Malignant Biliary and Gastric Outlet Obstruction in Peri-Ampullary Cancers

Yeganeh Rostamianmoghaddam

Division of Experimental Medicine, Faculty of Medicine and Health Sciences

McGill University, Montreal, Canada

July, 2024

A thesis submitted to McGill University in partial fulfillment of the requirements of the degree of

Master of Science.

Table of Contents

Glossary of Abbreviations

aHR: Adjusted hazard ratio

AE: Adverse Events

CCA: Cholangiocarcinoma

CDS: Choledochoduodenostomy

CI: Confidence interval

DCCA: Distal Cholangiocarcinoma

EPASS: Endoscopic Ultrasound-guided Double Balloon-occluded Gastrojejunostomy Bypass

ERCP: Endoscopic retrograde cholangiopancreatography

ERCP-M: Endoscopic retrograde cholangiopancreatography with metal stenting

ES: Enteral stenting

EUS-BD: Endoscopic ultrasound-guided biliary drainage-biliary drainage

EUS-CDS: Endoscopic ultrasound-guided choledochoduodenostomy with a lumen-apposing metal stent

EUS-CDSL: EUS-guided choledochoduodenostomy using a lumen apposing metal stent

EUS-GE: Endoscopic ultrasound-guided gastroenterostomy

FOLFIRINOX: Leucovorin, fluorouracil, irinotecan, and oxaliplatin

GB cancer: Gallbladder cancer

HGS: Hepatico-gastrostomy

IPD: Individual patient data

LAMS: lumen apposing metal stents

MDBO: Malignant distal biliary obstruction

MGOO: Malignant gastric outlet obstruction

PSC: Primary sclerosing cholangitis

PTBD: Traditional Management: Percutaneous Transhepatic Biliary Drainage

PTC: Percutaneous transhepatic cholangiographic drainage

RCT: Randomized controlled trial

SEMS: Self-expandable metal stent

SGJ: Surgical gastrojejunostomy

Abstract (English)

Background: Malignant distal biliary obstruction (MDBO) and malignant gastric outlet obstruction (MGOO) are frequent complications in patients with advanced pancreatic and biliary cancers. For MDBO, the current standard of care is endoscopic retrograde cholangiopancreatography (ERCP). EUS-guided choledochoduodenostomy (EUS-CDS) using lumen apposing metal stents (LAMS) offers a promising alternative with randomized controlled trials suggesting comparable outcomes with shorter procedure time and potentially higher technical success, however, its safety has not been adequately defined. Malignant gastric outlet obstruction (MGOO) is a morbid complication of pancreatic head cancer with a lack of contemporary epidemiological data characterizing its incidence and outcomes, particularly in patients with unresectable pancreatic head cancer undergoing leucovorin, fluorouracil, irinotecan, and oxaliplatin (FOLFIRINOX®) chemotherapy. Determining the incidence and outcomes of MGOO is crucial for developing effective management strategies.

Objectives: Our aim was to 1) better characterize the safety of EUS-CDS in MDBO when compared to ERCP and 2) to ascertain the incidence of MGOO in patients with pancreatic cancer treated with FOLFIRINOX.

Methods: To assess the safety of EUS-CDS when compared to ERCP, we undertook aggregate and individual patient data (IPD) meta-analyses following the PRISMA-IPD statement. A literature search was performed from January 2013 to November 2023 using OVID MEDLINE, EMBASE, Cochrane Library, and ISI Web of Science. RCTs comparing EUS-CDSL to ERCP were included. The primary outcome was the rate of procedure related severe or fatal adverse events (AE). In the second study, a retrospective, single-center study was conducted involving patients with pancreatic head cancer treated with FOLFIRINOX between January 2017 and December

2022. Patients were assessed for incidence and clinical outcomes of MGOO. The primary endpoint was the rate of malignant gastric outlet obstruction.

Results: For the meta-analysis, a total of 2241 citations were screened with two RCTs included (299 patients). There was no difference in severe or fatal AEs between EUS-CDSL and ERCP (OR 0.47, 95% CI 0.12-1.93 for IPD data and RR 0.62, 95% CI 0.22, 1.77 for aggregate data). Technical success was greater for EUS-CDSL (OR 3.95, 95% CI 1.86-8.37 and RR 1.17, 95% CI 1.07, 1.29) with faster procedural time (mean difference -10.01 minutes (95% CI 19.30, -0.87). In the single-center retrospective study, 44 patients with pancreatic head cancer (40.90% female, mean age 59.3 ± 8.5 years) were included. The incidence of MGOO in patients with pancreatic head cancer was 36.36%. Patients who never developed MGOO experienced significantly shorter unplanned hospitalizations (mean ± SD: 20.8 ± 18.30 days) compared to those with MGOO (mean ± SD: 50.33 ± 41.22 days; p = 0.0175).

Conclusion: Our aggregate and IPD meta-analyses support using EUS-CDSL as a safe and effective first-line alternative to ERCP in advanced MDBO with superior technical efficiency and success. The development of MGOO was associated with longer total hospitalization when compared to patients who never developed MGOO. The high incidence of MGOO in pancreatic head cancer patients undergoing FOLFIRINOX treatment highlights the need for further research to improve management strategies for this morbid and costly complication.

Abstract (French)

Contexte: L'obstruction biliaire distale maligne (MDBO) et l'obstruction maligne de la sortie gastrique (MGOO) sont des complications fréquentes chez les patients atteints de cancers pancréatiques et biliaires avancés. Pour la MDBO, la cholédocoduodénostomie guidée par échoendoscopie (EUS-CDS) utilisant des stents métalliques apposés par lumière (LAMS) offre une alternative prometteuse, avec des essais suggérant des résultats comparables, un temps de procédure plus court et un succès technique plus élevé, bien que sa sécurité reste à définir. La MGOO est une complication courante du cancer de la tête du pancréas, mais il manque des données épidémiologiques récentes, surtout chez les patients sous chimiothérapie FOLFIRINOX®. Déterminer l'incidence et les résultats de la MGOO est crucial pour améliorer les stratégies de gestion.

Objectifs: Notre objectif était de 1) mieux caractériser la sécurité de l'EUS-CDS dans la MDBO par rapport à l'ERCP, et 2) déterminer l'incidence de la MGOO chez les patients atteints de cancer du pancréas traités avec FOLFIRINOX. Les objectifs secondaires incluent l'évaluation des résultats cliniques de la MGOO.

Méthodes: Pour évaluer la sécurité de l'EUS-CDS par rapport à l'ERCP, nous avons entrepris des méta-analyses de données agrégées et de données de patients individuels (IPD) suivant la déclaration PRISMA-IPD. Une recherche bibliographique a été effectuée de janvier 2013 à novembre 2023 en utilisant OVID MEDLINE, EMBASE, Cochrane Library et ISI Web of Science. Les ECR comparant l'EUS-CDSL à l'ERCP ont été inclus. Le principal résultat était le taux d'événements indésirables graves ou fatals liés à la procédure (AE). Dans la deuxième étude, une étude rétrospective, monocentrique a été menée impliquant des patients atteints de cancer de la tête du pancréas traités par FOLFIRINOX entre janvier 2017 et décembre 2022. Les patients ont

été évalués pour l'incidence et les résultats cliniques de la MGOO. Le principal critère d'évaluation était le taux d'obstruction maligne de la sortie gastrique.

Résultats: Pour la méta-analyse, un total de 2241 citations ont été examinées avec deux ECR inclus (299 patients). Il n'y avait pas de différence dans les AE graves ou fatals entre l'EUS-CDSL et l'ERCP (OR 0,47, IC 95 % 0,12-1,93 pour les données IPD et RR 0,62, IC 95 % 0,22-1,77 pour les données agrégées). Le succès technique était supérieur pour l'EUS-CDSL (OR 3,95, IC 95 % 1,86-8,37 et RR 1,17, IC 95 % 1,07-1,29) avec un temps de procédure plus rapide (différence moyenne -10,01 minutes, IC 95 % 19,30, -0,87). Dans l'étude rétrospective monocentrique, 44 patients atteints de cancer de la tête du pancréas (40,90 % de femmes, âge moyen 59,3 ± 8,5 ans) ont été inclus. L'incidence de la MGOO chez les patients atteints de cancer de la tête du pancréas était de 36,36 %. Les patients qui n'ont jamais développé de MGOO ont connu des hospitalisations imprévues significativement plus courtes (moyenne ± SD: 20,8 ± 18,30 jours) par rapport à ceux ayant développé une MGOO (moyenne ± SD: 50,33 ± 41,22 jours ; p = 0,0175).

Conclusion: Nos méta-analyses de données agrégées et IPD soutiennent l'utilisation de l'EUS-CDSL comme alternative de première ligne sûre et efficace à l'ERCP dans la MDBO avancée, avec une efficacité technique et un succès supérieur. Le développement de la MGOO était associé à une hospitalisation totale plus longue par rapport aux patients qui n'ont jamais développé de MGOO. La forte incidence de la MGOO chez les patients atteints de cancer de la tête du pancréas sous traitement FOLFIRINOX met en évidence la nécessité de recherches supplémentaires pour améliorer les stratégies de gestion de cette complication grave et coûteuse.

Acknowledgments

The work put into this thesis, the studies composing it, and the day-to-day research behind it is a result of the collaboration of many individuals. I could not have accomplished this work without any of you. I am eternally humbled and grateful.

I owe an enormous debt of gratitude to my supervisor, Dr. Yen-I Chen, for allowing me to take part in this process, for entrusting me with his vision for his research, and for giving me the space to develop into the researcher (and more importantly person) that I have become. I have gained extensive knowledge from him, not only in my academic pursuits but also in understanding what it means to be a good person. I am deeply thankful for his genuine commitment to my success, including the time, energy, and devotion he has invested. I feel truly fortunate to have him as a mentor.

I want to extend my heartfelt thanks to my co-supervisor, Yidan Lu, for always being there for me. I wish to express my sincere gratitude to Myriam Martel for consistently answering my questions and providing unwavering support throughout this journey. She has a remarkable ability to explain complex statistical topics clearly and easily and I have gained invaluable knowledge from her guidance. Thank you to my academic advisor, Sampath Loganathan, and thesis committee members Drs. Jeffrey Barkun and Ali Bessissow, for their constructive and substantial support throughout my master's work. Thanks to Olivia Geraci for helping me with data collection. I am grateful to my co-authors, Abdulrahman Qatomah and Clara Long, for their contributions to this study and for their friendship.

Lastly, I owe a particular debt of gratitude to my parents, Kobra Pourmand and Abbas Rostamianmoghaddam, for raising me to be who I am and my sister, Yalda Rostamianmoghaddam,

whose unwavering belief in me has been a constant source of strength. Despite the distance, your support has been immense, inspiring me to pursue my dreams with determination. I am profoundly grateful for your love and encouragement. I would like to dedicate this thesis to my spouse, Seyed Mohammad Reza Ahmadi Namin. He has been a constant source of inspiration. His encouragement and support have helped me through challenging periods during this journey.

Contribution of Authors

I am the lead author of the manuscripts presented. I have been involved in all aspects of this research, including the conceptual design of the studies, literature reviews, statistical modeling and analysis, and the interpretation and presentation of results.

As my thesis supervisor, Dr. Chen contributed to and supervised all components of the conducted research. Dr. Barkun contributed to the study design and interpretation of results for both manuscripts. Myriam Martel performed the statistical analysis for the systematic review and meta-analysis and provided ongoing counsel regarding this analysis.

List of Figures

List of Tables

1. Chapter 1: Introduction and Literature Review

1.1. Introduction

1.1.1. Malignant Distal Biliary Obstruction (MDBO)

Malignant distal biliary obstruction (MDBO) is a common complication of advanced periampullary cancer, causing painless jaundice.[1] Restoring bile flow is crucial for reducing cholestasis symptoms, enhancing patients' quality of life, and enabling the administration of chemotherapy.[2], [3] Endoscopic retrograde cholangiopancreatography (ERCP) has been the preferred treatment for over 40 years[4], but it is associated with a notable technical failure rate and a substantial risk for complications.[4], [5], [6] EUS-guided choledochoduodenostomy (EUS-CDS) using a lumen apposing metal stent (LAMS) is an emerging approach in MDBO.[7], [8] Recent randomized controlled trials have shown EUS-CDSL to be comparable to ERCP, with better technical success and shorter procedure times.[6], [7]

1.1.2. Malignant Gastric Outlet Obstruction (MGOO)

MGOO is a common and morbid complication of advanced periampullary cancer.[9] Traditional management includes surgical bypass and endoscopic enteral stenting, both with limitations.[10], [11], [12], [13], [14] Endoscopic enteral stenting often requires reintervention due to obstruction recurrence, while surgical bypass has high rates of adverse events and complications[10], [11], [12], [13], [14] EUS-guided gastroenterostomy (EUS-GE) has emerged as an effective technique, combining the benefits of traditional approaches and minimizing disadvantages.[15], [16]

1.1.3. Study Aims and Objectives

1.1.3.1. Topic 1: EUS-CDS using a lumen apposing metal stent vs ERCP

Our meta-analysis aimed to evaluate the safety and technical efficiency of EUS-CDSL compared to ERCP in MDBO. The primary objective is to assess the safety of EUS-CDSL, hypothesizing it is comparable to ERCP in safety and exhibits superior technical efficiency and success.

1.1.3.2. Topic 2: Incidence of Malignant Gastric Outlet Obstruction (MGOO)

Our single-center retrospective study aimed to determine the prevalence and clinical outcomes of MGOO in these patients. Primary endpoints include the rate of MGOO, with secondary endpoints such as hospitalization length and success rates of endoscopic or surgical management.

1.2.Literature Review of Malignant Distal Biliary Obstruction (MDBO)

The most common presentation of peri-ampullary cancers is through painless jaundice caused by malignant distal biliary obstruction (MDBO).[1] Malignant distal bile obstruction (MDBO) develops when a tumor obstructs the lower part of the bile duct, close to where it enters the duodenum. This blockage causes symptoms such as jaundice, pruritus, and cholangitis. [2] The primary causes of this condition are pancreatic adenocarcinoma, which is primarily found in the head or uncinate process of the pancreas, and cholangiocarcinoma (CCA). Additional causes including ampullary/duodenal carcinoma, gallbladder (GB) cancer, and metastatic diseases that affect the head of the pancreas and the common bile duct.[17] [18] (Figure 1) In this setting, Malignant Distal Biliary Obstruction becomes a significant complication of such illnesses.

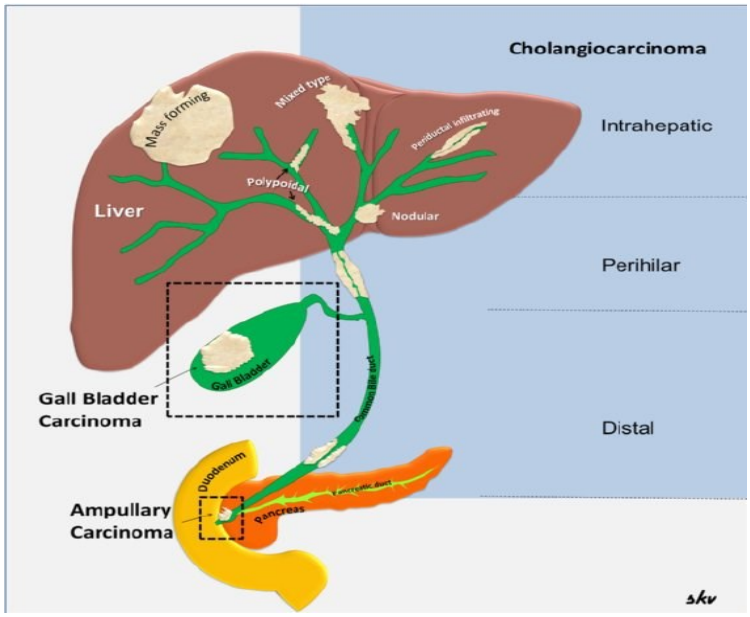


Figure 1. Malignancies of the biliary tract. Diagram showing the biliary tract and the various malignancies arising from the tract from T. Hennedige, W. Neo, and S. Venkatesh, "Imaging of malignancies of the biliary tract- an update," *Cancer Imaging*.[18]

By 2030, pancreatic cancer is expected to become the second leading cause of cancer-related death, making it the second most common digestive cancer in the United states.[19] Approximately 70% of patients diagnosed with pancreatic cancer develop symptoms of MDBO.[2]

Cholangiocarcinoma (CCA) stands as the second most prevalent hepatobiliary cancer worldwide.[2] Distal CCA (DCCA) represents approximately 20-30% of all cholangiocarcinomas reported globally.[20] Thailand has the highest occurrence of CCA worldwide, with around 100 cases per 100,000 people.[20] This is primarily due to the widespread presence of liver-fluke infections, specifically Clonorchis sinensis and Opisthorchis viverrini.[20], [21] In Western countries, the incidence rate varies from 0.5 to 2.0 per 100,000 individuals.[20] While the majority of cases are occasional, chronic inflammation of the biliary tree is often linked to different factors such as primary sclerosing cholangitis (PSC) and chronic infection.[22] Other underlying conditions include fibropolycystic liver disease, Caroli's disease, and choledochal cysts.[22] Gallbladder adenocarcinoma is one of the top five cancers affecting the digestive system and is the most frequently occurring cancer in the biliary tract globally.[23] Cholelithiasis is a recognized risk factor for gallbladder cancer, although only a small percentage (1-3%) of patients with gallstones will develop GB cancer.[24] Additionally, patients who experience porcelain gallbladder, gallbladder polyps, congenital biliary cysts, and abnormal pancreaticobiliary duct junction are more likely to develop GB cancer.[25] Ampullary cancers account for 0.2% of all digestive cancers, while periampullary cancers make up 7% of the total. [26] Achieving successful biliary decompression is crucial for the administration of hepatotoxic chemotherapy and significantly affects the quality of life of patients.[3], [27]

1.2.1. Current Management of Malignant distal biliary obstruction

MDBO is currently managed through Endoscopic retrograde cholangiopancreatography (ERCP), Percutaneous drain, and endoscopic ultrasound guided biliary drainage.

1.2.1.1. Traditional Management: Endoscopic retrograde cholangiopancreatography (ERCP)

Endoscopic retrograde cholangiopancreatography (ERCP) was first developed in 1968 as a means of diagnosing medical conditions.[28] Patients would be administered a dye injection and referred to an interventional radiologist or surgeon for any necessary further treatment.[28] Dr. William S. McCune, an obstetrician, performed the initial successful ERCP (endoscopic retrograde cholangiopancreatography) using a fiber duodenoscope.[28] This was achieved by attaching an external accessory channel to the scope shaft and using a balloon catheter for cannulation.[28] In 1972, Dr. Peter Cotton reported the process of cannulation in a total of 60 patients.[28] Following that, Dr. Meinhard Classen in Germany and Dr. Keiichi Kawai in Japan independently performed the first biliary sphincterotomy.[28] Afterwards, ERCP has progressed from being a means of diagnosis to becoming an approach for treatments.[28]

Endoscopic retrograde cholangiopancreatography (ERCP) with biliary stent placement has been considered the gold standard for over 40 years for relieving obstruction, and a less aggressive alternative when compared to surgery and percutaneous transhepatic biliary drainage.[4], [29] Endoscopic retrograde cholangiopancreatography (ERCP) with the placement of a self-expanding metal stent (SEMS) is presently suggested for palliation of malignant distal biliary obstructions (MDBOs) in patients with unresectable pancreatico-biliary malignancies.[30] The 1-year stent patency rates varied from 50.0% to 76.7%. Randomized studies evaluating uncovered self-expanding metal stents (SEMS) with covered SEMS (CSEMS) have yielded inconsistent findings, with neither type of stent demonstrating superiority.[31], [32], [33], [34] Despite endoscopic retrograde cholangiopancreatography (ERCP) being now regarded as the most reliable method, the transpapillary route faces a significant chance of adverse events (AEs), such as post-ERCP

pancreatitis.[5], [35], [36] Furthermore, the occurrence of stent dysfunction caused by obstruction from malignant tissue ingrowth or overgrowth maintains prevalent, even when self-expanding metal stents are employed, and has been reported in approximately 20%–30% of cases.[5], [7], [37], [38], [39](Figure 2) These consequences may include severe complications including cholangitis, interruptions in chemotherapy treatment, and significant expenses.[40]

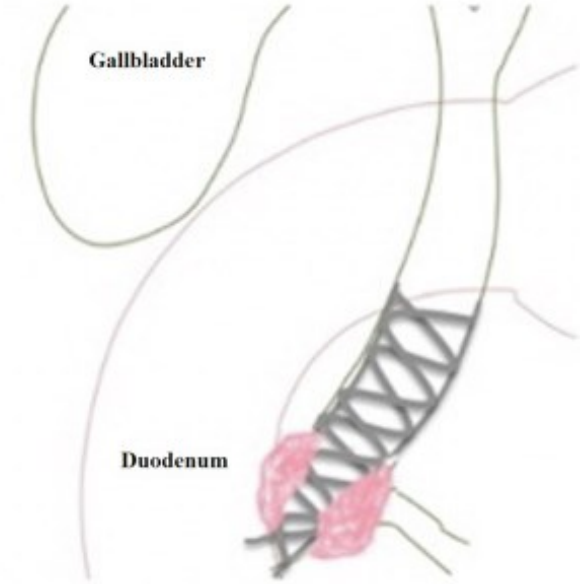


Figure 2.ERCP with insertion of traditional metal stent through the tumor from Y.-I. Chen *et al.*, "Endoscopic Ultrasound-Guided Biliary Drainage of First Intent With a Lumen-Apposing Metal Stent vs Endoscopic Retrograde Cholangiopancreatography in Malignant Distal Biliary Obstruction: A Multicenter Randomized Controlled Study (ELEMENT Trial).[7]

