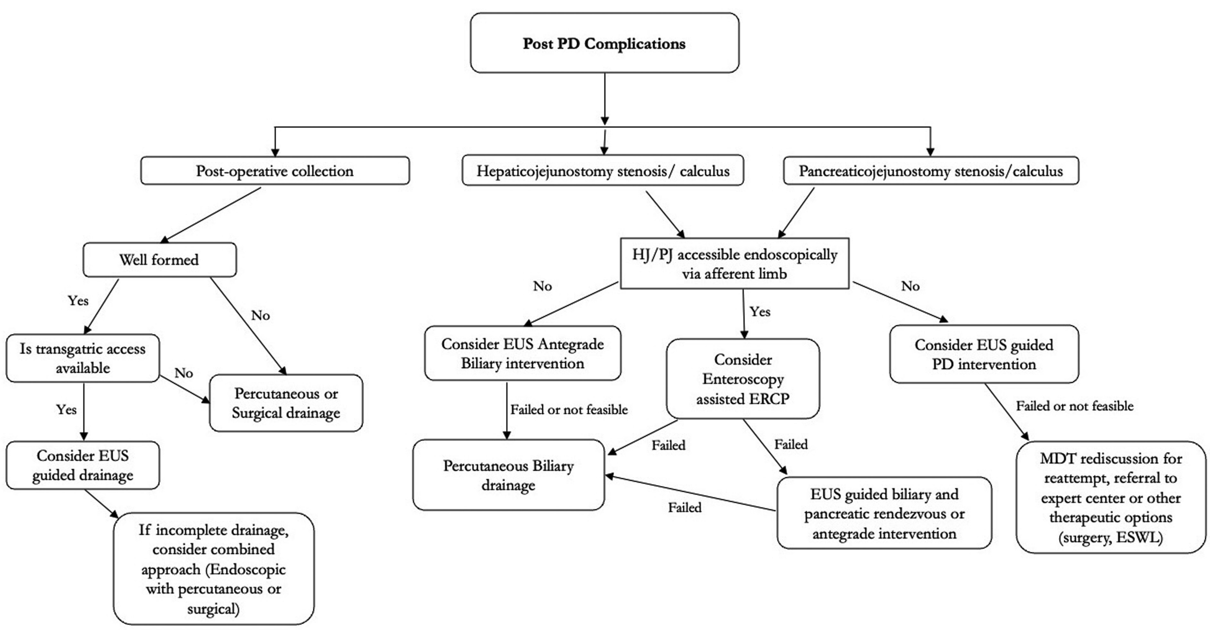

Fig. 7 Algorithm for management of postpancreaticoduodenectomy collections and pancreaticobiliary complications.

of EUS-PDD was 84% and the pooled clinical success was 89%. AEs were observed in 18.1% of patients (pancreatitis 6.6%, bleeding 4.1%, perforation and/or pneumoperitoneum 3.1%, pancreatic leak, and/or PFC 2.3%, infection 2.8%).[72] EUS-PDD can be attempted in expert hands in situations where e-ERCP is not feasible or expertise is not available. ►**Fig. 7** discusses an approach to post-PD collections and pancreaticobiliary complications.

Conclusion

Endoscopy is an essential tool in the evaluation of various complications post-PD. Knowledge of postsurgical anatomy is critical. There is a definitive role for endoscopy in the evaluation and management of delayed bleeding post-PD and also evaluation of Grade B and C DGE. In patients with postoperative collections, EUS drainage is an emerging option. Lastly, for pancreaticobiliary complications, ERCP is feasible and EUS-guided biliary and pancreatic ductal drainage are rescue options. More studies are needed to evaluate the role of endoscopic modalities for the evaluation and management of post-PD complications.

Conflict of Interest
None declared.

Acknowledgments
None.

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