1.2.1.2. Traditional Management: Percutaneous Transhepatic Biliary Drainage (PTBD)

Although endoscopic retrograde cholangiopancreatography is the standard treatment for malignant distal biliary obstruction (MDBO), it is a challenging procedure with a technical failure rate of 10-20% and leads to a high chance of complications, such as post-ERCP pancreatitis.[4], [5], [6] Percutaneous transhepatic biliary drainage (PTBD) is an effective procedure to access the biliary tree, particularly when the biliary tree cannot be reached using endoscopy. PTBD techniques can be classified into two methods: fluoroscopy-guided PTBD and ultrasound (US)-guided PTBD.[41]

Fluoroscopy-guided percutaneous transhepatic biliary drainage (PTBD) was first reported in 1962 and has since been recognized as an effective treatment for benign or malignant bile duct stenoses or obstructions.[42], [43] While percutaneous transhepatic biliary drainage have a more advantageous record of adverse events compared to surgical decompression, it remains associated with complications such as fistula formation, the need for repeat interventions, recurrent infections, and the requirement for long-term external catheter drainage, consequently, resulting in a decreasing quality of life.[44], [45], [46] Percutaneous transhepatic biliary drainage has been associated to a significant incidence of adverse events, with reported rates as high as 34% in some studies.[47], [48], [49], [50]

1.2.1.3. New modality: Endoscopic ultrasound-guided biliary drainage-biliary drainage (EUS-BD)

The first report of Endoscopic ultrasound-guided biliary drainage (EUS- BD) was published in 2001 by Giovannini et al.[51] EUS-BD is considered as a minimally invasive alternative method after unsuccessful biliary cannulation. It offers the visualization and accessibility of the biliary tree through the utilization of echoendoscopy and fluoroscopy.[51], [52] With accumulating evidence, this procedure has been recognized as a superior alternative to PTBD for achieving biliary drainage in cases where ERCP is unsuccessful.[53], [54] Potential benefits of EUS-BD include the ability to access the bile duct from the stomach or duodenum, regardless of the accessibility of the papilla. Its use of specialized stents designed for draining the bile duct through the wall of the gastrointestinal tract may result in longer-lasting stent effectiveness.[8] In 2022, a comprehensive systematic review and meta-analysis concluded that while both EUS-BD and PTBD were equally successful in treating malignant biliary obstruction, EUS-BD had a notably lower occurrence of procedural adverse events as well as lower rates of re-intervention compared to PTBD.[53]

EUS-BD can be performed using either a transgastric-transhepatic approach (hepatico-gastrostomy, HGS) or a transduodenal-transcholedochal approach (choledochoduodenostomy, CDS).[8] At first, EUS-BD was performed using biliary self-expanding metal stents (SEMS) obtained from the ERCP armamentarium. A new type of self-expandable lumen-apposing metal stents (LAMS), measuring 6-8 mm in diameter, has recently been developed for EUS-CDS. These stents are equipped with a cystotome capability on the tip of the device, allowing for a single-step procedure. [7], [8](Figure 3). The introduction of the cautery-assisted LAMS technique has significantly simplified EUS-CDSL by enabling for a direct stent insertion without the requirement of a separate access device, wire guidance, or tract dilation.[55], [56], [57] Two recent randomized controlled trials (RCTs) have shown that EUS-CDSL is comparable to ERCP in the treatment of MDBO (one of the RCTs led by our group). These trials found that EUS-CDSL had similar or better technical success rates and shorter procedure times compared to ERCP. Additionally, there were no significant differences in stent patency or adverse events between the two procedures.[6], [7] These findings suggest that EUS-CDs can be the most effective strategy to managing MDBO, demonstrating a higher technical success and shorter procedural time in comparison to ERCP and fewer adverse events in comparison to PTBD.[6], [7], [53]

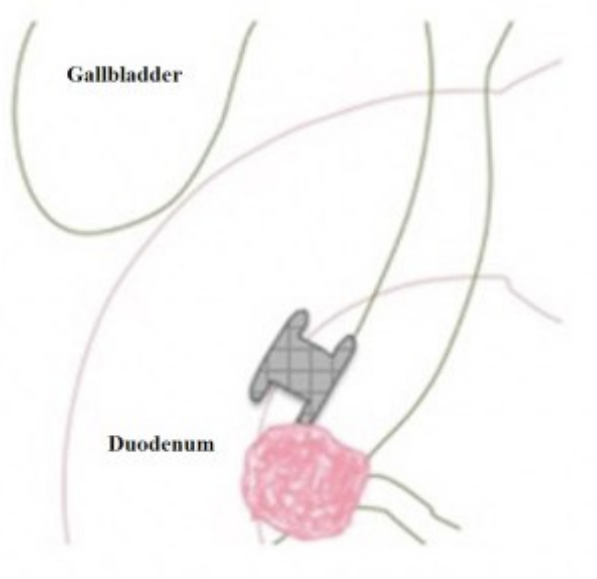


Figure 3.EUS-CDS: LAMS deployed via EUS connecting the duodenum and bile duct from Y.-I. Chen *et al.*, "Endoscopic Ultrasound-Guided Biliary Drainage of First Intent With a Lumen-Apposing Metal Stent vs Endoscopic Retrograde Cholangiopancreatography in Malignant Distal Biliary Obstruction: A Multicenter Randomized Controlled Study (ELEMENT Trial)[7]

1.2.2. Comparison of traditional and modern management of MDBO

1.2.2.1. Comparison of ERCP vs. PTBD

ERCP has been the gold standard for MDBO management, but its technical failure rate and associated adverse events such as post-ERCP pancreatitis are significant. [4], [5], [6] PTBD is an alternative procedure for managing MDBO when ERCP fails.[53] In 2010, a prospective study on PTBD for malignant biliary obstruction in 21 patients (median age 70) found a significant reduction in serum bilirubin from 397 to 226 μmol/L ($p<0.001$). Complications included cholangitis (19%) and acute pancreatitis (10%), with a high 30-day mortality rate of 43%. The prognosis was poor, with no patients surviving beyond 193 days.[48]

In 2020, a retrospective cohort study examined the outcomes of percutaneous transhepatic biliary drainage (PTBD) for malignant biliary obstruction in England between 2001 and 2014 to identify risk factors for poor outcomes in these patients. This study included 16,822 patients, with a

significant portion diagnosed with pancreatic (58%) and biliary tract (30%) cancers. The study found in-hospital mortality was 15.3% and 30-day mortality was 23.1%. Complications occurred in 20.2% of patients within three months. Higher 30-day mortality was associated with high comorbidity (Charlson score 20+, OR: 3.10, p<0.001), pre-existing renal dysfunction (OR: 2.37, p<0.001), and non-pancreatic cancer (OR: 1.28, p=0.004). Lower mortality was observed in patients treated at higher-volume centers (84–180 PTBDs per year, OR: 0.68, p<0.001.[58]

A retrospective cohort study conducted in 2021 evaluated the effects of ERCP compared to PTBD on the survival rates of patients with unresectable pancreatic cancer. The study included data from the SEER-Medicare database from 2003 to 2013. Among 14,808 patients, 8,898 (60%) underwent biliary drainage, with 93% receiving ERCP and 7% receiving PTBD. The study indicated that ERCP was associated to a significantly longer median survival time compared to PTBD (7.4 months vs. 5.8 months; $p < 0.001$) and a decrease in mortality (aHR: 0.67 [95% CI: 0.60–0.75]; $P < 0.001$). Both ERCP and PTBD were associated with improved survival compared to no biliary intervention (aHR: 0.51 [95% CI: 0.49–0.54]; $P < 0.001$ and aHR: 0.53 [95% CI: 0.48–0.59]; $P < 0.001$, respectively). Additionally, patients who underwent ERCP had shorter hospital stays (7.0 ± 5.7 days vs. 9.6 ± 6.6 days; $P < 0.001$) and lower hospital charges ($54,899.25 vs. $75,246.00; $P < 0.001$) compared to those who underwent PTBD. This study underscores the advantages of ERCP over PTBD in managing biliary obstruction in pancreatic cancer patients, highlighting its role in improving survival, reducing hospital stay length, and lowering healthcare costs.[59]

1.2.2.2. Comparison of PTBD vs. EUS-BD

In 2022, a comprehensive systematic review and meta-analysis compared the use of EUS-BD and PTBD in patients with malignant biliary obstruction who were not successfully treated with ERCP. The purpose was to assess the effectiveness of these two methods for relieving biliary obstruction.

This study included a total of ten studies, consisting of four retrospective studies and six randomized controlled trials. The results showed that there was no statistically significant difference in the rates of technical success (OR: 0.47 [95% CI: 0.20–1.07]; P = 0.27) or clinical success (OR: 2.24 [95% CI: 1.10–4.55]; P = 0.51) between the EUS-BD and PTC groups. However, EUS-BD was associated with a significantly lower number of procedural adverse events (odds ratio: 0.17 [95% confidence interval: 0.09–0.31]; P = 0.03) and total adverse events (odds ratio: 0.09 [95% confidence interval: 0.02–0.38]; P < 0.01). The rate of re-intervention for the procedures has been reported in six studies. The rate of re-intervention for the EUS-BD group was 3.7%, whereas it was 13.8% for the PTC group. The rates of re-intervention were significantly lower in the EUS-BD group compared to the PTC group (OR:0.27 [95% CI: 0.16-0.45]; P = 0.001). The mortality rate after the procedure was 1.4% for both groups (OR: 0.99 [95% CI: 0.37–0.266]; P = 0.99). The results showed that although both methods are equally effective in terms of technical and clinical success, EUS-BD is safer, with a lower incidence of acute and overall adverse events compared to PTBD.[53]

Between 2014 and 2016, a prospective study compared the efficacy and safety of endoscopic ultrasonography-guided biliary drainage (EUS-BD) and percutaneous transhepatic biliary drainage (PTBD) in patients with malignant obstructive jaundice after failed ERCP. This study included 66 patients, with 36 undergoing EUS-BD and 30 undergoing PTBD. The results showed that there was a statistically significant difference in clinical success rate (88.89% vs. 66.67%; χ=4.84), complications (5.56% vs. 23.33%; χ=4.39), length of hospital stay (11.54±3.73 days vs. 15.68±6.56 days; t=8.17), and hospital costs (23.52±8.44 thousand yuan vs. 32.81±6.06 thousand yuan; t=16.28) between the EUS-BD and PTBD groups. Although the technical success rate was higher in the EUS-BD group compared to the PTBD group, the difference did not reach statistical

significance (94.44% vs. 86.67%; χ=1.20; P>0.05). The results indicated that EUS-BD is safer and more effective than PTBD, with fewer complications, shorter hospital stays, and lower hospital costs.[60]

1.2.2.3. Comparison of EUS-BD vs. ERCP

In 2023, a multicenter international randomized controlled study compared EUS-CDS with ERCP in patients with unresectable MDBO.[6] The study included a total number of 155 patients from January 2017 and February 2021 (EUS-CDS: 79, ERCP: 76) and assessed outcomes including 1-year stent patency, technical and clinical success, adverse events, and overall survival.[6] The 1-year stent patency rates indicated no significant differences between the two groups (EUS-CDS: 91.1%, ERCP: 88.1%, P = 0.52).[6] However, EUS-CDS demonstrated significantly higher technical success (EUS-CDS: 96.2%, ERCP: 76.3%, P < .001) and shorter procedural time (EUS-CDS: 10 minutes, ERCP: 25 minutes, P < .001).[6] The incidence of adverse events and mortality within 30 days was similar between the groups.[6] The study found that both procedures are effective choices for primary biliary drainage in cases of unresectable MDBO. However, EUS-CDS may be superior when complex ERCPs are expected due to its higher technical success and shorter procedural time.[6]

Shortly after a second multicenter randomized controlled study compared EUS-CDS to ERCP-M in patients with MDBO emerged from our group in Canada.[7] The trial included 144 patients from February 2019 to February 2022 (EUS-CDS: 73, ERCP-M: 71).[7] The primary endpoint was the rate of stent dysfunction during one year. The results showed no significant difference in the rates of stent dysfunction (EUS-CDS: 9.6%, ERCP-M: 9.9%, P = 0.96).[7] The procedure time was significantly shorter for EUS-CDS (mean: 14.0 minutes) compared to ERCP-M (mean: 23.1 minutes, P < 0.01).[7] There was no significant difference in technical success rates (EUS-CDS:

90.4%, ERCP-M: 83.1%).[7] No significant differences were observed in adverse events, pancreaticoduodenectomy, oncologic outcomes, or quality of life.[7] Overall, this study showed that EUS-CDS is a safe and reliable alternative for ERCP-M in patients with MDBO, supporting its implementation in clinical practice.[7]

1.3.Literature Review of Malignant Gastric Outlet Obstruction (MGOO)

Various forms of cancer develop in the upper GI tract, however; cancers of the pancreas, biliary tract, and gastro-duodenum are often diagnosed at advanced stages.[61] In many cases, these cancers cannot be cured with surgical intervention and require palliative care.[61] In this setting, malignant gastric outlet obstruction (MGOO) a common and morbid complication.

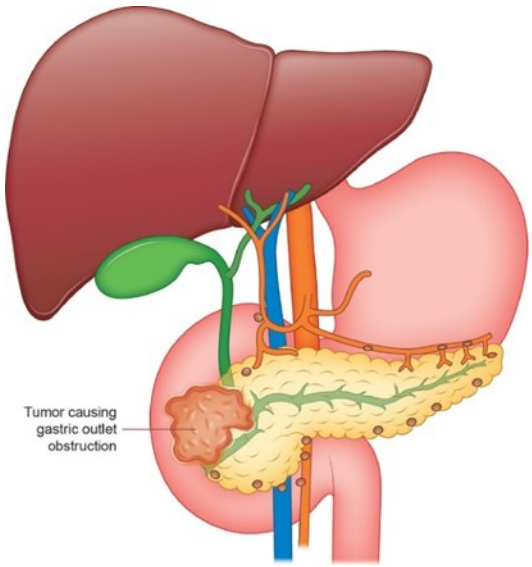


Figure 4. Malignant Gastric Outlet Obstruction in patients with Pancreatic Cancer. From: J. Klose, U. Ronellenfitsch, and J. Kleeff, “Management problems in patients with pancreatic cancer from a surgeon’s perspective,” [62]

MGOO occurs when the pylorus or duodenum is mechanically blocked by a tumor.[62], [63](Figure 4) In 2014, a study discovered that 38% of patients with unresectable pancreatic head cancer eventually developed MGOO following chemotherapy and/or radiation therapy.[64] This reflects historical data, and given the lack of contemporary data to fill this gap, our study aims to

provide updated insights. Patients suffering from MGOO generally experience symptoms such as nausea and vomiting, which may be followed by abdominal pain, weight loss, malnutrition, dehydration due to inadequate oral consumption, decreased quality of life, and chemotherapy interruptions or even premature cessation.[9], [65]

The public health impact of these conditions is significant. MGOO causes substantial costs, with an estimated financial burden ranging from $50,000 to $125,000 per hospitalization and an overall annual expense between $550 million and $1.3 billion in the United States.[66] Furthermore, the prevalence of pancreatic cancer is expected to rise significantly over the next four decades.[67], [68]

1.3.1. Current Management of MGOO

MGOO is currently managed through endoscopic enteral stenting, surgical gastrojejunostomy, or endoscopic ultrasound guided gastroenterotomy (EUS-GE).

1.3.1.1. Traditional management: Surgical Bypass Technique (SGJ)

The traditional approach to treating gastric outlet obstruction (GOO) is the surgical gastrojejunostomy (SGJ), which was first introduced by Wolfer in 1881.[69] The procedure consists of several steps to establish a connection between the stomach and the jejunum, usually by hand-sewn or stapling techniques.[70], [71], [72] (Figure 5) The anastomosis is then constructed, followed by a leak test to ensure its integrity.[72]

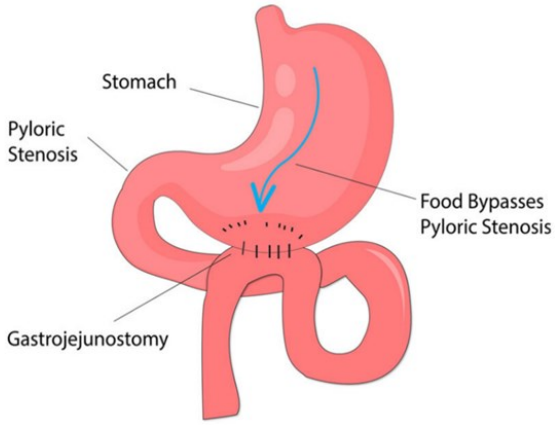


Figure 5. Surgical Gastrojejunostomy (SGJ) from Dr. R. Padmakumar's website[70]

This procedure has remained the standard treatment for patients who can tolerate the surgery and have an expected survival of several months, which is sufficient to cope with the short-term post-procedure complications.[73], [74] SGJ demonstrates efficacy in providing long-term relief from MGOO, with a reduced risk of recurrent obstruction for patients who achieve clinical success in restarting oral intake and successfully navigate the recovery period.[74] However, compared to endoscopic enteral stenting (ES) and endoscopy ultrasound guided gastro enterostomy (EUS-GE), SGJ requires a longer recovery time, resulting in extended hospitalization and an increased risk of adverse events.[11], [12]

1.3.1.2. Traditional Management: Endoscopic Enteral Stenting (ES)

During the 1990s, a less invasive but effective alternative to surgery emerged in the form of an endoscopic approach utilizing self-expandable metallic stents (SEMS).[61] Endoscopic stenting (ES) is a procedure where a large metallic stent is inserted into the narrowed area under endoscopic and fluoroscopic guidance (Figure 6).[61] The procedure typically starts by passing a wire through the gastro-duodenal stricture with the help of endoscopic and fluoroscopic support. A stent is then inserted across the stricture over the wire. [61] These stents are made of flexible and long-lasting nitinol (a combination of nickel and titanium), making them ideal for the managing sharply

angulated strictures.[61] However, their radial expansion force is somewhat lower than that of other metal stents.[61] Deployment involves the act of releasing the stent across the stenosis by employing either the over-the-wire or through-the-scope technique.[61]

Over time, multiple versions SEMS have been developed, demonstrating differences in terms of their length, diameter, and radial expansive force (Figure 7).[61], [75] One example is the polyurethane-covered Niti-S stent (A- Figure 7), which is made of nitinol monofilament woven in an interlacing pattern, with flared ends to prevent migration and a string at the proximal end for endoscopic removal. Another example is the HANAROSTENT (B-Figure 7), woven from a single nitinol wire in an interlocking pattern and covered with a silicon membrane; it has a bare section at the proximal end to prevent migration. Additionally, the Dual duodenal stent (C-Figure 7) is composed of an inner bare stent and an outer partially covered stent, designed to be placed coaxially. The inner stent is knitted from a single nitinol wire with flared ends, while the outer stent (D-Figure 7) includes a proximal bare nitinol section, a nylon mesh, and a distal bare nitinol section.[75] Nitinol stents are currently used as the standard due to their flexibility, which is beneficial for the complicated structure of gastro-duodenal strictures (Figure 8).[61], [75]

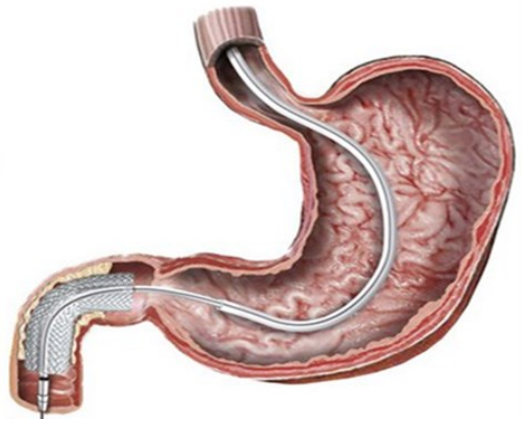


Figure 6. Endoscopic Enteral Stenting (ES) from U. F. O. Themes, “Intervention for Gastric Outlet and Duodenal Obstruction,” Radiology Key[75]

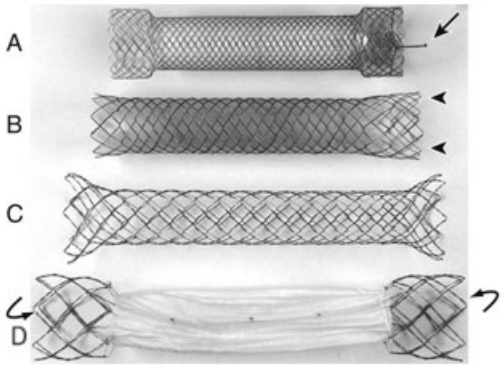
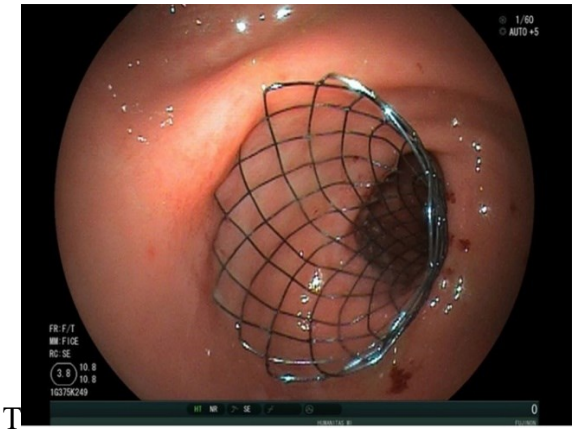


Figure 7. Multiple types of covered gastroduodenal stents. A) A polyurethane-covered Niti-S, B) A HANAROSTENT, C) A Dual duodenal stent. D) Outer partially covered stent from U. F. O. Themes, "Intervention for Gastric Outlet and Duodenal Obstruction," Radiology Key[75]



T

Figure 8. Duodenal uncovered self-expanding metal stent for managing GOO in a patient with pancreatic cancer from E. Troncone *et al.*, "Malignant gastric outlet obstruction: Which is the best therapeutic option?," World J. Gastroenterol[61]

Endoscopic enteral stenting (ES) has been shown to have high rates of both technical and clinical success.[13] Clinical success, as demonstrated by the return to oral intake, typically happens within a short period of time, with symptoms resolving in an average of 4 days according to a systematic review of 32 studies.[13] In addition, rare occurrences of procedure-related adverse events, such as perforation and bleeding, have been reported.[13] Compared to surgical gastrojejunostomy (SGJ), ES offers a shorter procedure time, faster resumption of oral intake, and a shorter hospitalization, making it an effective and less invasive therapeutic option for the treatment of

MGOO.[10], [69] Nevertheless, the primary disadvantage of this approach is the association with a 30-40% risk of stent obstruction and the frequent requirement for reintervention due to tumor ingrowth or overgrowth.[13], [14]

1.3.1.3. Comparison of traditional managements of MGOO

When directly comparing these traditional methods for managing MGOO, numerous retrospective studies and a small number of randomized trials have been conducted. A comprehensive evaluation and statistical analysis of 2,354 patients showed that using the technique of stenting reduced the time before patients could resume oral intake and resulted in a shorter hospitalization compared to surgical gastrojejunostomy. However, it was observed that the enteral stenting group had a significantly higher risk of recurrent obstruction, primarily due to stent dysfunction.[69] In the updated systematic review study in 2022, several retrospective studies and a limited number of randomized trials have been conducted to compare Gastrojejunostomy (GJ) and endoscopic stenting (ES) for managing malignant gastric outlet obstruction (GOO).[76] A comprehensive analysis of 2,444 patients revealed that GJ had higher technical success rates compared to ES (Table 1).[76] However, ES showed better outcomes in terms of shorter hospitalization and faster resumption of oral intake.[76] Despite these benefits, the ES group experienced a significantly higher risk of recurrent obstruction, mainly due to stent dysfunction.[76] The SUSTENT Study, a small randomized controlled trial conducted in the Netherlands, discovered that the group of patients who received stents experienced earlier relief from symptoms, while the group who underwent surgery had more sustained outcomes.[77] Taking into account the effectiveness and potential disadvantages of each method, Surgical Gastrojejunostomy (SGJ) provides a long-lasting solution but may lead to complications for the patients. In contrast, Endoscopic Stenting (ES) is a safe option in the short term but may not be as successful over the long term. As a result, the typical

recommendation for managing Malignant Gastric Outlet Obstruction (MGOO) is to choose surgical bypass in patients with a life expectancy more than two months, while endoscopic stenting is preferred for those with a shorter life expectancy.[78]

Table 1. Comparison of ES vs. SGJ from J. Hong et al., "Comparison of gastrojejunostomy to endoscopic stenting for gastric outlet obstruction: An updated Systematic Review and Meta-analysis," Am. J. Surg.[76]

Comparison	**ES (n=1368, 56%)**	**SGJ (n=1076, 44%)**	**p-value**
Technical Success	Lower	Higher	0.003
Clinical Success	Similar	Similar	0.50
GOO Hospitalization	Shorter	Longer	
Re-obstruction	Higher	Lower	
Re-intervention	Higher	Lower	
Survival in Gastric Cancer Patients	Lower	Higher	0.009

1.3.1.4. New modality: EUS-guided Gastroenterostomy (EUS-GE)

Endoscopic ultrasound (EUS) was established in the 1980s by combining the techniques of flexible endoscopy and ultrasonography.[79] In 1991, the invention of fine needle aspiration enabled healthcare professionals, for the first time, to observe and interact with areas of the digestive tract that were previously inaccessible using endoscopy alone.[80] Currently, EUS is recognized as an established technique for observing previously inaccessible areas and diagnosing tissue conditions.[81] Due to advancements in axial imaging and the development of the linear

echoendoscope with a larger instrument channel, EUS has become increasingly valuable for therapeutic purposes.[81]

A gastroenterostomy, also known as EUS-GE, is a procedure that creates a direct connection between the stomach and small intestine to bypass an obstruction (Figure 9).[82]

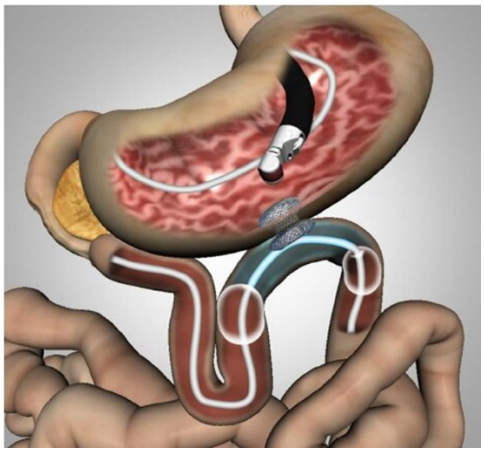


Figure 9. Endoscopic Ultrasonography-Guided Gastrojejunostomy (EUS-GJ) from T. Itoi et al., “Prospective evaluation of endoscopic ultrasonography-guided double-balloon-occluded gastrojejunostomy bypass (EPASS) for malignant gastric outlet obstruction,” Gut[82]

In 2002, the first EUS-GE was successfully conducted in an animal model.[83] However, a major technological advance emerged with the development of the lumen-apposing metal stent (LAMS), which significantly improved the procedure and made it possible to perform it in humans.[84] The LAMS is a self-expanding metal device that is completely covered and has flanges on both ends, arranged in a "dumb-bell" shape (Figure 10).[85] This design ensures stable alignment of two lumens and prevents movement.[9] Electrocautery was used to achieve additional improvement. This enhancement made it possible to deliver the desired outcome in a single step, resolving the need for a more complicated insertion process.[9]

Figure 10. Lumen-apposing metal stents (LAMS): A) the AXIOS™ stent, B) the Spaxus™ stent from M. Rimbaș, K. W. Lau, G. Tripodi, G. Rizzatti, and A. Larghi, "The Role of Luminal Apposing, Metal Stents on the Treatment of Malignant and Benign Gastric Outlet Obstruction," Diagnostics.[85]

There are three primary methods for performing EUS-guided gastrojejunostomy (EUS-GE): the direct technique, the balloon-assisted technique, and the EUS-guided double-balloon-occluded gastrojejunostomy bypass (EPASS) technique.[11], [16], [61], [63] The direct method involves distending the small intestine beyond the blockage with a saline and contrast mix, sometimes including methylene blue.[16] This infusion can be performed either directly through the endoscope or using a catheter that crosses the narrowed area.[16] The ideal site for connecting the small intestine to the stomach is determined using endoscopic ultrasound (EUS) and fluoroscopy, after which a lumen-apposing metal stent (LAMS) is placed directly using cautery assistance.[16] Alternatively, the balloon-assisted technique utilizes either an extraction or dilation balloon, which is passed over a guidewire through the blockage and inflated with contrast to ascertain the obstruction site.[16] This site is pinpointed using EUS, with a 19-gauge needle piercing through the stomach to the small intestine, confirmed by the balloon bursting.[16] A guidewire is then passed through the needle into the small intestine, and a LAMS is inserted over this wire.[16] A retrospective study comparing these methods showed that there is no significant difference in the rate of technical and clinical success or complications.[16] However, the direct method significantly reduced the average duration of the procedure (35.7 ± 32.1 minutes compared to 89.9 ± 33.3 minutes, $P < 0.001$).[16]

The EPASS method involves inflating two balloons with dye to fix the bowel loop, filling the segment between the balloons with a solution, and deploying a lumen-apposing metal stent (LAMS) under endoscopic ultrasound guidance.[82] The process has been refined to ensure the target intestine is correctly punctured and the stent is accurately placed.[82] The current findings indicate that EUS-GE is a potential treatment option for MGOO.[86] A systematic review and meta-analysis of 5 studies, including 199 patients (four retrospective and one prospective), revealed a technical success rate of 92.90% (95% CI: [88.26 - 95.79]) and a clinical success rate of 90.11% (95% CI: [84.64 - 93.44]).[86] However, there was no statistically significant difference observed in either outcome.[86] Recent studies have highlighted its effectiveness and technical success.[82] In a prospective study, the EPASS technique demonstrated a 100% technical success rate once the over-the-wire deployment was abandoned, achieving this in a median time of 36 minutes.[82]

A recent international, multicenter, randomized controlled trial published in 2024 demonstrated that endoscopic ultrasonography-guided gastroenterostomy (EUS-GE) with a double balloon occlude was associated with fewer requirements for further medical intervention within a 6-month period when compared to the traditional approach of duodenal stenting for patients with MGOO.[87] This study involved 97 patients diagnosed with unresectable primary gastroduodenal or pancreatobiliary malignancies who were randomized to receive either EUS-GE or duodenal stenting.[87] The rate of reintervention within 6 months was significantly lower in the EUS-GE group (4%) compared to the duodenal stent group (29%) ($p=0.0020$; risk ratio 0.15 [95% CI 0.04–0.61]), and stent patency was longer (HR 0.13 [95% CI 0.08–0.22], log-rank $p<0.0001$).[87] In addition, the gastric outlet obstruction score (GOOS) at 1 month was significantly higher in the EUS-GE group (mean 2.41 [SD 0.7]) compared to the duodenal stent group (1.91 [SD 0.9],

p=0.012).[87] These results suggest that patients in the EUS-GE group have the ability to consume a more advanced diet compared to those in the duodenal stent group, as a higher GOOS score indicates greater dietary intake. There were no significant differences in 30-day mortality, technical success, clinical success, or quality-of-life scores after 1 month between the two groups, and adverse events within 30 days were comparable (23% vs. 24%, p=1.00). These findings suggest EUS-GE is the treatment of choice over duodenal stenting for MGOO, provided that the required expertise and devices are accessible.[87]

In the updated systematic review study published in July 2023, randomized controlled trials as well as observational studies of retrospective or prospective cohorts were included to compare EUS-guided gastroenterostomy (EUS-GE), surgical gastrojejunostomy (SGJ), and endoscopic stenting (ES) for managing malignant gastric outlet obstruction (MGOO).[15] The meta-analysis, which included 16 studies involving 1541 patients, found that EUS-GE had higher clinical success rates without recurrent gastric outlet obstruction compared to ES and SGJ combined (OR: 2.60, 95% CI: [1.58-4.28]).[15] More precisely, EUS-GE was significantly more effective than ES alone (OR: 5.08, 95% CI: [3.42-7.55]), while no significant difference was found compared to SGJ alone (OR: 1.94, 95% CI: [0.97-3.88]).[15] Additionally, EUS-GE was associated with fewer adverse events compared to SGJ (OR: 0.17, 95% CI: [0.10-0.30]) and to both SGJ and ES combined (OR: 0.34, 95% CI: [0.20-0.58]), but not significantly different from ES alone (OR: 0.57, 95% CI: [0.29-1.14]).[15] These findings suggest that EUS-GE is the most effective strategy to managing MGOO, demonstrating a lower risk of recurrent obstruction in comparison to ES and fewer adverse events in comparison to SGJ.[15]

References

[1] M. Porta *et al.*, “Exocrine pancreatic cancer: symptoms at presentation and their relation to tumour site and stage,” *Clin. Transl. Oncol. Off. Publ. Fed. Span. Oncol. Soc. Natl. Cancer Inst. Mex.*, vol. 7, no. 5, pp. 189–197, Jun. 2005, doi: 10.1007/BF02712816.

[2] M. Fernandez Y Viesca and M. Arvanitakis, “Early Diagnosis And Management Of Malignant Distal Biliary Obstruction: A Review On Current Recommendations And Guidelines,” *Clin. Exp. Gastroenterol.*, vol. 12, pp. 415–432, Nov. 2019, doi: 10.2147/CEG.S195714.

[3] N. S. Abraham, J. S. Barkun, and A. N. Barkun, “Palliation of malignant biliary obstruction: a prospective trial examining impact on quality of life,” *Gastrointest. Endosc.*, vol. 56, no. 6, pp. 835–841, Dec. 2002, doi: 10.1067/mge.2002.129868.

[4] B. J. Elmunzer *et al.*, “ACG Clinical Guideline: Diagnosis and Management of Biliary Strictures,” *Am. J. Gastroenterol.*, vol. 118, no. 3, pp. 405–426, Mar. 2023, doi: 10.14309/ajg.0000000000002190.

[5] W. H. Paik *et al.*, “EUS-Guided Biliary Drainage Versus ERCP for the Primary Palliation of Malignant Biliary Obstruction: A Multicenter Randomized Clinical Trial,” *Am. J. Gastroenterol.*, vol. 113, no. 7, pp. 987–997, Jul. 2018, doi: 10.1038/s41395-018-0122-8.

[6] A. Y. B. Teoh *et al.*, “EUS-Guided Choledocho-duodenostomy Using Lumen Apposing Stent Versus ERCP With Covered Metallic Stents in Patients With Unresectable Malignant Distal Biliary Obstruction: A Multicenter Randomized Controlled Trial (DRA-MBO Trial),” *Gastroenterology*, vol. 165, no. 2, pp. 473-482.e2, Aug. 2023, doi: 10.1053/j.gastro.2023.04.016.

[7] Y.-I. Chen *et al.*, “Endoscopic Ultrasound-Guided Biliary Drainage of First Intent With a Lumen-Apposing Metal Stent vs Endoscopic Retrograde Cholangiopancreatography in Malignant Distal Biliary Obstruction: A Multicenter Randomized Controlled Study (ELEMENT Trial),” *Gastroenterology*, vol. 165, no. 5, pp. 1249-1261.e5, Nov. 2023, doi: 10.1053/j.gastro.2023.07.024.

[8] K. W. Lau, M. Rimbaș, G. Tripodi, and A. Larghi, “Endoscopic Ultrasound Biliary Drainage in Pancreatic Cancer,” *J. Gastrointestin. Liver Dis.*, vol. 32, no. 4, Art. no. 4, Dec. 2023, doi: 10.15403/jgld-4922.

[9] Y.-I. Chen *et al.*, “EUS-guided gastroenterostomy is comparable to enteral stenting with fewer re-interventions in malignant gastric outlet obstruction,” *Surg. Endosc.*, vol. 31, no. 7, pp. 2946–2952, Jul. 2017, doi: 10.1007/s00464-016-5311-1.

[10] S.-B. Bian, W.-S. Shen, H.-Q. Xi, B. Wei, and L. Chen, “Palliative Therapy for Gastric Outlet Obstruction Caused by Unresectable Gastric Cancer: A Meta-analysis Comparison of Gastrojejunostomy with Endoscopic Stenting,” *Chin. Med. J. (Engl.)*, vol. 129, no. 9, pp. 1113–1121, May 2016, doi: 10.4103/0366-6999.180530.

[11] S. L. H. Cheung and A. Y. B. Teoh, “Optimal Management of Gastric Outlet Obstruction in Unresectable Malignancies,” *Gut Liver*, vol. 16, no. 2, pp. 190–197, Mar. 2022, doi: 10.5009/gnl210010.

[12] T. Itoi *et al.*, “Technical review of endoscopic ultrasonography-guided gastroenterostomy in 2017,” *Dig. Endosc.*, vol. 29, no. 4, pp. 495–502, 2017, doi: 10.1111/den.12794.

[13] A. Dormann, S. Meisner, N. Verin, and A. Wenk Lang, “Self-expanding metal stents for gastroduodenal malignancies: systematic review of their clinical effectiveness,” *Endoscopy*, vol. 36, no. 6, pp. 543–550, Jun. 2004, doi: 10.1055/s-2004-814434.

[14] M. Khashab *et al.*, "Enteral stenting versus gastrojejunostomy for palliation of malignant gastric outlet obstruction," *Surg. Endosc.*, vol. 27, no. 6, pp. 2068–2075, Jun. 2013, doi: 10.1007/s00464-012-2712-7.
[15] C. Miller *et al.*, "EUS-guided gastroenterostomy vs. surgical gastrojejunostomy and enteral stenting for malignant gastric outlet obstruction: a meta-analysis," *Endosc. Int. Open*, vol. 11, no. 7, pp. E660–E672, Jul. 2023, doi: 10.1055/a-2098-2570.
[16] Y.-I. Chen *et al.*, "EUS-guided gastroenterostomy: a multicenter study comparing the direct and balloon-assisted techniques," *Gastrointest. Endosc.*, vol. 87, no. 5, pp. 1215–1221, May 2018, doi: 10.1016/j.gie.2017.07.030.
[17] A. Singh, A. Gelrud, and B. Agarwal, "Biliary strictures: diagnostic considerations and approach," *Gastroenterol. Rep.*, vol. 3, no. 1, pp. 22–31, Feb. 2015, doi: 10.1093/gastro/gou072.
[18] T. Hennedige, W. Neo, and S. Venkatesh, "Imaging of malignancies of the biliary tract-an update," *Cancer Imaging*, vol. 14, Apr. 2014, doi: 10.1186/1470-7330-14-14.
[19] L. Rahib, B. D. Smith, R. Aizenberg, A. B. Rosenzweig, J. M. Fleshman, and L. M. Matrisian, "Projecting cancer incidence and deaths to 2030: the unexpected burden of thyroid, liver, and pancreas cancers in the United States," *Cancer Res.*, vol. 74, no. 11, pp. 2913–2921, Jun. 2014, doi: 10.1158/0008-5472.CAN-14-0155.
[20] S. I. Ilyas, S. A. Khan, C. L. Hallemeier, R. K. Kelley, and G. J. Gores, "Cholangiocarcinoma — evolving concepts and therapeutic strategies," *Nat. Rev. Clin. Oncol.*, vol. 15, no. 2, pp. 95–111, Feb. 2018, doi: 10.1038/nrclinonc.2017.157.
[21] B. I. Choi, J. K. Han, S. T. Hong, and K. H. Lee, "Clonorchiasis and Cholangiocarcinoma: Etiologic Relationship and Imaging Diagnosis," *Clin. Microbiol. Rev.*, vol. 17, no. 3, pp. 540–552, Jul. 2004, doi: 10.1128/CMR.17.3.540-552.2004.
[22] Y. Shaib and H. B. El-Serag, "The epidemiology of cholangiocarcinoma," *Semin. Liver Dis.*, vol. 24, no. 2, pp. 115–125, May 2004, doi: 10.1055/s-2004-828889.
[23] R. Hundal and E. A. Shaffer, "Gallbladder cancer: epidemiology and outcome," *Clin. Epidemiol.*, vol. 6, pp. 99–109, Mar. 2014, doi: 10.2147/CLEP.S37357.
[24] A. Sharma, K. L. Sharma, A. Gupta, A. Yadav, and A. Kumar, "Gallbladder cancer epidemiology, pathogenesis and molecular genetics: Recent update," *World J. Gastroenterol.*, vol. 23, no. 22, pp. 3978–3998, Jun. 2017, doi: 10.3748/wjg.v23.i22.3978.
[25] A. Duffy *et al.*, "Gallbladder cancer (GBC): 10-year experience at Memorial Sloan-Kettering Cancer Centre (MSKCC)," *J. Surg. Oncol.*, vol. 98, no. 7, pp. 485–489, Dec. 2008, doi: 10.1002/jso.21141.
[26] D. H. Ahn and T. Bekaii-Saab, "Ampullary Cancer: An Overview," *Am. Soc. Clin. Oncol. Educ. Book ASCO Am. Soc. Clin. Oncol. Meet.*, pp. 112–115, 2014, doi: 10.14694/EdBook_AM.2014.34.112.
[27] W.-C. Liao *et al.*, "Adjuvant treatments for resected pancreatic adenocarcinoma: a systematic review and network meta-analysis," *Lancet Oncol.*, vol. 14, no. 11, pp. 1095–1103, Oct. 2013, doi: 10.1016/S1470-2045(13)70388-7.
[28] R. A. Kozarek, "The Past, Present, and Future of Endoscopic Retrograde Cholangiopancreatography," *Gastroenterol. Hepatol.*, vol. 13, no. 10, p. 620, Oct. 2017.
[29] A. Canakis and M. Kahaleh, "Endoscopic palliation of malignant biliary obstruction," *World J. Gastrointest. Endosc.*, vol. 14, no. 10, pp. 581–596, Oct. 2022, doi: 10.4253/wjge.v14.i10.581.

[30] J.-M. Dumonceau *et al.*, “Endoscopic biliary stenting: Indications, choice of stents, and results: European Society of Gastrointestinal Endoscopy (ESGE) Clinical Guideline - Updated October 2017,” *Endoscopy*, vol. 50, no. 9, pp. 910–930, 2018, doi: 10.1055/a-0659-9864.
[31] H. Isayama *et al.*, “A prospective randomised study of ‘covered’ versus ‘uncovered’ diamond stents for the management of distal malignant biliary obstruction,” *Gut*, vol. 53, no. 5, pp. 729–734, 2004, doi: 10.1136/gut.2003.018945.
[32] J. J. Telford *et al.*, “A randomized trial comparing uncovered and partially covered self-expandable metal stents in the palliation of distal malignant biliary obstruction,” *Gastrointest. Endosc.*, vol. 72, no. 5, pp. 907–914, Nov. 2010, doi: 10.1016/j.gie.2010.08.021.
[33] E. Kullman *et al.*, “Covered versus uncovered self-expandable nitinol stents in the palliative treatment of malignant distal biliary obstruction: results from a randomized, multicenter study,” *Gastrointest. Endosc.*, vol. 72, no. 5, pp. 915–923, Nov. 2010, doi: 10.1016/j.gie.2010.07.036.
[34] M. Kitano *et al.*, “Covered Self-Expandable Metal Stents With an Anti-Migration System Improve Patency Duration Without Increased Complications Compared With Uncovered Stents for Distal Biliary Obstruction Caused by Pancreatic Carcinoma: A Randomized Multicenter Trial,” *Off. J. Am. Coll. Gastroenterol. ACG*, vol. 108, no. 11, p. 1713, Nov. 2013, doi: 10.1038/ajg.2013.305.
[35] M. L. Freeman *et al.*, “Complications of endoscopic biliary sphincterotomy,” *N. Engl. J. Med.*, vol. 335, no. 13, pp. 909–918, Sep. 1996, doi: 10.1056/NEJM199609263351301.
[36] B. Kochar *et al.*, “Incidence, severity, and mortality of post-ERCP pancreatitis: a systematic review by using randomized, controlled trials,” *Gastrointest. Endosc.*, vol. 81, no. 1, pp. 143-149.e9, Jan. 2015, doi: 10.1016/j.gie.2014.06.045.
[37] M. A. Almadi, A. Barkun, and M. Martel, “Self-expandable metal stents versus plastic stents for malignant biliary obstruction,” *Gastrointest. Endosc.*, vol. 83, no. 4, pp. 852–853, Apr. 2016, doi: 10.1016/j.gie.2015.10.035.
[38] M. A. Almadi, J. S. Barkun, and A. N. Barkun, “Stenting in Malignant Biliary Obstruction,” *Gastrointest. Endosc. Clin. N. Am.*, vol. 25, no. 4, pp. 691–711, Oct. 2015, doi: 10.1016/j.giec.2015.06.002.
[39] T. B. Gardner *et al.*, “Cost-effectiveness and clinical efficacy of biliary stents in patients undergoing neoadjuvant therapy for pancreatic adenocarcinoma in a randomized controlled trial,” *Gastrointest. Endosc.*, vol. 84, no. 3, pp. 460–466, Sep. 2016, doi: 10.1016/j.gie.2016.02.047.
[40] A. N. Barkun, V. Adam, M. Martel, K. AlNaamani, and P. L. Moses, “Partially covered self-expandable metal stents versus polyethylene stents for malignant biliary obstruction: a cost-effectiveness analysis,” *Can. J. Gastroenterol. Hepatol.*, vol. 29, no. 7, pp. 377–383, Oct. 2015, doi: 10.1155/2015/743417.
[41] S. E. Park *et al.*, “Effectiveness of ultrasound-guided percutaneous transhepatic biliary drainage to reduce radiation exposure: A single-center experience,” *PloS One*, vol. 17, no. 11, p. e0277272, 2022, doi: 10.1371/journal.pone.0277272.
[42] F. Glenn, J. A. Evans, Z. Mujahed, and B. Thorbjarnarson, “Percutaneous Transhepatic Cholangiography,” *Ann. Surg.*, vol. 156, no. 3, pp. 451–460, Sep. 1962.
[43] W. E. A. Saad, M. J. Wallace, J. C. Wojak, S. Kundu, and J. F. Cardella, “Quality improvement guidelines for percutaneous transhepatic cholangiography, biliary drainage, and

percutaneous cholecystostomy," *J. Vasc. Interv. Radiol. JVIR*, vol. 21, no. 6, pp. 789–795, Jun. 2010, doi: 10.1016/j.jvir.2010.01.012.
[44] V. Piñol *et al.*, "Percutaneous self-expanding metal stents versus endoscopic polyethylene endoprostheses for treating malignant biliary obstruction: randomized clinical trial," *Radiology*, vol. 225, no. 1, pp. 27–34, Oct. 2002, doi: 10.1148/radiol.2243011517.
[45] J. S. Laméris *et al.*, "Malignant biliary obstruction: percutaneous use of self-expandable stents," *Radiology*, vol. 179, no. 3, pp. 703–707, Jun. 1991, doi: 10.1148/radiology.179.3.2027978.
[46] E. L. A. Artifon *et al.*, "Surgery or Endoscopy for Palliation of Biliary Obstruction Due to Metastatic Pancreatic Cancer," *Off. J. Am. Coll. Gastroenterol. ACG*, vol. 101, no. 9, p. 2031, Sep. 2006.
[47] H. Asadi *et al.*, "A review of percutaneous transhepatic biliary drainage at a tertiary referral centre," *Clin. Radiol.*, vol. 71, no. 12, p. 1312.e7-1312.e11, Dec. 2016, doi: 10.1016/j.crad.2016.05.013.
[48] M. Sut, R. Kennedy, J. McNamee, A. Collins, and B. Clements, "Long-Term Results of Percutaneous Transhepatic Cholangiographic Drainage for Palliation of Malignant Biliary Obstruction," *J. Palliat. Med.*, vol. 13, no. 11, pp. 1311–1313, Nov. 2010, doi: 10.1089/jpm.2010.0205.
[49] P. A. Heedman, E. Åstradsson, K. Blomquist, and R. Sjödahl, "Palliation of Malignant Biliary Obstruction: Adverse Events are Common after Percutaneous Transhepatic Biliary Drainage," *Scand. J. Surg.*, vol. 107, no. 1, pp. 48–53, Mar. 2018, doi: 10.1177/1457496917731192.
[50] R. Uberoi, N. Das, J. Moss, and I. Robertson, "British Society of Interventional Radiology: Biliary Drainage and Stenting Registry (BDSR)," *Cardiovasc. Intervent. Radiol.*, vol. 35, no. 1, pp. 127–138, Feb. 2012, doi: 10.1007/s00270-011-0103-4.
[51] M. Giovannini, V. Moutardier, C. Pesenti, E. Bories, B. Lelong, and J. R. Delpero, "Endoscopic ultrasound-guided bilioduodenal anastomosis: a new technique for biliary drainage," *Endoscopy*, vol. 33, no. 10, pp. 898–900, Oct. 2001, doi: 10.1055/s-2001-17324.
[52] M. A. Khashab and J. Dewitt, "EUS-guided biliary drainage: is it ready for prime time? Yes!," *Gastrointest. Endosc.*, vol. 78, no. 1, pp. 102–105, Jul. 2013, doi: 10.1016/j.gie.2013.03.004.
[53] U. Hayat *et al.*, "EUS-guided versus percutaneous transhepatic cholangiography biliary drainage for obstructed distal malignant biliary strictures in patients who have failed endoscopic retrograde cholangiopancreatography: A systematic review and meta-analysis," *Endosc. Ultrasound*, vol. 11, no. 1, p. 4, Feb. 2022, doi: 10.4103/EUS-D-21-00009.
[54] H. Moole *et al.*, "Endoscopic versus Percutaneous Biliary Drainage in Palliation of Advanced Malignant Hilar Obstruction: A Meta-Analysis and Systematic Review," *Can. J. Gastroenterol. Hepatol.*, vol. 2016, no. 1, p. 4726078, 2016, doi: 10.1155/2016/4726078.
[55] G. Dell'Anna, T. Ogura, G. Vanella, H. Nishikawa, S. Lakhtakia, and P. G. Arcidiacono, "Endoscopic ultrasound guided biliary interventions," *Best Pract. Res. Clin. Gastroenterol.*, vol. 60–61, p. 101810, Sep. 2022, doi: 10.1016/j.bpg.2022.101810.
[56] R. Kunda *et al.*, "EUS-guided choledochoduodenostomy for malignant distal biliary obstruction using a lumen-apposing fully covered metal stent after failed ERCP," *Surg. Endosc.*, vol. 30, no. 11, pp. 5002–5008, Nov. 2016, doi: 10.1007/s00464-016-4845-6.

[57] J. Jacques *et al.*, “Endoscopic ultrasound-guided choledochoduodenostomy with electrocautery-enhanced lumen-apposing stents: a retrospective analysis,” *Endoscopy*, vol. 51, no. 6, pp. 540–547, Jun. 2019, doi: 10.1055/a-0735-9137.
[58] J. Rees, J. Mytton, F. Evison, K. S. Mangat, P. Patel, and N. Trudgill, “The outcomes of biliary drainage by percutaneous transhepatic cholangiography for the palliation of malignant biliary obstruction in England between 2001 and 2014: a retrospective cohort study,” *BMJ Open*, vol. 10, no. 1, p. e033576, Jan. 2020, doi: 10.1136/bmjopen-2019-033576.
[59] A. Tavakkoli *et al.*, “Survival analysis among unresectable pancreatic adenocarcinoma patients undergoing endoscopic or percutaneous interventions,” *Gastrointest. Endosc.*, vol. 93, no. 1, pp. 154-162.e5, Jan. 2021, doi: 10.1016/j.gie.2020.05.061.
[60] P. Huang, H. Zhang, X.-F. Zhang, W. Lv, and S. Lou, “Comparison of Endoscopic Ultrasonography Guided Biliary Drainage and Percutaneous Transhepatic Biliary Drainage in the Management of Malignant Obstructive Jaundice After Failed ERCP,” *Surg. Laparosc. Endosc. Percutan. Tech.*, vol. 27, no. 6, pp. e127–e131, Dec. 2017, doi: 10.1097/SLE.0000000000000485.
[61] E. Troncone *et al.*, “Malignant gastric outlet obstruction: Which is the best therapeutic option?,” *World J. Gastroenterol.*, vol. 26, no. 16, pp. 1847–1860, Apr. 2020, doi: 10.3748/wjg.v26.i16.1847.
[62] J. Klose, U. Ronellenfitsch, and J. Kleeff, “Management problems in patients with pancreatic cancer from a surgeon’s perspective,” *Semin. Oncol.*, vol. 48, no. 1, pp. 76–83, Feb. 2021, doi: 10.1053/j.seminoncol.2021.02.008.
[63] I. S. Papanikolaou and P. D. Siersema, “Gastric Outlet Obstruction: Current Status and Future Directions,” *Gut Liver*, vol. 16, no. 5, pp. 667–675, Sep. 2022, doi: 10.5009/gnl210327.
[64] A. Shah, A. Fehmi, and T. J. Savides, “Increased rates of duodenal obstruction in pancreatic cancer patients receiving modern medical management,” *Dig. Dis. Sci.*, vol. 59, no. 9, pp. 2294–2298, Sep. 2014, doi: 10.1007/s10620-014-3170-y.
[65] B. Brimhall and D. G. Adler, “Enteral Stents for Malignant Gastric Outlet Obstruction,” *Gastrointest. Endosc. Clin. N. Am.*, vol. 21, no. 3, pp. 389–403, Jul. 2011, doi: 10.1016/j.giec.2011.04.002.
[66] A. Kouanda, K. Binmoeller, C. Hamerski, A. Nett, J. Bernabe, and R. Watson, “Endoscopic ultrasound-guided gastroenterostomy versus open surgical gastrojejunostomy: clinical outcomes and cost effectiveness analysis,” *Surg. Endosc.*, vol. 35, no. 12, pp. 7058–7067, Dec. 2021, doi: 10.1007/s00464-020-08221-z.
[67] A. Jaroenlapnopparat, C. Jani, H. Singh, D. C. Marshall, J. D. Salciccioli, and J. Shalhoub, “An estimate of the burden of pancreatic cancer globally and its comparison with different WHO regions using Global Burden of Disease Database: A retrospective population-based analysis.,” *J. Clin. Oncol.*, May 2023, doi: 10.1200/JCO.2023.41.16_suppl.e16321.
[68] G. Lippi and C. Mattiuzzi, “The global burden of pancreatic cancer,” *Arch. Med. Sci. AMS*, vol. 16, no. 4, pp. 820–824, May 2020, doi: 10.5114/aoms.2020.94845.
[69] I. Mintziras, M. Miligkos, S. Wächter, J. Manoharan, and D. K. Bartsch, “Palliative surgical bypass is superior to palliative endoscopic stenting in patients with malignant gastric outlet obstruction: systematic review and meta-analysis,” *Surg. Endosc.*, vol. 33, no. 10, pp. 3153–3164, Oct. 2019, doi: 10.1007/s00464-019-06955-z.

[70] "Gastrojejunostomy - What is Laparoscopic Gastrojejunostomy?" Accessed: May 15, 2024. [Online]. Available: https://www.drrpadmakumar.com/blog/laparoscopic-gastrojejunostomy/
[71] J. L. Salluzzo and K. E. Roberts, "Laparoscopic Gastrojejunostomy," in *Operative Dictations in General and Vascular Surgery*, J. J. Hoballah, C. E. H. Scott-Conner, and H. S. Chong, Eds., Cham: Springer International Publishing, 2017, pp. 75–76. doi: 10.1007/978-3-319-44797-1_21.
[72] D. F. Sigmon and P. P. Lopez, "Gastrojejunostomy," in *StatPearls*, Treasure Island (FL): StatPearls Publishing, 2024. Accessed: May 15, 2024. [Online]. Available: http://www.ncbi.nlm.nih.gov/books/NBK560493/
[73] S. M. Singh, W. P. Longmire, and H. A. Reber, "Surgical palliation for pancreatic cancer. The UCLA experience.," *Ann. Surg.*, vol. 212, no. 2, pp. 132–139, Aug. 1990.
[74] E. Upchurch, M. Ragusa, and R. Cirocchi, "Stent placement versus surgical palliation for adults with malignant gastric outlet obstruction," *Cochrane Database Syst. Rev.*, vol. 5, no. 5, p. CD012506, May 2018, doi: 10.1002/14651858.CD012506.pub2.
[75] U. F. O. Themes, "Intervention for Gastric Outlet and Duodenal Obstruction," Radiology Key. Accessed: May 15, 2024. [Online]. Available: https://radiologykey.com/intervention-for-gastric-outlet-and-duodenal-obstruction/
[76] J. Hong *et al.*, "Comparison of gastrojejunostomy to endoscopic stenting for gastric outlet obstruction: An updated Systematic Review and Meta-analysis," *Am. J. Surg.*, vol. 223, no. 6, pp. 1067–1078, Jun. 2022, doi: 10.1016/j.amjsurg.2021.10.038.
[77] S. M. Jeurnink *et al.*, "Surgical gastrojejunostomy or endoscopic stent placement for the palliation of malignant gastric outlet obstruction (SUSTENT study): a multicenter randomized trial," *Gastrointest. Endosc.*, vol. 71, no. 3, pp. 490–499, Mar. 2010, doi: 10.1016/j.gie.2009.09.042.
[78] O. Ahmed, J. H. Lee, C. C. Thompson, and A. Faulx, "AGA Clinical Practice Update on the Optimal Management of the Malignant Alimentary Tract Obstruction: Expert Review," *Clin. Gastroenterol. Hepatol. Off. Clin. Pract. J. Am. Gastroenterol. Assoc.*, vol. 19, no. 9, pp. 1780–1788, Sep. 2021, doi: 10.1016/j.cgh.2021.03.046.
[79] S. R. Friedberg and J. Lachter, "Endoscopic ultrasound: Current roles and future directions," *World J. Gastrointest. Endosc.*, vol. 9, no. 10, pp. 499–505, Oct. 2017, doi: 10.4253/wjge.v9.i10.499.
[80] P. Vilmann, G. K. Jacobsen, F. W. Henriksen, and S. Hancke, "Endoscopic ultrasonography with guided fine needle aspiration biopsy in pancreatic disease," *Gastrointest. Endosc.*, vol. 38, no. 2, pp. 172–173, Mar. 1992, doi: 10.1016/S0016-5107(92)70385-X.
[81] G. Vanella *et al.*, "Current landscape of therapeutic EUS: Changing paradigms in gastroenterology practice," *Endosc. Ultrasound*, vol. 12, no. 1, pp. 16–28, Sep. 2022, doi: 10.4103/EUS-D-21-00177.
[82] T. Itoi *et al.*, "Prospective evaluation of endoscopic ultrasonography-guided double-balloon-occluded gastrojejunostomy bypass (EPASS) for malignant gastric outlet obstruction," *Gut*, vol. 65, no. 2, pp. 193–195, Feb. 2016, doi: 10.1136/gutjnl-2015-310348.
[83] A. Fritscher-Ravens, C. A. Mosse, D. Mukherjee, T. Mills, P.-O. Park, and C. P. Swain, "Transluminal endosurgery: single lumen access anastomotic device for flexible endoscopy," *Gastrointest. Endosc.*, vol. 58, no. 4, pp. 585–591, Oct. 2003, doi: 10.1016/s0016-5107(03)02006-6.

[84] K. F. Binmoeller and J. N. Shah, “Endoscopic ultrasound-guided gastroenterostomy using novel tools designed for transluminal therapy: a porcine study,” *Endoscopy*, vol. 44, no. 5, pp. 499–503, May 2012, doi: 10.1055/s-0032-1309382.
[85] M. Rimbaș, K. W. Lau, G. Tripodi, G. Rizzatti, and A. Larghi, “The Role of Luminal Apposing Metal Stents on the Treatment of Malignant and Benign Gastric Outlet Obstruction,” *Diagnostics*, vol. 13, no. 21, Art. no. 21, Jan. 2023, doi: 10.3390/diagnostics13213308.
[86] T. R. McCarty, R. Garg, C. C. Thompson, and T. Rustagi, “Efficacy and safety of EUS-guided gastroenterostomy for benign and malignant gastric outlet obstruction: a systematic review and meta-analysis,” *Endosc. Int. Open*, vol. 7, no. 11, pp. E1474–E1482, Nov. 2019, doi: 10.1055/a-0996-8178.
[87] A. Y. B. Teoh *et al.*, “Endoscopic ultrasonography-guided gastroenterostomy versus uncovered duodenal metal stenting for unresectable malignant gastric outlet obstruction (DRA-GOO): a multicentre randomised controlled trial,” *Lancet Gastroenterol. Hepatol.*, vol. 9, no. 2, pp. 124–132, Feb. 2024, doi: 10.1016/S2468-1253(23)00242-X.
[88] D. Moher *et al.*, “Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement,” *Syst. Rev.*, vol. 4, no. 1, p. 1, Jan. 2015, doi: 10.1186/2046-4053-4-1.
[89] L. A. Stewart *et al.*, “Preferred Reporting Items for Systematic Review and Meta-Analyses of individual participant data: the PRISMA-IPD Statement,” *JAMA*, vol. 313, no. 16, pp. 1657–1665, Apr. 2015, doi: 10.1001/jama.2015.3656.
[90] “Cochrane Handbook for Systematic Reviews of Interventions.” Accessed: Jul. 09, 2024. [Online]. Available: https://training.cochrane.org/handbook
[91] G. H. Guyatt *et al.*, “GRADE: an emerging consensus on rating quality of evidence and strength of recommendations,” *BMJ*, vol. 336, no. 7650, pp. 924–926, Apr. 2008, doi: 10.1136/bmj.39489.470347.AD.
[92] P. B. Cotton *et al.*, “A lexicon for endoscopic adverse events: report of an ASGE workshop,” *Gastrointest. Endosc.*, vol. 71, no. 3, pp. 446–454, Mar. 2010, doi: 10.1016/j.gie.2009.10.027.
[93] J. Y. Bang, U. Navaneethan, M. Hasan, R. Hawes, and S. Varadarajulu, “Stent placement by EUS or ERCP for primary biliary decompression in pancreatic cancer: a randomized trial (with videos),” *Gastrointest. Endosc.*, vol. 88, no. 1, pp. 9–17, Jul. 2018, doi: 10.1016/j.gie.2018.03.012.
[94] M. A. Almadi, A. Barkun, and M. Martel, “Plastic vs. Self-Expandable Metal Stents for Palliation in Malignant Biliary Obstruction: A Series of Meta-Analyses,” *Am. J. Gastroenterol.*, vol. 112, no. 2, pp. 260–273, Feb. 2017, doi: 10.1038/ajg.2016.512.
[95] S. Kiriyama *et al.*, “Tokyo Guidelines 2018: diagnostic criteria and severity grading of acute cholangitis (with videos),” *J. Hepato-Biliary-Pancreat. Sci.*, vol. 25, no. 1, pp. 17–30, Jan. 2018, doi: 10.1002/jhbp.512.
[96] G. B. Stewart, D. G. Altman, L. M. Askie, L. Duley, M. C. Simmonds, and L. A. Stewart, “Statistical analysis of individual participant data meta-analyses: a comparison of methods and recommendations for practice,” *PloS One*, vol. 7, no. 10, p. e46042, 2012, doi: 10.1371/journal.pone.0046042.
[97] B. A. Holt *et al.*, “Biliary drainage: role of EUS guidance,” *Gastrointest. Endosc.*, vol. 83, no. 1, pp. 160–165, Jan. 2016, doi: 10.1016/j.gie.2015.06.019.

[98] V. Palmieri *et al.*, “EUS-guided biliary drainage in malignant distal biliary obstruction: An international survey to identify barriers of technology implementation,” *Endosc. Ultrasound*, vol. 12, no. 1, pp. 104–110, 2023, doi: 10.4103/EUS-D-21-00137.
[99] J. S. Barkun *et al.*, “Evaluation and stages of surgical innovations,” *Lancet Lond. Engl.*, vol. 374, no. 9695, pp. 1089–1096, Sep. 2009, doi: 10.1016/S0140-6736(09)61083-7.
[100] M. Bronswijk *et al.*, “Same-session double EUS-guided bypass versus surgical gastroenterostomy and hepaticojejunostomy: an international multicenter comparison,” *Gastrointest. Endosc.*, vol. 98, no. 2, pp. 225-236.e1, Aug. 2023, doi: 10.1016/j.gie.2023.03.019.
[101] L. A. Stewart and J. F. Tierney, “To IPD or not to IPD?: Advantages and Disadvantages of Systematic Reviews Using Individual Patient Data,” *Eval. Health Prof.*, vol. 25, no. 1, pp. 76–97, Mar. 2002, doi: 10.1177/0163278702025001006.
[102] K. D. Lillemoe *et al.*, “Is prophylactic gastrojejunostomy indicated for unresectable periampullary cancer? A prospective randomized trial,” *Ann. Surg.*, vol. 230, no. 3, pp. 322–328; discussion 328-330, Sep. 1999, doi: 10.1097/00000658-199909000-00005.
[103] T. Conroy *et al.*, “FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer,” *N. Engl. J. Med.*, vol. 364, no. 19, pp. 1817–1825, May 2011, doi: 10.1056/NEJMoa1011923.
[104] S. Gourgou-Bourgade *et al.*, “Impact of FOLFIRINOX Compared With Gemcitabine on Quality of Life in Patients With Metastatic Pancreatic Cancer: Results From the PRODIGE 4/ACCORD 11 Randomized Trial,” *J. Clin. Oncol.*, vol. 31, no. 1, pp. 23–29, Jan. 2013, doi: 10.1200/JCO.2012.44.4869.
[105] N. T. van Heek, “Palliative treatment in ‘peri’-pancreatic carcinoma : stenting or surgical therapy ?,” 2002.
[106] J. Espinel, S. Vivas, F. Muñoz, F. Jorquera, and J. L. Olcoz, “Palliative treatment of malignant obstruction of gastric outlet using an endoscopically placed enteral Wallstent,” *Dig. Dis. Sci.*, vol. 46, no. 11, pp. 2322–2324, Nov. 2001, doi: 10.1023/a:1012378509762.
[107] S. Y. Oh *et al.*, “Survival and clinical outcome after endoscopic duodenal stent placement for malignant gastric outlet obstruction: comparison of pancreatic cancer and nonpancreatic cancer,” *Gastrointest. Endosc.*, vol. 82, no. 3, pp. 460-468.e2, Sep. 2015, doi: 10.1016/j.gie.2015.01.026.

2. Chapter 2: Original Research Manuscripts

2.1. Manuscript 1

EUS-guided choledochoduodenostomy with a lumen apposing metal stent is a secure first-line modality for malignant biliary obstruction: an individual patient data meta-analysis

Yeganeh Rostamian Moghaddam[1], Bertrand Napoleon[2], Anand Sahai[3], Gianfranco Donatelli[4], Rastislav Kunda[5,6], Myriam Martel[1], Sharif Yassin[1], Shannon Melissa Chan[7], Paolo Giorgio Arcidiacono[8], Eric Lam[9], Pradermchai Kongkam[10], Nauzer Forbes[11], Alberto Larghi[12], Jeff Mosko[13], Schalk Van der Merwe[14], Ian Gan[15], Jeremie Jacques[16], Sana Kenshil[17], Ratanachu-Ek Thawee[18], Corey Miller[19], Payal Saxena[20], Etienne Desilets[21], Gurpal Sandha[22], Kevin Kwok Chai NG[7], Enders Kwok Wai Ng[7], Yidan Lu[1], Amine Benmassaoud[1], Davide Maggio[23], Alan Barkun[1], Philip Wai Yan Chiu[7], Anthony Yuen Bun Teoh[7], Yen-I Chen[1]

1. Division of Gastroenterology and Hepatology, McGill University Health Centre, Montreal, QC, Canada

2. Hopital Privé Jean Mermoz, Ramsay Santé, Lyon Cedex 08, France.

3. Service de Gastroentérologie, Centre Hospitalier de l'Université de Montréal, Montréal, QC, Canada

4. Unité d'Endoscopie Interventionnelle, Hôpital Privé des Peupliers, Paris, France

5. Department of Surgery, Department of Gastroenterology-Hepatology, Department of Advanced Interventional Endoscopy, Universitair Ziekenhuis Brussel, Vrije Universiteit Brussel, Brussels, Belgium

6. Department of Surgical Gastroenterology, Aarhus University Hospital, Aarhus, Denmark

7. Department of Surgery, Prince of Wales Hospital, The Chinese University of Hong Kong, Hong Kong SAR, China

8. Pancreato-Biliary Endoscopy and Endosonography Division, Pancreas Translational & Clinical Research Center, San Raffaele Scientific Institute IRCCS, Vita Salute San Raffaele University, Milan, Italy

9. Division of Gastroenterology and Hepatology, St-Paul Hospital, Vancouver, BC, Canada

10. Division of Hospital and Ambulatory Medicine and Division of Gastroenterology, Department of Medicine, Faculty of Medicine, Chulalongkorn University and King Chulalongkorn Memorial Hospital, Thai Red Cross Society, Bangkok, Thailand.

11. Division of Gastroenterology and Hepatology, University of Calgary, Calgary, AB, Canada

12. Digestive Endoscopy Unit, Fondazione Policlinico Universitario A. Gemelli, IRCCS, Rome, Italy

13. Division of Gastroenterology, St-Michael's Hospital, University of Toronto, Toronto, On, Canada

14. Department of Gastroenterology and Hepatology, The University of Leuven, Leuven, Belgium.

15. Division of Gastroenterology and Hepatology, Vancouver General Hospital, Vancouver, BC, Canada

16. Gastroenterology Department, Dupuytren University Hospital, Limoges, France.

17. Division of Gastroenterology and Hepatology, Ottawa Hospital, Ottawa, On, Canada

18. Department of Surgery, Rajavithi Hospital, Bangkok, Thailand.

19. Division of Gastroenterology and Hepatology, Jewish General Hospital, Montreal, QC, Canada

20. Department of Gastroenterology, Royal Prince Alfred Hospital, Sidney, Australia.

21. Division of Gastroenterology, Hôpital Charles-Le Moyne, Longeuil, QC, Canada

22. Division of Gastroenterology and Hepatology, University of Alberta Hospital, Edmonton, Alberta, Canada

23. Division of Gastroenterology, Santa-Cabrini Hospital, Montreal, QC, Canada

Correspondence: Anthony Yuen Bun Teoh MD

Honorary Consultant in General Surgery, HK Sanatorium Hospital

Clinical Associate Professor (Honorary) and Consultant (Honorary), The Chinese University of Hong Kong

Conflict of Interest: Yen-I Chen is a consultant for Boston Scientific, has received research funding from Boston Scientific and is the co-founder of Chess Medical Inc. Bertrand Napoleon has received honorarium for proctoring endoscopy training from Maunea Kea, Boston Scientific, Olympus, and Taewoong Medical. Anand Sahai is a consultant Boston Scientific and Pentax. Rastislav Kunda is a consultant for Boston Scientific, Olympus, M.I.Tech, Omega Medical

Imaging, Q3 Medical-AMG International and EndoGastricSolutions. Nauzer Forbes is a consultant and speaker for Boston Scientific and Pentax Medical, a speaker for AstraZeneca, and has received research funding from Pentax Medical. Anthony Yuen Bun Teoh is a consultant for Boston Scientific, Cook, Taewoong, Microtech, and MI Tech Medical Corporations.

All other authors have no relevant conflict of interest.

Data used for this meta-analysis is not publicly availably

Funding: Canadian Institute of Health research and the Fonds de Recherche du Québec - Santé (FRQS)

Keywords: ERCP, Endoscopic retrograde cholangiopancreatography, EUS-guided biliary drainage, Endosonography, EUS-guided choledochoduodenostomy.

Abstract

Objective: EUS-guided choledochoduodenostomy using a lumen apposing metal stent (EUS-CDSL) has been shown in randomized controlled trials (RCT) to be effective when compared to endoscopic retrograde cholangiopancreatography (ERCP) in patients with advanced malignant distal biliary obstruction (MDBO). We aimed to further ascertain the safety of EUS-CDSL, which has been limited by inadequate trial sample sizes.

Design: We undertook aggregate and individual patient data (IPD) meta-analyses following the PRISMA-IPD statement. A literature search was performed from January 2013 to November 2023 using OVID MEDLINE, EMBASE, Cochrane Library, and ISI Web of Science. RCTs comparing EUS-CDSL to ERCP were included. The primary outcome was the rate of procedure related severe or fatal adverse events (AE). Secondary outcomes include technical success, 30-day AE, clinical success, stent dysfunction, and procedure time.

Results: A total of 2241 citations were screened with two RCTs included (299 patients). There was no difference in severe or fatal AEs between EUS-CDSL and ERCP (OR 0.47, 95% CI 0.12-1.93 for IPD data and RR 0.62, 95% CI 0.22, 1.77 for aggregate data). Technical success was greater for EUS-CDSL (OR 3.95, 95% CI 1.86-8.37 and RR 1.17, 95% CI 1.07, 1.29) with faster procedural time (mean difference -10.01 minutes (95% CI 19.30, -0.87). No significant differences were noted in 30-day AEs, clinical success, and stent dysfunction.

Conclusion: Our aggregate and IPD meta-analyses demonstrate the safety of EUS-CDSL as a first-line alternative to ERCP in advanced MDBO. In addition, EUS-CDSL appears to be technically superior in terms of success rate and procedure time.

Introduction

Malignant distal biliary obstruction (MDBO) leading to painless jaundice is the most common presentation of peri-ampullary cancers.[1][1] Restoring bile flow has been associated with increased survival and is essential in alleviating symptoms of cholestasis, improving patients' quality of life, and allowing for chemotherapy administration.[3], [59][2,3] Endoscopic retrograde cholangiopancreatography (ERCP) has been the standard of care for relieving MDBO for over four decades.[4][4] ERCP, however, remains a challenging procedure with up to 10-20% technical failure in MDBO along with significant risk for complications such as post ERCP pancreatitis.[4], [5], [6][4-6] EUS-guided choledochoduodenostomy (EUS-CDS) using a lumen apposing metal stent (LAMS) is an emerging modality, which achieves biliary drainage through the creation of an anastomosis between the extra-hepatic bile duct and the duodenum proximal to the ampulla. The advent of the cautery-assisted LAMS technique has greatly simplified EUS-CDSL allowing for direct stent insertion without the need for a separate access device, wire guidance, and/or tract dilation.[55], [56], [57][7-9] Two recent randomized controlled trials (RCTs) comparing EUS-CDSL vs. ERCP in MDBO have demonstrated comparable or better technical success, and shorter procedure time, without significant differences in stent patency and adverse events.[6], [7][6,10] These multicenter RCTs have provided high quality data supporting an alternative first-line modality to ERCP. Like most interventional trials, however, these studies were not sufficiently powered to adequately assess comparability in terms of adverse events. As EUS-CDSL gains clinical adoption given its technical ease, especially considering the recent RCT data supporting its use, it is imperative to adequately assess its safety while also better characterizing other important clinical outcomes.

The primary aim of our aggregate and individual patient data (IPD) meta-analyses is to assess the safety of EUS-CDSL while further defining other technical and clinical outcomes when compared to ERCP as a first-line approach in MDBO. We hypothesize that EUS-CDSL is akin in safety to ERCP. In addition, we postulate that EUS-CDSL is superior in technical efficiency and success along with comparable stent function.

Methods

- **Overview**

We performed a systematic review and meta-analysis following the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRIMSA) reporting standards.[88][11] An IPD meta-analysis was also undertaken according to the PRISMA-IPD statement.[89][12] Our study was registered with the International Prospective Register of Systematic Reviews (CRD 485070) and was approved by the research ethics board at the coordinating sites. Our primary outcome was the risk for severe or fatal procedure related adverse events. Secondary outcomes include technical success, overall, 30-day adverse events, clinical success, stent dysfunction, and procedure time.

- **Search Strategy and Study Selection**

A comprehensive literature search was performed from Jan 2013 to Nov 2023 using OVID MEDLINE, EMBASE, Cochrane Library, and ISI Web of Science with MeSH and controlled vocabulary for terms specified for 1) endoscopic ultrasound guided biliary drainage, 2) endoscopic ultrasound guided choledochoduodenostomy, 3) endosonography guided biliary drainage, 4) endosonography guided choledochoduodenostomy. Two reviewers (YR and SY) performed title and abstract screens of every identified work. A third reviewer was involved for conflict resolution (YC).

- **Eligibility**

A study was included if it met all the following inclusion criteria: The study was a RCT involving adult patients with MDBO, the experimental arm was EUS-CDS using a LAMS as a first line modality, the control arm was ERCP with transpapillary self-expanding metal stent insertion (SEMS), and the study was published as a full manuscript. Studies assessing EUS-CDS using other types of stents other than biliary LAMS were excluded.

- **Data extraction and study quality**

Following identification of the eligible studies, the corresponding authors of each trial were contacted for patient-level data. Sharing of deidentified data occurred only following research ethics approval at each of the included RCT principal investigator sites. A data extraction form was created to collate all data from all studies using unified definitions and scales. The collated data were reviewed by three reviewers (YC, MM, and AYBT). Two reviewers were also involved in the assessment of bias (YC and MM). Risk for bias was ascertained using the Cochrane Risk of Bias Tool for Randomized Trials[90][13], and certainty of the evidence was determined using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework.[91][14] Given the lack of grading system for IPD, the GRADE was performed solely on the results of an aggregated meta-analysis. The certainty of evidence for each selected outcome of interest was rated as high, moderate, low, or very low, using the GRADEpro GDT software (Evidence Prime Inc., Hamilton, Ontario, Canada).

- **Outcomes**

The primary outcome was the rate of procedure related severe or fatal adverse events as defined by American Society for Gastrointestinal Endoscopy lexicon for endoscopic adverse events.[92][15]

Secondary endpoints include overall 30-day adverse events as per the ASGE lexicon, technical success, procedure time, clinical success, and stent dysfunction. Technical success was defined as successful insertion of a transpapillary stent or choledochoduodenostomy stent at the index procedure. Procedure time was defined as the time from scope insertion to scope withdrawal. Clinical success was defined as a 50% decrease in bilirubin within 2 weeks post-stent insertion or achieving a value of less than 25% of pre-procedure bilirubin levels within 4 weeks post stent insertion.[5], [93], [94][5,16,17] Stent dysfunction was defined as endoscopic or radiologic re-intervention confirming stent blockage or migration needing stent cleaning, stent change, and/or additional stent insertion, and at least one of the following: 1) suspected cholangitis (Tokyo consensus definition[95][18]), 2) definite cholangitis (Tokyo definition[95][18]), 3) ≥50% increase in bilirubin from the lowest level post index procedure, 4) ≥20% increase in bilirubin from the lowest level post index procedure as well as evidence of obstruction on imaging.[7][10] Patients with a bilirubin that never decreased post index stenting were not classified as experiencing stent dysfunction but rather were categorized as not achieving initial clinical success.

- **Statistical Analysis**

Both an IPD and an aggregate meta-analysis were performed as described below. IPD were interpretated using standardized definitions for each endpoint across both trials and all analyses were based on the intention-to-treat principle. A one-stage approach was adopted a priori as this method uses a more exact statistical methodology than normal approximation and is the preferred technique when only few studies are available.[96][19] We reported unadjusted odds ratios (OR) and 95% confidence intervals (CI). Estimation of adjusted ORs were also attempted using a generalized logistic mixed effect model (PROC GLIMMIX, SAS, Cary, NC), however, the model

did not converge due to the limited sample size. A two-sided p-value of 0.05 or less was considered evidence of statistical significance.

For the aggregate meta-analysis, effect size was calculated with mean differences for continuous variables and risk ratios (RRs) for categorical variables. The DerSimonian and Laird method for random effect models was applied to all outcomes to determine corresponding overall effect sizes and their confidence intervals. Sensitivity analyses were performed using the Mantel-Haenszel method with random effect models; however fixed effects models were used when no statistical heterogeneity was noted. Mean differences were handled as continuous variables using the inverse variance approach. The Higgins I2 statistic was calculated to quantify the proportion of variation in intervention effects attributable to between-study heterogeneity. Values 0%-40%; 30%-60%; 50%-90%; 75%-100% represent a potential of low; moderate; substantial and considerable heterogeneity, respectively and were interpreted with the size and direction of effect as well as the strength of evidence of heterogeneity using a Chi-square test of homogeneity with a 0.10 significance level.[90][13] Analyses were done using Meta package in R version 2.13.0 (R Foundation for Statistical Computing, Vienna, Austria, 2008).

Results

A total of 2241 citations were identified through the electronic search. Ultimately, two RCTs6, 10 were selected for analysis using the pre-defined eligibility criteria (Figure 11). All first authors provided anonymized individual patient level data from their respective published trials and no issues were noted with either of the individual datasets. Low incidence and limited sample size prevented a hierarchical-level analysis by studies and therefore results are reported using unadjusted odds ratios.

Of the 299 patients receiving biliary drainage in the meta-analysis, 152 patients were allocated to EUS-CDSL and 147 to ERCP. IPD were available for all 299 patients. Both trials were multicentered with widespread geographical representation including centers from Canada, China, France, Belgium, Italy, Netherlands, Australia, and Thailand. The Cochrane risk bias tool revealed a high potential for performance bias across studies since all were single-blinded (participating endoscopists could not be blinded due to the nature of the intervention) (Figure 12). The grading of the evidence based on aggregate data was "moderate" for all outcomes (Table 3).

Patient demographics from pooled IPD from both trials are summarized in (Table 2). Using IPD, the pooled rates of severe or fatal procedure-related adverse events were 2.0% (3/152) and 4.1% (6/147) for EUS-CDSL and ERCP, respectively, p=0.33. The pooled rate for technical success was 93.4% for EUS-CDSL and 78.2% for ERCP, p<0.01 with a mean procedure time of 16.2 ± 15.3 minutes and 26.3 ± 17.8 minutes, respectively p<0.01. There were no significant differences in the pooled rates of overall 30-day adverse events, clinical success, and stent dysfunction (Table 3).

The IPD meta-analysis showed no significant difference in the odds of severe or fatal AEs between EUS-CDSL and ERCP (odds ratio (OR) 0.47, 95% confidence interval (CI): 0.12-1.93)) (Figure 14**,** Figure 14). Using the aggregate data, EUS-CDSL was also associated with a comparable risk of severe or fatal AEs as for ERCP (relative risk (RR) 0.62, 95% CI: 0.22, 1.77).

The IPD meta-analysis demonstrated that the odds of technical success were higher with EUS-CDS (OR 3.95, 95% CI:1.86, 8.37) when compared to ERCP. The aggregate data meta-analysis, similarly, showed that EUS-CDSL was associated with greater technical success (RR 1.17, 95% CI:1.07, 1.29) and shorter procedure time (mean difference of -10.01 minutes, 95% CI: -19.30, -0.87).

Lastly, IPD and aggregate data meta-analyses yielded no significant differences in 30-day AEs (OR 0.77, 95% CI:0.40, 1.48 and RR 0.80, 95% CI:0.45, 1.40), clinical success (OR 1.15, 95% CI:0.62, 2.10 and RR 1.01, 95% CI:0.93, 1.10), or stent dysfunction (OR 0.88, 95% CI: 0.37, 2.06 and RR 0.85, 95% CI:0.43, 1.67). No significant heterogeneity was noted and publication bias could not be assessed with only 2 trials. Given the rare event rate of severe or fatal procedure related adverse events, subgroup analysis was not possible.

Despite being identified as a research priority by the American Society of Gastrointestinal Endoscopy (ASGE) in 2008, EUS-biliary drainage has not attained clinical dissemination beyond expert centers over the past 15 years.[97][20] The lack of dedicated devices has made EUS-biliary drainage technically taxing while the scarcity of high-quality data has further hindered its adoption.[98][21] When assessing the clinical state of EUS-biliary drainage using the IDEAL framework for technology assessment[99], EUS-biliary drainage has remained in stage 2, or the early stages of development where only a few select experts are performing the procedure for a few select patients. The advent of the biliary LAMS has greatly simplified the technique. The cautery LAMS allows for a one step biliary drainage using only one device without needing needle puncture, expert guidewire manipulation, and tract dilation.[7], [55][7,10] The newfound ease of technical adoption is highlighted in the relative inexperience of the operators in the trials that were included in the meta-analysis, especially in the trial by Chen *et al.* where the median number of EUS-CDSL by operators prior to entry into the study was only 2. In contrast, operators had to have performed at least 20 EUS-CDSL to be eligible to participate in the study by Teoh *et al*. These numbers are in stark contrast to the control arm of ERCP, which included only operator with more than 1000 ERCPs performed. Despite the disproportionate advantage in experience in favor of the the ERCP arm, our IPD meta-analysis showed that EUS-CDSL outperformed ERCP in technical

success and procedure time while having comparable risk and odds for severe or fatal procedure related severe adverse events and overall 30-day adverse events, although confidence intervals remain wide for fatal and severe adverse events due to their scarcity. Taken together, our data suggest that EUS-CDSL may be a technically easier and more efficient procedure than ERCP. This efficiency is likely further highlighted when EUS-guided tissue diagnosis is needed such that EUS-CDSL can be performed with the same echoendoscope instead of processing a second duodenoscope for ERCP. In addition, EUS-CDSL can be performed without fluoroscopic guidance, which further streamlines its use.

Both on aggregate and IPD meta-analysis, our data demonstrated comparable risks and odds for clinical success and stent dysfunction between EUS-CDSL and ERCP in MDBO. It is important to note that only unresectable peri-ampullary cancers or locally advanced/borderline resectable cancers who were not candidates for upfront resection were included. No current RCT data exist for EUS-biliary drainage in resectable patients. Although EUS-CDSL has the theoretical advantage of providing a bypass and thus preventing stent dysfunction from direct tumor tissue stent ingrowth and overgrowth, other causes of stent dysfunction may occur, including food impaction and sump syndrome.[6], [7], [56], [57][6,8-10] It is important to note that studies in the meta-analysis did not include patients with clinical evidence of malignant gastric outlet obstruction (MGOO). Given that MGOO is most often post bulbar, stent patency is likely a major problem in this setting where there is stasis of food in the duodenal bulb and inability for the bile to flow caudally down the GI tract. As such, in the setting of MGOO, EUS-CDSL likely requires concomitant endoscopic relief of MGOO either through enteral stenting or EUS-guided gastroenterostomy[100][23] to achieve adequate stent patency. These are a patient population whose optimal palliation requires further study.

The cost of LAMS has been identified as a major barrier to the widespread clinical adoption of EUS-CDSL.[98][21] There are no cost-effectiveness data available to inform whether the greater efficiency and technical success of EUS-CDSL can offset the higher upfront cost of LAMS. This significant hurdle will likely continue to limit clinical use of EUS-CDSL, highlighting the need for alternative device options to reduce cost. Once the cost of a dedicated EUS-CDSL stent achieves an acceptable willingness to pay threshold, the widespread adoption of EUS-CDSL as a first-line modality in patients with MDBO will likely ensue.

Strengths of our meta-analysis include the use of high-quality RCTs with both IPD and aggregate meta-analytical methodologies. IPD allowed the use a homogenous definition for each endpoint, thus enhancing the precision, directness, and overall certainty of the data. Indeed, an IPD meta-analysis is widely considered the gold standard for systematic reviews, when one can be carried out.[101][24] The multicenter design, across several continents, for the two included trials also increases the generalizability of our data with regards to location, patient demographics, and health care systems. The inclusion of operators with limited experience in performing EUS-CDSL also greatly increases the generalizability of the conclusions. Limitations of our IPD meta-analysis include the identification of only two RCTs, which prevented a hierarchical study level analysis. The small event rate of the primary endpoint of severe or fatal adverse events also led to a relatively wide confidence interval. Nevertheless, given the consistent findings across both trials, it is somewhat unlikely that other RCTs will be performed, making the current analysis the most authoritative data-driven conclusions to inform guidelines on the role of EUS-CDSL in patients with MDBO who are not candidates for upfront pancreaticoduodenectomy.

In conclusion, our IPD and aggregate meta-analyses of RCTs provide compelling evidence supporting the adoption of EUS-CDSL as a safe, efficient, and technically superior first-line

alternative to ERCP when managing patients with malignant distal biliary obstruction who are not candidates for upfront curative surgical resection. Characterization of the cost-effectiveness is needed to optimize clinical implementation of EUS-CDSL.

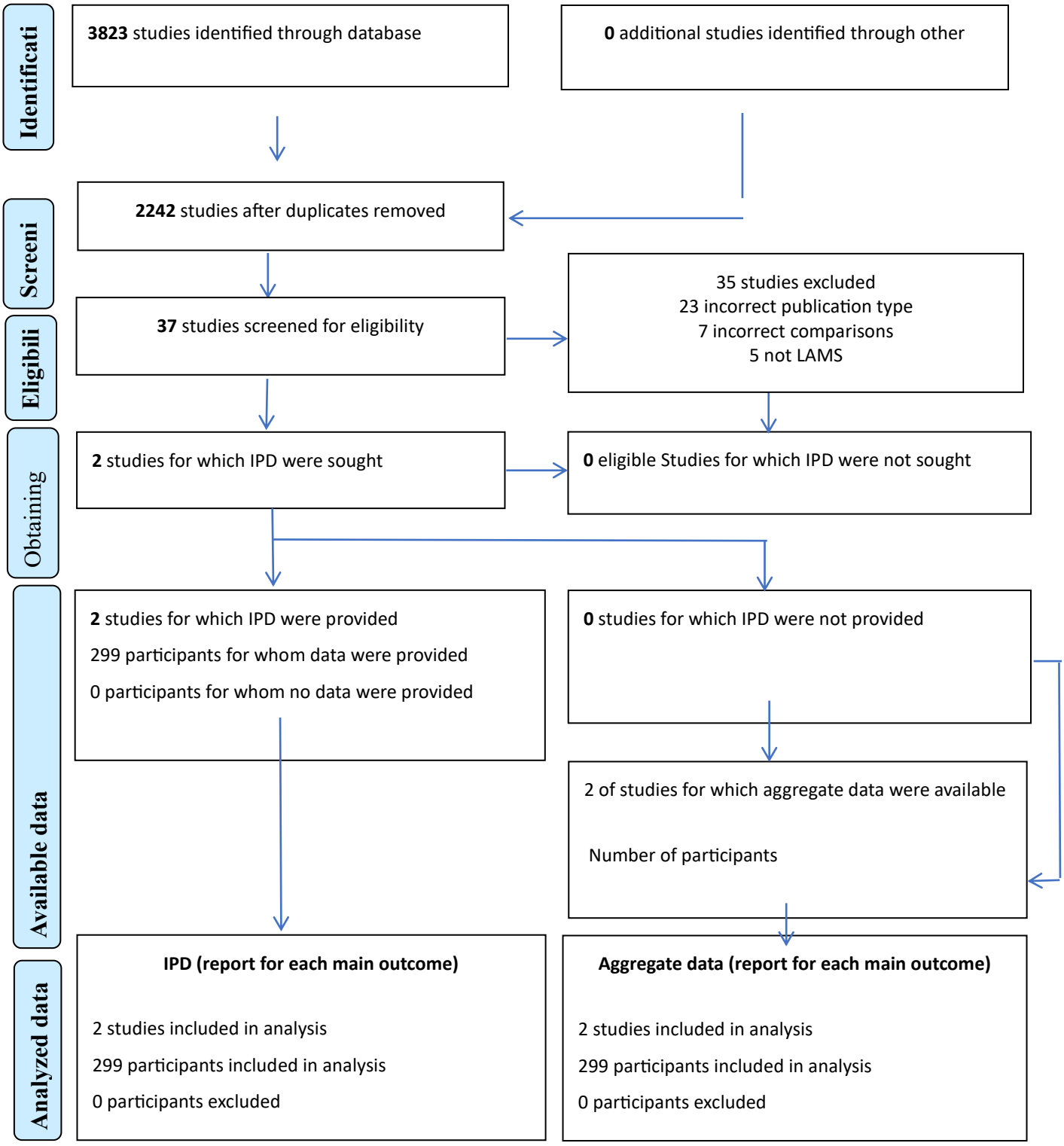


Figure 11. Flow diagram (Manuscript 1)

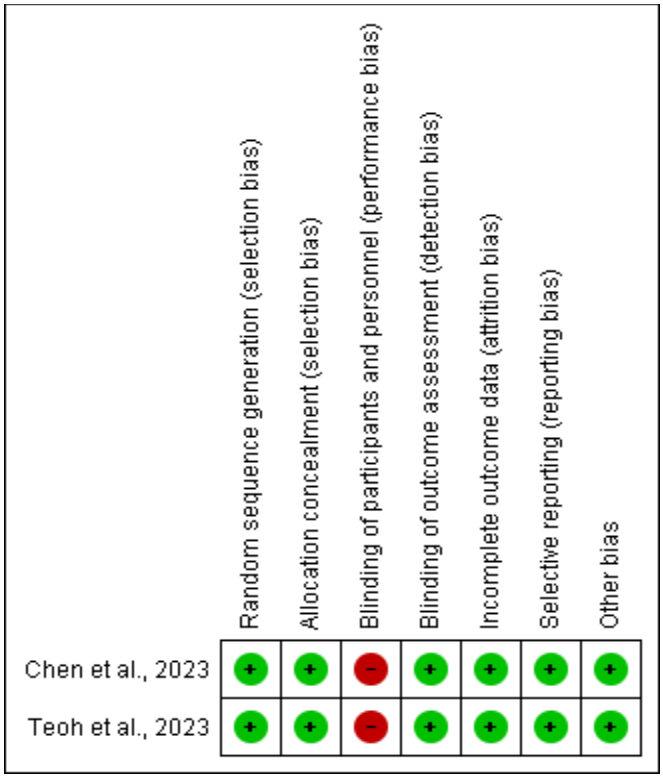
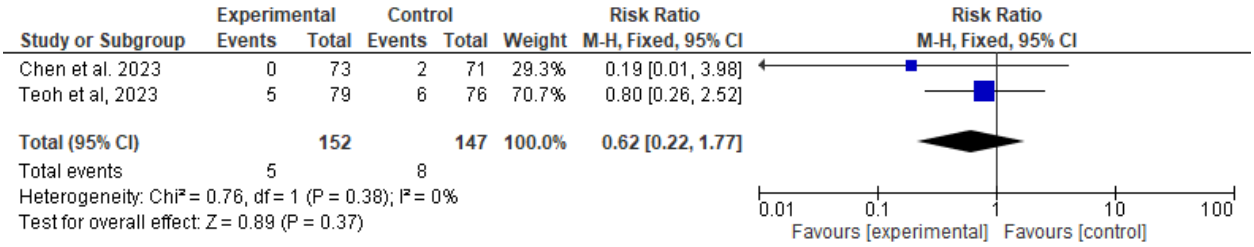


Figure 12. Cochrane Risk of Bias (Manuscript 1)

A



B

C

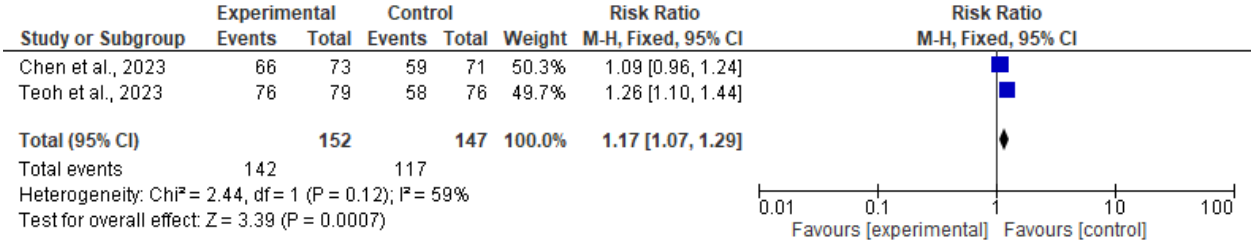
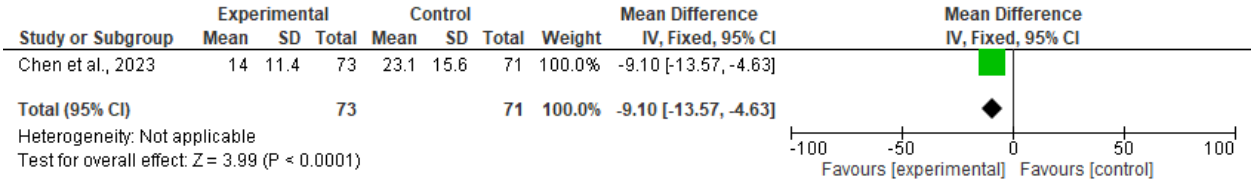


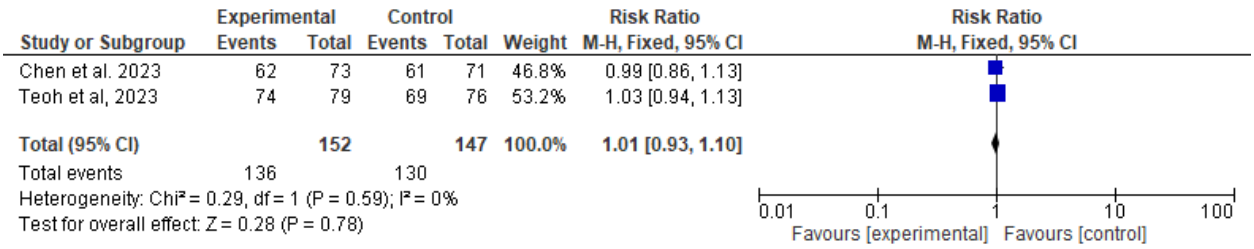
Figure 13.Aggregate meta-analysis. Forrest plot demonstrating the relative risk of A) severe or fatal procedure related severe adverse events, B) overall 30-day adverse event, C) technical success (Manuscript 1)

D-



* Teoh et al reported median and ranges. The latter could not be converted to standard deviation.

E



F

Figure 14. Aggregate meta-analysis. Forrest plot demonstrating the relative risk of D) procedure time, E) clinical success, F) stent dysfunction (Manuscript 1)

Table 2. Pooled patient demographics using individual patient data (Manuscript 1)

Variable	Overall n=299	EUS-CDS (n=152)	ERCP-M (n=147)	p-value
Age	72.8 ± 11.6	74.3 ± 11.2	71.4 ± 11.8	0.03
Female	129 (43.1%)	73 (48.0%)	56 (38.1%)	0.08
ASA				
I-II	201 (67.2%)	98 (64.5%)	103 (70.1%)	0.30
III-IV	98 (32.8%)	54 (35.5%)	44 (29.9%)	
Etiology of MDBO				
Pancreatic cancer	279 (93.3%)	139 (91.5%)	140 (95.2%)	0.19
Cholangiocarcinoma/gallbladder cancer	10 (3.3%)	7 (4.6%)	3 (2.0%)	0.24
Ampullary cancer	4 (1.3%)	2 (1.3%)	2 (1.4%)	1.00
Other	6 (2.0%)	4 (2.7%)	2 (1.4%)	0.68
Tumor Stage				
Borderline/locally advanced	243 (81.3%)	31 (20.4%)	25 (17.1%)	0.45
Unresectable	56 (18.7%)	121 (79.6%)	122 (83.0%)	
Baseline Bilirubin level	240.6 ± 141.1	235.3 ± 130.3	246.0 ± 151.6	0.51

Table 3. Pooled rates or primary and secondary endpoints using individual patient data (Manuscript 1)

Variable	Overall n=299	EUS-CDS (n=152) n (%)	ERCP-M (n=147) n (%)	Meta-analysis aggregate data Risk ratio (95%CI) Or WMD (95%CI) I^2	Meta-analysis Individual patient data Odds ratio (95%CI) or WMD (95%CI)
Primary outcome					
Severe or fatal procedure related adverse events (within 14 days of the procedure) *	9 (3.0%)	3 (2.0%)	6 (4.1%)	0.62 (0.22, 1.77) $I^2 = 0.38$	0.47 (0.12, 1.93)
Secondary outcome					
All 30-day adverse events	42 (14.0%)	19 (12.5%)	23 (15.6%)	0.80 (0.45, 1.40) $I^2= 0\%$	0.77 (0.40; 1.48)
Stent dysfunction	23 (7.7%)	11 (7.2%)	12 (8.2%)	0.85 (0.43, 1.67) $I^2= 0\%$	0.88 (0.37; 2.06)

Variable	Overall n=299	EUS-CDS (n=152) n (%)	ERCP-M (n=147) n (%)	Meta-analysis aggregate data Risk ratio (95%CI) Or WMD (95%CI) I^2	Meta-analysis Individual patient data Odds ratio (95%CI) or WMD (95%CI)
Technical success	252 (84.3%)	142 (93.4%)	115 (78.2%)	1.17 (1.07, 1.29) I^2= 59%	3.95 (1.86; 8.37)
Clinical success	249 (83.3%)	128 (84.2%)	121 (82.3%)	(0.93, 1.10) I^2= 0%	1.15 (0.62; 2.10)
Procedure time	21.1 ± 17.2	16.2 ± 15.3	26.3 ± 17.8	I^2=N/A	-10.1 (-19.3; -0.87)

** Teoh et al reported median and ranges. The latter could not be converted to standard deviation., N/A: not applicable

References

[1] M. Porta *et al.*, "Exocrine pancreatic cancer: symptoms at presentation and their relation to tumour site and stage," *Clin. Transl. Oncol. Off. Publ. Fed. Span. Oncol. Soc. Natl. Cancer Inst. Mex.*, vol. 7, no. 5, pp. 189–197, Jun. 2005, doi: 10.1007/BF02712816.

[2] M. Fernandez Y Viesca and M. Arvanitakis, "Early Diagnosis And Management Of Malignant Distal Biliary Obstruction: A Review On Current Recommendations And Guidelines," *Clin. Exp. Gastroenterol.*, vol. 12, pp. 415–432, Nov. 2019, doi: 10.2147/CEG.S195714.

[3] N. S. Abraham, J. S. Barkun, and A. N. Barkun, "Palliation of malignant biliary obstruction: a prospective trial examining impact on quality of life," *Gastrointest. Endosc.*, vol. 56, no. 6, pp. 835–841, Dec. 2002, doi: 10.1067/mge.2002.129868.

[4] B. J. Elmunzer *et al.*, "ACG Clinical Guideline: Diagnosis and Management of Biliary Strictures," *Am. J. Gastroenterol.*, vol. 118, no. 3, pp. 405–426, Mar. 2023, doi: 10.14309/ajg.0000000000002190.

[5] W. H. Paik *et al.*, "EUS-Guided Biliary Drainage Versus ERCP for the Primary Palliation of Malignant Biliary Obstruction: A Multicenter Randomized Clinical Trial," *Am. J. Gastroenterol.*, vol. 113, no. 7, pp. 987–997, Jul. 2018, doi: 10.1038/s41395-018-0122-8.

[6] A. Y. B. Teoh *et al.*, "EUS-Guided Choledocho-duodenostomy Using Lumen Apposing Stent Versus ERCP With Covered Metallic Stents in Patients With Unresectable Malignant Distal Biliary Obstruction: A Multicenter Randomized Controlled Trial (DRA-MBO Trial)," *Gastroenterology*, vol. 165, no. 2, pp. 473-482.e2, Aug. 2023, doi: 10.1053/j.gastro.2023.04.016.

[7] Y.-I. Chen *et al.*, "Endoscopic Ultrasound-Guided Biliary Drainage of First Intent With a Lumen-Apposing Metal Stent vs Endoscopic Retrograde Cholangiopancreatography in Malignant Distal Biliary Obstruction: A Multicenter Randomized Controlled Study (ELEMENT Trial)," *Gastroenterology*, vol. 165, no. 5, pp. 1249-1261.e5, Nov. 2023, doi: 10.1053/j.gastro.2023.07.024.

[8] K. W. Lau, M. Rimbaș, G. Tripodi, and A. Larghi, "Endoscopic Ultrasound Biliary Drainage in Pancreatic Cancer," *J. Gastrointestin. Liver Dis.*, vol. 32, no. 4, Art. no. 4, Dec. 2023, doi: 10.15403/jgld-4922.

[9] Y.-I. Chen *et al.*, "EUS-guided gastroenterostomy is comparable to enteral stenting with fewer re-interventions in malignant gastric outlet obstruction," *Surg. Endosc.*, vol. 31, no. 7, pp. 2946–2952, Jul. 2017, doi: 10.1007/s00464-016-5311-1.

[10] S.-B. Bian, W.-S. Shen, H.-Q. Xi, B. Wei, and L. Chen, "Palliative Therapy for Gastric Outlet Obstruction Caused by Unresectable Gastric Cancer: A Meta-analysis Comparison of Gastrojejunostomy with Endoscopic Stenting," *Chin. Med. J. (Engl.)*, vol. 129, no. 9, pp. 1113–1121, May 2016, doi: 10.4103/0366-6999.180530.

[11] S. L. H. Cheung and A. Y. B. Teoh, "Optimal Management of Gastric Outlet Obstruction in Unresectable Malignancies," *Gut Liver*, vol. 16, no. 2, pp. 190–197, Mar. 2022, doi: 10.5009/gnl210010.

[12] T. Itoi *et al.*, "Technical review of endoscopic ultrasonography-guided gastroenterostomy in 2017," *Dig. Endosc.*, vol. 29, no. 4, pp. 495–502, 2017, doi: 10.1111/den.12794.

[13] A. Dormann, S. Meisner, N. Verin, and A. Wenk Lang, "Self-expanding metal stents for gastroduodenal malignancies: systematic review of their clinical effectiveness," *Endoscopy*, vol. 36, no. 6, pp. 543–550, Jun. 2004, doi: 10.1055/s-2004-814434.

[14] M. Khashab *et al.*, "Enteral stenting versus gastrojejunostomy for palliation of malignant gastric outlet obstruction," *Surg. Endosc.*, vol. 27, no. 6, pp. 2068–2075, Jun. 2013, doi: 10.1007/s00464-012-2712-7.
[15] C. Miller *et al.*, "EUS-guided gastroenterostomy vs. surgical gastrojejunostomy and enteral stenting for malignant gastric outlet obstruction: a meta-analysis," *Endosc. Int. Open*, vol. 11, no. 7, pp. E660–E672, Jul. 2023, doi: 10.1055/a-2098-2570.
[16] Y.-I. Chen *et al.*, "EUS-guided gastroenterostomy: a multicenter study comparing the direct and balloon-assisted techniques," *Gastrointest. Endosc.*, vol. 87, no. 5, pp. 1215–1221, May 2018, doi: 10.1016/j.gie.2017.07.030.
[17] A. Singh, A. Gelrud, and B. Agarwal, "Biliary strictures: diagnostic considerations and approach," *Gastroenterol. Rep.*, vol. 3, no. 1, pp. 22–31, Feb. 2015, doi: 10.1093/gastro/gou072.
[18] T. Hennedige, W. Neo, and S. Venkatesh, "Imaging of malignancies of the biliary tract-an update," *Cancer Imaging*, vol. 14, Apr. 2014, doi: 10.1186/1470-7330-14-14.
[19] L. Rahib, B. D. Smith, R. Aizenberg, A. B. Rosenzweig, J. M. Fleshman, and L. M. Matrisian, "Projecting cancer incidence and deaths to 2030: the unexpected burden of thyroid, liver, and pancreas cancers in the United States," *Cancer Res.*, vol. 74, no. 11, pp. 2913–2921, Jun. 2014, doi: 10.1158/0008-5472.CAN-14-0155.
[20] S. I. Ilyas, S. A. Khan, C. L. Hallemeier, R. K. Kelley, and G. J. Gores, "Cholangiocarcinoma — evolving concepts and therapeutic strategies," *Nat. Rev. Clin. Oncol.*, vol. 15, no. 2, pp. 95–111, Feb. 2018, doi: 10.1038/nrclinonc.2017.157.
[21] B. I. Choi, J. K. Han, S. T. Hong, and K. H. Lee, "Clonorchiasis and Cholangiocarcinoma: Etiologic Relationship and Imaging Diagnosis," *Clin. Microbiol. Rev.*, vol. 17, no. 3, pp. 540–552, Jul. 2004, doi: 10.1128/CMR.17.3.540-552.2004.
[22] Y. Shaib and H. B. El-Serag, "The epidemiology of cholangiocarcinoma," *Semin. Liver Dis.*, vol. 24, no. 2, pp. 115–125, May 2004, doi: 10.1055/s-2004-828889.
[23] R. Hundal and E. A. Shaffer, "Gallbladder cancer: epidemiology and outcome," *Clin. Epidemiol.*, vol. 6, pp. 99–109, Mar. 2014, doi: 10.2147/CLEP.S37357.
[24] A. Sharma, K. L. Sharma, A. Gupta, A. Yadav, and A. Kumar, "Gallbladder cancer epidemiology, pathogenesis and molecular genetics: Recent update," *World J. Gastroenterol.*, vol. 23, no. 22, pp. 3978–3998, Jun. 2017, doi: 10.3748/wjg.v23.i22.3978.
[25] A. Duffy *et al.*, "Gallbladder cancer (GBC): 10-year experience at Memorial Sloan-Kettering Cancer Centre (MSKCC)," *J. Surg. Oncol.*, vol. 98, no. 7, pp. 485–489, Dec. 2008, doi: 10.1002/jso.21141.
[26] D. H. Ahn and T. Bekaii-Saab, "Ampullary Cancer: An Overview," *Am. Soc. Clin. Oncol. Educ. Book ASCO Am. Soc. Clin. Oncol. Meet.*, pp. 112–115, 2014, doi: 10.14694/EdBook_AM.2014.34.112.
[27] W.-C. Liao *et al.*, "Adjuvant treatments for resected pancreatic adenocarcinoma: a systematic review and network meta-analysis," *Lancet Oncol.*, vol. 14, no. 11, pp. 1095–1103, Oct. 2013, doi: 10.1016/S1470-2045(13)70388-7.
[28] R. A. Kozarek, "The Past, Present, and Future of Endoscopic Retrograde Cholangiopancreatography," *Gastroenterol. Hepatol.*, vol. 13, no. 10, p. 620, Oct. 2017.
[29] A. Canakis and M. Kahaleh, "Endoscopic palliation of malignant biliary obstruction," *World J. Gastrointest. Endosc.*, vol. 14, no. 10, pp. 581–596, Oct. 2022, doi: 10.4253/wjge.v14.i10.581.

[30] J.-M. Dumonceau *et al.*, “Endoscopic biliary stenting: Indications, choice of stents, and results: European Society of Gastrointestinal Endoscopy (ESGE) Clinical Guideline - Updated October 2017,” *Endoscopy*, vol. 50, no. 9, pp. 910–930, 2018, doi: 10.1055/a-0659-9864.
[31] H. Isayama *et al.*, “A prospective randomised study of ‘covered’ versus ‘uncovered’ diamond stents for the management of distal malignant biliary obstruction,” *Gut*, vol. 53, no. 5, pp. 729–734, 2004, doi: 10.1136/gut.2003.018945.
[32] J. J. Telford *et al.*, “A randomized trial comparing uncovered and partially covered self-expandable metal stents in the palliation of distal malignant biliary obstruction,” *Gastrointest. Endosc.*, vol. 72, no. 5, pp. 907–914, Nov. 2010, doi: 10.1016/j.gie.2010.08.021.
[33] E. Kullman *et al.*, “Covered versus uncovered self-expandable nitinol stents in the palliative treatment of malignant distal biliary obstruction: results from a randomized, multicenter study,” *Gastrointest. Endosc.*, vol. 72, no. 5, pp. 915–923, Nov. 2010, doi: 10.1016/j.gie.2010.07.036.
[34] M. Kitano *et al.*, “Covered Self-Expandable Metal Stents With an Anti-Migration System Improve Patency Duration Without Increased Complications Compared With Uncovered Stents for Distal Biliary Obstruction Caused by Pancreatic Carcinoma: A Randomized Multicenter Trial,” *Off. J. Am. Coll. Gastroenterol. ACG*, vol. 108, no. 11, p. 1713, Nov. 2013, doi: 10.1038/ajg.2013.305.
[35] M. L. Freeman *et al.*, “Complications of endoscopic biliary sphincterotomy,” *N. Engl. J. Med.*, vol. 335, no. 13, pp. 909–918, Sep. 1996, doi: 10.1056/NEJM199609263351301.
[36] B. Kochar *et al.*, “Incidence, severity, and mortality of post-ERCP pancreatitis: a systematic review by using randomized, controlled trials,” *Gastrointest. Endosc.*, vol. 81, no. 1, pp. 143-149.e9, Jan. 2015, doi: 10.1016/j.gie.2014.06.045.
[37] M. A. Almadi, A. Barkun, and M. Martel, “Self-expandable metal stents versus plastic stents for malignant biliary obstruction,” *Gastrointest. Endosc.*, vol. 83, no. 4, pp. 852–853, Apr. 2016, doi: 10.1016/j.gie.2015.10.035.
[38] M. A. Almadi, J. S. Barkun, and A. N. Barkun, “Stenting in Malignant Biliary Obstruction,” *Gastrointest. Endosc. Clin. N. Am.*, vol. 25, no. 4, pp. 691–711, Oct. 2015, doi: 10.1016/j.giec.2015.06.002.
[39] T. B. Gardner *et al.*, “Cost-effectiveness and clinical efficacy of biliary stents in patients undergoing neoadjuvant therapy for pancreatic adenocarcinoma in a randomized controlled trial,” *Gastrointest. Endosc.*, vol. 84, no. 3, pp. 460–466, Sep. 2016, doi: 10.1016/j.gie.2016.02.047.
[40] A. N. Barkun, V. Adam, M. Martel, K. AlNaamani, and P. L. Moses, “Partially covered self-expandable metal stents versus polyethylene stents for malignant biliary obstruction: a cost-effectiveness analysis,” *Can. J. Gastroenterol. Hepatol.*, vol. 29, no. 7, pp. 377–383, Oct. 2015, doi: 10.1155/2015/743417.
[41] S. E. Park *et al.*, “Effectiveness of ultrasound-guided percutaneous transhepatic biliary drainage to reduce radiation exposure: A single-center experience,” *PloS One*, vol. 17, no. 11, p. e0277272, 2022, doi: 10.1371/journal.pone.0277272.
[42] F. Glenn, J. A. Evans, Z. Mujahed, and B. Thorbjarnarson, “Percutaneous Transhepatic Cholangiography,” *Ann. Surg.*, vol. 156, no. 3, pp. 451–460, Sep. 1962.
[43] W. E. A. Saad, M. J. Wallace, J. C. Wojak, S. Kundu, and J. F. Cardella, “Quality improvement guidelines for percutaneous transhepatic cholangiography, biliary drainage, and

percutaneous cholecystostomy," *J. Vasc. Interv. Radiol. JVIR*, vol. 21, no. 6, pp. 789–795, Jun. 2010, doi: 10.1016/j.jvir.2010.01.012.
[44] V. Piñol *et al.*, "Percutaneous self-expanding metal stents versus endoscopic polyethylene endoprostheses for treating malignant biliary obstruction: randomized clinical trial," *Radiology*, vol. 225, no. 1, pp. 27–34, Oct. 2002, doi: 10.1148/radiol.2243011517.
[45] J. S. Laméris *et al.*, "Malignant biliary obstruction: percutaneous use of self-expandable stents," *Radiology*, vol. 179, no. 3, pp. 703–707, Jun. 1991, doi: 10.1148/radiology.179.3.2027978.
[46] E. L. A. Artifon *et al.*, "Surgery or Endoscopy for Palliation of Biliary Obstruction Due to Metastatic Pancreatic Cancer," *Off. J. Am. Coll. Gastroenterol. ACG*, vol. 101, no. 9, p. 2031, Sep. 2006.
[47] H. Asadi *et al.*, "A review of percutaneous transhepatic biliary drainage at a tertiary referral centre," *Clin. Radiol.*, vol. 71, no. 12, p. 1312.e7-1312.e11, Dec. 2016, doi: 10.1016/j.crad.2016.05.013.
[48] M. Sut, R. Kennedy, J. McNamee, A. Collins, and B. Clements, "Long-Term Results of Percutaneous Transhepatic Cholangiographic Drainage for Palliation of Malignant Biliary Obstruction," *J. Palliat. Med.*, vol. 13, no. 11, pp. 1311–1313, Nov. 2010, doi: 10.1089/jpm.2010.0205.
[49] P. A. Heedman, E. Åstradsson, K. Blomquist, and R. Sjödahl, "Palliation of Malignant Biliary Obstruction: Adverse Events are Common after Percutaneous Transhepatic Biliary Drainage," *Scand. J. Surg.*, vol. 107, no. 1, pp. 48–53, Mar. 2018, doi: 10.1177/1457496917731192.
[50] R. Uberoi, N. Das, J. Moss, and I. Robertson, "British Society of Interventional Radiology: Biliary Drainage and Stenting Registry (BDSR)," *Cardiovasc. Intervent. Radiol.*, vol. 35, no. 1, pp. 127–138, Feb. 2012, doi: 10.1007/s00270-011-0103-4.
[51] M. Giovannini, V. Moutardier, C. Pesenti, E. Bories, B. Lelong, and J. R. Delpero, "Endoscopic ultrasound-guided bilioduodenal anastomosis: a new technique for biliary drainage," *Endoscopy*, vol. 33, no. 10, pp. 898–900, Oct. 2001, doi: 10.1055/s-2001-17324.
[52] M. A. Khashab and J. Dewitt, "EUS-guided biliary drainage: is it ready for prime time? Yes!," *Gastrointest. Endosc.*, vol. 78, no. 1, pp. 102–105, Jul. 2013, doi: 10.1016/j.gie.2013.03.004.
[53] U. Hayat *et al.*, "EUS-guided versus percutaneous transhepatic cholangiography biliary drainage for obstructed distal malignant biliary strictures in patients who have failed endoscopic retrograde cholangiopancreatography: A systematic review and meta-analysis," *Endosc. Ultrasound*, vol. 11, no. 1, p. 4, Feb. 2022, doi: 10.4103/EUS-D-21-00009.
[54] H. Moole *et al.*, "Endoscopic versus Percutaneous Biliary Drainage in Palliation of Advanced Malignant Hilar Obstruction: A Meta-Analysis and Systematic Review," *Can. J. Gastroenterol. Hepatol.*, vol. 2016, no. 1, p. 4726078, 2016, doi: 10.1155/2016/4726078.
[55] G. Dell'Anna, T. Ogura, G. Vanella, H. Nishikawa, S. Lakhtakia, and P. G. Arcidiacono, "Endoscopic ultrasound guided biliary interventions," *Best Pract. Res. Clin. Gastroenterol.*, vol. 60–61, p. 101810, Sep. 2022, doi: 10.1016/j.bpg.2022.101810.
[56] R. Kunda *et al.*, "EUS-guided choledochoduodenostomy for malignant distal biliary obstruction using a lumen-apposing fully covered metal stent after failed ERCP," *Surg. Endosc.*, vol. 30, no. 11, pp. 5002–5008, Nov. 2016, doi: 10.1007/s00464-016-4845-6.

[57] J. Jacques *et al.*, “Endoscopic ultrasound-guided choledochoduodenostomy with electrocautery-enhanced lumen-apposing stents: a retrospective analysis,” *Endoscopy*, vol. 51, no. 6, pp. 540–547, Jun. 2019, doi: 10.1055/a-0735-9137.
[58] J. Rees, J. Mytton, F. Evison, K. S. Mangat, P. Patel, and N. Trudgill, “The outcomes of biliary drainage by percutaneous transhepatic cholangiography for the palliation of malignant biliary obstruction in England between 2001 and 2014: a retrospective cohort study,” *BMJ Open*, vol. 10, no. 1, p. e033576, Jan. 2020, doi: 10.1136/bmjopen-2019-033576.
[59] A. Tavakkoli *et al.*, “Survival analysis among unresectable pancreatic adenocarcinoma patients undergoing endoscopic or percutaneous interventions,” *Gastrointest. Endosc.*, vol. 93, no. 1, pp. 154-162.e5, Jan. 2021, doi: 10.1016/j.gie.2020.05.061.
[60] P. Huang, H. Zhang, X.-F. Zhang, W. Lv, and S. Lou, “Comparison of Endoscopic Ultrasonography Guided Biliary Drainage and Percutaneous Transhepatic Biliary Drainage in the Management of Malignant Obstructive Jaundice After Failed ERCP,” *Surg. Laparosc. Endosc. Percutan. Tech.*, vol. 27, no. 6, pp. e127–e131, Dec. 2017, doi: 10.1097/SLE.0000000000000485.
[61] E. Troncone *et al.*, “Malignant gastric outlet obstruction: Which is the best therapeutic option?,” *World J. Gastroenterol.*, vol. 26, no. 16, pp. 1847–1860, Apr. 2020, doi: 10.3748/wjg.v26.i16.1847.
[62] J. Klose, U. Ronellenfitsch, and J. Kleeff, “Management problems in patients with pancreatic cancer from a surgeon’s perspective,” *Semin. Oncol.*, vol. 48, no. 1, pp. 76–83, Feb. 2021, doi: 10.1053/j.seminoncol.2021.02.008.
[63] I. S. Papanikolaou and P. D. Siersema, “Gastric Outlet Obstruction: Current Status and Future Directions,” *Gut Liver*, vol. 16, no. 5, pp. 667–675, Sep. 2022, doi: 10.5009/gnl210327.
[64] A. Shah, A. Fehmi, and T. J. Savides, “Increased rates of duodenal obstruction in pancreatic cancer patients receiving modern medical management,” *Dig. Dis. Sci.*, vol. 59, no. 9, pp. 2294–2298, Sep. 2014, doi: 10.1007/s10620-014-3170-y.
[65] B. Brimhall and D. G. Adler, “Enteral Stents for Malignant Gastric Outlet Obstruction,” *Gastrointest. Endosc. Clin. N. Am.*, vol. 21, no. 3, pp. 389–403, Jul. 2011, doi: 10.1016/j.giec.2011.04.002.
[66] A. Kouanda, K. Binmoeller, C. Hamerski, A. Nett, J. Bernabe, and R. Watson, “Endoscopic ultrasound-guided gastroenterostomy versus open surgical gastrojejunostomy: clinical outcomes and cost effectiveness analysis,” *Surg. Endosc.*, vol. 35, no. 12, pp. 7058–7067, Dec. 2021, doi: 10.1007/s00464-020-08221-z.
[67] A. Jaroenlapnopparat, C. Jani, H. Singh, D. C. Marshall, J. D. Salciccioli, and J. Shalhoub, “An estimate of the burden of pancreatic cancer globally and its comparison with different WHO regions using Global Burden of Disease Database: A retrospective population-based analysis.,” *J. Clin. Oncol.*, May 2023, doi: 10.1200/JCO.2023.41.16_suppl.e16321.
[68] G. Lippi and C. Mattiuzzi, “The global burden of pancreatic cancer,” *Arch. Med. Sci. AMS*, vol. 16, no. 4, pp. 820–824, May 2020, doi: 10.5114/aoms.2020.94845.
[69] I. Mintziras, M. Miligkos, S. Wächter, J. Manoharan, and D. K. Bartsch, “Palliative surgical bypass is superior to palliative endoscopic stenting in patients with malignant gastric outlet obstruction: systematic review and meta-analysis,” *Surg. Endosc.*, vol. 33, no. 10, pp. 3153–3164, Oct. 2019, doi: 10.1007/s00464-019-06955-z.

[70] "Gastrojejunostomy - What is Laparoscopic Gastrojejunostomy?" Accessed: May 15, 2024. [Online]. Available: https://www.drrpadmakumar.com/blog/laparoscopic-gastrojejunostomy/
[71] J. L. Salluzzo and K. E. Roberts, "Laparoscopic Gastrojejunostomy," in *Operative Dictations in General and Vascular Surgery*, J. J. Hoballah, C. E. H. Scott-Conner, and H. S. Chong, Eds., Cham: Springer International Publishing, 2017, pp. 75–76. doi: 10.1007/978-3-319-44797-1_21.
[72] D. F. Sigmon and P. P. Lopez, "Gastrojejunostomy," in *StatPearls*, Treasure Island (FL): StatPearls Publishing, 2024. Accessed: May 15, 2024. [Online]. Available: http://www.ncbi.nlm.nih.gov/books/NBK560493/
[73] S. M. Singh, W. P. Longmire, and H. A. Reber, "Surgical palliation for pancreatic cancer. The UCLA experience.," *Ann. Surg.*, vol. 212, no. 2, pp. 132–139, Aug. 1990.
[74] E. Upchurch, M. Ragusa, and R. Cirocchi, "Stent placement versus surgical palliation for adults with malignant gastric outlet obstruction," *Cochrane Database Syst. Rev.*, vol. 5, no. 5, p. CD012506, May 2018, doi: 10.1002/14651858.CD012506.pub2.
[75] U. F. O. Themes, "Intervention for Gastric Outlet and Duodenal Obstruction," Radiology Key. Accessed: May 15, 2024. [Online]. Available: https://radiologykey.com/intervention-for-gastric-outlet-and-duodenal-obstruction/
[76] J. Hong *et al.*, "Comparison of gastrojejunostomy to endoscopic stenting for gastric outlet obstruction: An updated Systematic Review and Meta-analysis," *Am. J. Surg.*, vol. 223, no. 6, pp. 1067–1078, Jun. 2022, doi: 10.1016/j.amjsurg.2021.10.038.
[77] S. M. Jeurnink *et al.*, "Surgical gastrojejunostomy or endoscopic stent placement for the palliation of malignant gastric outlet obstruction (SUSTENT study): a multicenter randomized trial," *Gastrointest. Endosc.*, vol. 71, no. 3, pp. 490–499, Mar. 2010, doi: 10.1016/j.gie.2009.09.042.
[78] O. Ahmed, J. H. Lee, C. C. Thompson, and A. Faulx, "AGA Clinical Practice Update on the Optimal Management of the Malignant Alimentary Tract Obstruction: Expert Review," *Clin. Gastroenterol. Hepatol. Off. Clin. Pract. J. Am. Gastroenterol. Assoc.*, vol. 19, no. 9, pp. 1780–1788, Sep. 2021, doi: 10.1016/j.cgh.2021.03.046.
[79] S. R. Friedberg and J. Lachter, "Endoscopic ultrasound: Current roles and future directions," *World J. Gastrointest. Endosc.*, vol. 9, no. 10, pp. 499–505, Oct. 2017, doi: 10.4253/wjge.v9.i10.499.
[80] P. Vilmann, G. K. Jacobsen, F. W. Henriksen, and S. Hancke, "Endoscopic ultrasonography with guided fine needle aspiration biopsy in pancreatic disease," *Gastrointest. Endosc.*, vol. 38, no. 2, pp. 172–173, Mar. 1992, doi: 10.1016/S0016-5107(92)70385-X.
[81] G. Vanella *et al.*, "Current landscape of therapeutic EUS: Changing paradigms in gastroenterology practice," *Endosc. Ultrasound*, vol. 12, no. 1, pp. 16–28, Sep. 2022, doi: 10.4103/EUS-D-21-00177.
[82] T. Itoi *et al.*, "Prospective evaluation of endoscopic ultrasonography-guided double-balloon-occluded gastrojejunostomy bypass (EPASS) for malignant gastric outlet obstruction," *Gut*, vol. 65, no. 2, pp. 193–195, Feb. 2016, doi: 10.1136/gutjnl-2015-310348.
[83] A. Fritscher-Ravens, C. A. Mosse, D. Mukherjee, T. Mills, P.-O. Park, and C. P. Swain, "Transluminal endosurgery: single lumen access anastomotic device for flexible endoscopy," *Gastrointest. Endosc.*, vol. 58, no. 4, pp. 585–591, Oct. 2003, doi: 10.1016/s0016-5107(03)02006-6.

[84] K. F. Binmoeller and J. N. Shah, “Endoscopic ultrasound-guided gastroenterostomy using novel tools designed for transluminal therapy: a porcine study,” *Endoscopy*, vol. 44, no. 5, pp. 499–503, May 2012, doi: 10.1055/s-0032-1309382.
[85] M. Rimbaș, K. W. Lau, G. Tripodi, G. Rizzatti, and A. Larghi, “The Role of Luminal Apposing Metal Stents on the Treatment of Malignant and Benign Gastric Outlet Obstruction,” *Diagnostics*, vol. 13, no. 21, Art. no. 21, Jan. 2023, doi: 10.3390/diagnostics13213308.
[86] T. R. McCarty, R. Garg, C. C. Thompson, and T. Rustagi, “Efficacy and safety of EUS-guided gastroenterostomy for benign and malignant gastric outlet obstruction: a systematic review and meta-analysis,” *Endosc. Int. Open*, vol. 7, no. 11, pp. E1474–E1482, Nov. 2019, doi: 10.1055/a-0996-8178.
[87] A. Y. B. Teoh *et al.*, “Endoscopic ultrasonography-guided gastroenterostomy versus uncovered duodenal metal stenting for unresectable malignant gastric outlet obstruction (DRA-GOO): a multicentre randomised controlled trial,” *Lancet Gastroenterol. Hepatol.*, vol. 9, no. 2, pp. 124–132, Feb. 2024, doi: 10.1016/S2468-1253(23)00242-X.
[88] D. Moher *et al.*, “Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement,” *Syst. Rev.*, vol. 4, no. 1, p. 1, Jan. 2015, doi: 10.1186/2046-4053-4-1.
[89] L. A. Stewart *et al.*, “Preferred Reporting Items for Systematic Review and Meta-Analyses of individual participant data: the PRISMA-IPD Statement,” *JAMA*, vol. 313, no. 16, pp. 1657–1665, Apr. 2015, doi: 10.1001/jama.2015.3656.
[90] “Cochrane Handbook for Systematic Reviews of Interventions.” Accessed: Jul. 09, 2024. [Online]. Available: https://training.cochrane.org/handbook
[91] G. H. Guyatt *et al.*, “GRADE: an emerging consensus on rating quality of evidence and strength of recommendations,” *BMJ*, vol. 336, no. 7650, pp. 924–926, Apr. 2008, doi: 10.1136/bmj.39489.470347.AD.
[92] P. B. Cotton *et al.*, “A lexicon for endoscopic adverse events: report of an ASGE workshop,” *Gastrointest. Endosc.*, vol. 71, no. 3, pp. 446–454, Mar. 2010, doi: 10.1016/j.gie.2009.10.027.
[93] J. Y. Bang, U. Navaneethan, M. Hasan, R. Hawes, and S. Varadarajulu, “Stent placement by EUS or ERCP for primary biliary decompression in pancreatic cancer: a randomized trial (with videos),” *Gastrointest. Endosc.*, vol. 88, no. 1, pp. 9–17, Jul. 2018, doi: 10.1016/j.gie.2018.03.012.
[94] M. A. Almadi, A. Barkun, and M. Martel, “Plastic vs. Self-Expandable Metal Stents for Palliation in Malignant Biliary Obstruction: A Series of Meta-Analyses,” *Am. J. Gastroenterol.*, vol. 112, no. 2, pp. 260–273, Feb. 2017, doi: 10.1038/ajg.2016.512.
[95] S. Kiriyama *et al.*, “Tokyo Guidelines 2018: diagnostic criteria and severity grading of acute cholangitis (with videos),” *J. Hepato-Biliary-Pancreat. Sci.*, vol. 25, no. 1, pp. 17–30, Jan. 2018, doi: 10.1002/jhbp.512.
[96] G. B. Stewart, D. G. Altman, L. M. Askie, L. Duley, M. C. Simmonds, and L. A. Stewart, “Statistical analysis of individual participant data meta-analyses: a comparison of methods and recommendations for practice,” *PloS One*, vol. 7, no. 10, p. e46042, 2012, doi: 10.1371/journal.pone.0046042.
[97] B. A. Holt *et al.*, “Biliary drainage: role of EUS guidance,” *Gastrointest. Endosc.*, vol. 83, no. 1, pp. 160–165, Jan. 2016, doi: 10.1016/j.gie.2015.06.019.

[98] V. Palmieri *et al.*, “EUS-guided biliary drainage in malignant distal biliary obstruction: An international survey to identify barriers of technology implementation,” *Endosc. Ultrasound*, vol. 12, no. 1, pp. 104–110, 2023, doi: 10.4103/EUS-D-21-00137.
[99] J. S. Barkun *et al.*, “Evaluation and stages of surgical innovations,” *Lancet Lond. Engl.*, vol. 374, no. 9695, pp. 1089–1096, Sep. 2009, doi: 10.1016/S0140-6736(09)61083-7.
[100] M. Bronswijk *et al.*, “Same-session double EUS-guided bypass versus surgical gastroenterostomy and hepaticojejunostomy: an international multicenter comparison,” *Gastrointest. Endosc.*, vol. 98, no. 2, pp. 225-236.e1, Aug. 2023, doi: 10.1016/j.gie.2023.03.019.
[101] L. A. Stewart and J. F. Tierney, “To IPD or not to IPD?: Advantages and Disadvantages of Systematic Reviews Using Individual Patient Data,” *Eval. Health Prof.*, vol. 25, no. 1, pp. 76–97, Mar. 2002, doi: 10.1177/0163278702025001006.
[102] K. D. Lillemoe *et al.*, “Is prophylactic gastrojejunostomy indicated for unresectable periampullary cancer? A prospective randomized trial,” *Ann. Surg.*, vol. 230, no. 3, pp. 322–328; discussion 328-330, Sep. 1999, doi: 10.1097/00000658-199909000-00005.
[103] T. Conroy *et al.*, “FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer,” *N. Engl. J. Med.*, vol. 364, no. 19, pp. 1817–1825, May 2011, doi: 10.1056/NEJMoa1011923.
[104] S. Gourgou-Bourgade *et al.*, “Impact of FOLFIRINOX Compared With Gemcitabine on Quality of Life in Patients With Metastatic Pancreatic Cancer: Results From the PRODIGE 4/ACCORD 11 Randomized Trial,” *J. Clin. Oncol.*, vol. 31, no. 1, pp. 23–29, Jan. 2013, doi: 10.1200/JCO.2012.44.4869.
[105] N. T. van Heek, “Palliative treatment in ‘peri’-pancreatic carcinoma : stenting or surgical therapy ?,” 2002.
[106] J. Espinel, S. Vivas, F. Muñoz, F. Jorquera, and J. L. Olcoz, “Palliative treatment of malignant obstruction of gastric outlet using an endoscopically placed enteral Wallstent,” *Dig. Dis. Sci.*, vol. 46, no. 11, pp. 2322–2324, Nov. 2001, doi: 10.1023/a:1012378509762.
[107] S. Y. Oh *et al.*, “Survival and clinical outcome after endoscopic duodenal stent placement for malignant gastric outlet obstruction: comparison of pancreatic cancer and nonpancreatic cancer,” *Gastrointest. Endosc.*, vol. 82, no. 3, pp. 460-468.e2, Sep. 2015, doi: 10.1016/j.gie.2015.01.026.

2.2. Manuscript 2

Incidence of Malignant Gastric Outlet Obstruction in Unresectable Pancreatic Cancer: Contemporary Data in Pancreatic Cancer Patients Undergoing FOLFIRINOX Treatment

Authors: Yeganeh Rostamianmoghaddam[1,2], Jeff Barkun[1], Abdulrahman Qatomah[1], Clara Long[1], Yen-I Chen[1, 2]

Affiliations:

1. Division of Gastroenterology and Hepatology, McGill University Health Centre, Montreal, QC, Canada
2. Division of Experimental Medicine, Department of Medicine, McGill University Faculty of Medicine and Health Sciences, Montreal, Canada

Correspondence:

Yen-I Chen, MD

Assistant Professor of Medicine, Division of Gastroenterology and Hepatology

McGill University Health Center, McGill University, Montreal, QC, Canada

Conflict of Interest: Yen-I Chen is a consultant for Boston Scientific, has received research funding from Boston Scientific and is the co-founder of Chess Medical Inc.

Funding: Canadian Institute of Health research (CIHR)

Keywords: Malignant gastric outlet obstruction (MGOO), Pancreatic head cancer, Unresectable pancreatic cancer, FOLFIRINOX treatment, Endoscopy Ultrasound -guided gastro enterostomy (EUS-GE), Duodenal stent placement, Surgical gastrojejunostomy (SJ), Enteral stenting (ES)

Abstract

Background: Malignant gastric outlet obstruction (MGOO) is a common and morbid complication of periampullary cancer. There is limited epidemiological data on its incidence and outcomes, especially in unresectable cancer patients undergoing chemotherapy. Determining the incidence of MGOO is crucial for developing effective management strategies, including prophylactic endoscopic or surgical treatment.

Aim: This study aimed to ascertain the incidence of MGOO in unresectable pancreatic cancer patients undergoing FOLFIRINOX, evaluate the clinical outcomes of MGOO and identify potential predictors.

Methods: This was a retrospective, single-center study of consecutive pancreatic head cancer patients treated with FOLFIRINOX from January 1, 2017, to December 31, 2022. Exclusion: pancreatic cancer in the neck, body, and/or tail of the pancreas, predominantly cystic cancer, oncological resection, prophylactic surgical gastrojejunostomy, or metastatic cancer to the pancreas.

Results: The study included 44 patients (40.90% female, mean age 59.30 ± 8.50 years). No significant demographic differences were found between patients who developed MGOO and those who did not. Pancreatic head cancer patients had a 36.36% incidence of MGOO. Patients without MGOO had shorter unplanned hospitalizations (mean ± SD: 20.80 ± 18.30 days) compared to those with MGOO (mean ± SD: 50.33 ± 41.22 days; $p = 0.02$). The mean number of FOLFIRINOX cycles was 7.20 (±5.43) for patients without MGOO and 8.10 (±5.81) for those with MGOO ($p = 0.62$).

Conclusion: MGOO was observed in 36% of patients with advanced pancreatic head cancer who underwent FOLFIRINOX treatment, resulting in extended hospitalizations. Additional research is necessary to enhance the management strategies for MGOO.

Introduction

Malignant gastric outlet obstruction (MGOO) is a medical condition characterized by the mechanical blockage of the pylorus or duodenum by a tumor, leading to substantial morbidity and it frequently occurs in patients with periampullary cancer, specifically pancreatic head cancer.[9], [61][1, 2] The rate of MGOO has been described to be 20-30% in patients with cancers located in the head of the pancreas.[102][3] Patients suffering from MGOO typically face symptoms such as nausea and vomiting which may subsequently be accompanied by abdominal pain, loss of body mass, inadequate nourishment, dehydration resulting from insufficient oral intake, diminished quality of life, and disruptions in chemotherapy treatment.[9], [65][2, 4] As a result of advancements in chemotherapy, particularly the use of FOLFIRINOX (leucovorin, fluorouracil, irinotecan, and oxaliplatin), patients suffering from pancreatic cancer are achieving extended periods of survival.[103], [104][5, 6] However, there is limited contemporary data on the incidence and outcomes of MGOO in this patient population. This study aimed to address this gap by determining the incidence of MGOO and evaluating clinical outcomes and predictors in patients undergoing FOLFIRINOX treatment for unresectable pancreatic head cancer.

Methods

Study Design

This retrospective, single-center study included consecutive patients with unresectable pancreatic head cancer treated with FOLFIRINOX who did not undergo surgical resection between January 1, 2017, and December 31, 2022. Patients were identified using the FOLFIRINOX oncology pharmacy database at the McGill University Health Centre (MUHC). The study protocol was approval by the local research ethics board.

Study population

- **Inclusion and Exclusion Criteria**

Patients were considered for inclusion if they had a diagnosis of solid pancreatic adenocarcinoma located in the head of the pancreas and were treated with FOLFIRINOX chemotherapy. Patients were excluded if they had pancreatic cancer located in the neck, body, and/or tail of the pancreas, had predominantly cystic cancer, had oncological resection, had prophylactic surgical gastrojejunostomy, or had metastatic cancer to the pancreas. Patients were identified using the FOLFIRINOX oncology pharmacy database at the MUHC

Endpoints:

The primary endpoint was the rate of malignant gastric outlet obstruction (MGOO), which was defined as the presence of clinical symptoms of MGOO that were confirmed through axial imaging and/or endoscopy. Secondary endpoints included the duration of hospitalization for MGOO and the proportion of cases successfully managed through endoscopic or surgical methods.

- **Data Collection**

Data were retrieved on patient demographics, tumor characteristics, FOLFIRINOX treatment details, incidence and management of MGOO, and clinical outcomes. We defined clinical outcomes as the ability to tolerate oral intake without vomiting, and classified adverse events (AE) according to the American Society for Gastrointestinal Endoscopy lexicon for endoscopic adverse events (ASGE lexicon).

Statistical Analysis

All data analysis was performed using the R programming language. Chi-square tests and Fisher's exact tests were used to evaluate the differences between groups for categorical data, such as sex, cancer stage, intervention technical success, clinical success, adverse events, and GOO recurrence. Categorical variables were characterized using proportions and percentages. The continuous variables, such as age, number of FOLFIRINOX cycles, time from diagnosis to death, and length of hospitalization, were examined using two-sample t-tests and Wilcoxon Rank-Sum tests when applicable. The continuous variables were represented as the mean with the standard deviation (SD) and/or the median with the interquartile range (IQR). Prior to conducting the statistical tests, variance tests were performed to verify the equality of variances, thus ensuring the appropriate application of the tests. A stepwise multivariable logistic regression analysis was conducted to identify independent predictors of MGOO. The level of confidence for statistical significance was established at a p-value of less than 0.05.

Results

A total of 44 patients with pancreatic head cancer were included (40.90% female, mean age 59.30 ± 8.50 years) (Table 4). Patients who never developed malignant gastric outlet obstruction (MGOO) had a mean age of 61.00 (±7.90) years, while those who developed MGOO had a mean age of 56.30 (±9.10) years ($p = 0.082$) (Table 4). There were no significant sex distribution differences between the groups, with 39.30% female and 60.70% male in the no MGOO group compared to 43.75% female and 56.25% male in the MGOO group ($p = 0.772$) (Table 4). No statistically significant differences in tumor staging were observed between patients who developed MGOO and those who never developed MGOO: 6.80% Borderlines, 40.90% Metastatic, and 52.30% Locally advanced (Table 4). The incidence of MGOO in patients with

pancreatic head cancer was 36.36% (Table 4). The mean number of FOLFIRINOX cycles received was 7.20 (±5.43) for patients who never developed MGOO and 8.10 (±5.81) for patients with MGOO (p = 0.615) (Table 4). Patients who never developed MGOO experienced significantly shorter unplanned hospitalizations (mean ± SD: 20.80 ± 18.30 days) compared to those with MGOO (mean ± SD: 50.33 ± 41.22 days; p = 0.017) (Table 5). The number of unplanned visits from diagnosis to death was also analyzed, showing a mean of 2.80 (±2.10) visits for patients who never developed MGOO and 5.10 (±4.00) visits for those with MGOO, although this difference was not statistically significant (p = 0.051) (Table 5). Among patients who developed MGOO (n = 16), management strategies included EUS-guided gastrojejunostomy (43.75%), duodenal stent placement (31.25%), and medical management (25%) (Table 6). Technical success was achieved in 91.66% of cases overall, with 100% success in the EUS-guided gastrojejunostomy group and 80% success in the duodenal stent group (p = 0.417) (Table 6). Overall clinical success rates were 83.33%, with 85.71% for EUS-guided gastrojejunostomy and 80% for duodenal stent placement. The overall MGOO recurrence rate was 30.77%, with 14.29% in the EUS-guided gastrojejunostomy group and 60.00% in the duodenal stent group (p = 0.222) (Table 6).

Table 4. Baseline Characteristics of study patients (Manuscript 2)

Demographics	Total (N=44)	No GOO (n=28, 63.64%)	GOO (n=16, 36.36%)	P-Value
Age, years, Mean (±SD)	59.30 (±8.50)	61.00 (±7.90)	56.30 (±9.10)	**0.082**
Sex, n (%)				
Female	18 (40.90)	11 (39.30)	7 (43.75)	**0.772**
Male	26 (59.09)	17 (60.70)	9 (56.25)	
Cancer stage, n (%)				
Metastatic	18 (40.90)	13 (46.40)	5 (31.30)	**0.325**
Locally advanced	23 (52.30)	14 (50.00)	9 (56.25)	**0.690**
Borderline resectable	3 (6.80)	1 (3.60)	2 (12.50)	**0.543**
Number of Folfirinox cycles, Mean (±SD)	7.50 (±5.52)	7.20 (±5.43)	8.10 (±5.81)	**0.6152**

Table 5. Patient Outcomes (Manuscript 2)

Outcome	Total (N=40)	No GOO (n=25, 62.50%)	GOO (n=15, 37.50%)	p-value
Unplanned hospitalization (days)				**0.0175**
Mean (±SD)	31.90 (±32.20)	20.80 (±18.30)	50.33 (±41.22)	
Median (Q1, Q2)	23.50 (11.25, 48.50)	15.00 (7.00, 29.00)	37.00 (18.50, 63.00)	
unplanned visits (days)				**0.0516**
Mean (±SD)	3.70 (±3.10)	2.80 (±2.10)	5.10 (±4.00)	
Median (Q1, Q2)	3.00 (2.00, 4.25)	3.00 (1.00, 3.00)	4.00 (2.50, 5.50)	

Table 6. Description of the management of gastric outlet obstruction (GOO): EUS-GJ vs Duodenal Stent (Manuscript 2)

Management	Total (N=12)	EUS-GJ (n=7, 43.75%)	Duodenal Stent (n=5, 31.25%)	Medical RX (n=4, 25%)	p-value
Technical Success, n (%)					**0.417**
Yes	11 (91.66)	7 (100)	4 (80)		
No	1 (8.33)	0	1 (20)		
Clinical Success, n (%)					**1**
Yes	10 (83.33)	6 (85.71)	4 (80)		
No	2 (16.67)	1 (14.29)	1 (20)		
GOO Hospitalization,					**0.326**
Mean (±SD)	14.69 (±14.94)	21.43 (±20.55)	11.00 (±20.55)		
Median (Q1, Q3)	11.00 (5.75, 16.50)	11.00 (10.50, 22.00)	11.00(6.00, 15.00)		
Adverse Events, n (%)	4 (33.33%)	2 (28.57%)	2 (40.00%)		
GOO recurrence, n (%)					**0.222**
Yes	4 (30.77)	1 (14.29)	3 (60.00)	0	
No	9 (69.23)	6 (85.71)	2 (40.00)	4 (100)	

Discussion

MGOO frequently presents in patients with primary or metastatic malignancies affecting the upper gastrointestinal tract, resulting in decreased survival rates and significant morbidity.[102], [105], [106], [107][3, 7-9] Patients who developed MGOO generally experience symptoms such as nausea and vomiting, which may be followed by abdominal pain, weight loss, malnutrition, dehydration due to inadequate oral intake, reduced quality of life, and interruptions in chemotherapy treatment.[9], [65][2, 4] Therefore, ensuring adequate palliation by re-establishing oral alimentation is a fundamental objective in the management of these patients. With advancements in chemotherapy, particularly the utilization of FOLFIRINOX (leucovorin, fluorouracil, irinotecan, and oxaliplatin), individuals with pancreatic cancer are experiencing increased survival rates.[103], [104][5, 6] Consequently, managing MGOO becomes even more critical to maintaining quality of life during extended survival periods.

Our results from this single-center study support our hypothesis that contemporary patients with unresectable pancreatic head cancer undergoing FOLFIRINOX treatment have very high rates of MGOO (36%). The presence of MGOO was strongly correlated with prolonged hospitalizations, suggesting a substantial effect on patient morbidity and increased costs for both the healthcare system and patients. The occurrence of MGOO highlights the importance of careful monitoring and potentially taking preventing measures, such as performing prophylactic surgical gastrojejunostomy or endoscopic stenting, to reduce the impact of this complication.

The results of our study demonstrate that EUS-guided gastrojejunostomy has a high rate of success both technically and clinically and it could be emerging as the ideal way for managing MGOO. Nevertheless, the frequency of recurrence, particularly in the duodenal stent group, highlights the need for continuous monitoring and possible further interventions. Although EUS-GE has

improved the management of MGOO, it is still not adequate as patients are often presenting after the obstruction has already occurred. This underscores the need for improved strategies and early intervention to prevent the occurrence of MGOO and improve the quality of life for this patient population.

Despite the promising outcomes, our study has several notable limitations. The primary limitation is that the study was conducted at a single center, which might limit the generality of the findings to other settings, especially smaller or community-based healthcare organizations. In addition, our study design was retrospective, which inherently carries design limitations and potential biases. To minimize selection bias, we included consecutive patients; however, this approach does not completely eliminate the risk. Moreover, our study focused exclusively on patients with unresectable pancreatic head cancer, limiting the applicability of the findings to other patient populations or types of cancers. The absence of dedicated accessories for performing EUS-GE in many centers remains a significant impediment to its widespread adoption.[84][10] Despite these limitations, our findings underscore the critical need for early intervention and improved management strategies for MGOO in patients undergoing FOLFIRINOX treatment for pancreatic head cancer. Prophylactic EUS-GE may represent a valuable strategy to prevent the occurrence of MGOO, thereby improving patient outcomes and quality of life. A multi-center RCT assessing the potential benefit of prophylactic EUS-GE is currently underway by our group (please look up clinical trials.gov and cite the trial number).

Conclusion

Our contemporary data indicates a significant incidence of malignant gastric outlet obstruction (MGOO) at a rate of 36% in patients with advanced pancreatic head cancer who are receiving FOLFIRINOX treatment. MGOO was found to be associated with extended durations of

hospitalization in comparison to patients who did not develop MGOO. Although EUS-GE has improved the management of MGOO, it is still not adequate, as patients are presenting after obstruction occurs. Our study highlights the substantial negative consequences of MGOO, emphasizing the need for additional research to better understand its management including prophylactic measures such as prophylactic surgical gastrojejunostomy or even prophylactic endoscopic stenting to enhance the quality of life for this patient population.

References

[1] M. Porta *et al.*, “Exocrine pancreatic cancer: symptoms at presentation and their relation to tumour site and stage,” *Clin. Transl. Oncol. Off. Publ. Fed. Span. Oncol. Soc. Natl. Cancer Inst. Mex.*, vol. 7, no. 5, pp. 189–197, Jun. 2005, doi: 10.1007/BF02712816.

[2] M. Fernandez Y Viesca and M. Arvanitakis, “Early Diagnosis And Management Of Malignant Distal Biliary Obstruction: A Review On Current Recommendations And Guidelines,” *Clin. Exp. Gastroenterol.*, vol. 12, pp. 415–432, Nov. 2019, doi: 10.2147/CEG.S195714.

[3] N. S. Abraham, J. S. Barkun, and A. N. Barkun, “Palliation of malignant biliary obstruction: a prospective trial examining impact on quality of life,” *Gastrointest. Endosc.*, vol. 56, no. 6, pp. 835–841, Dec. 2002, doi: 10.1067/mge.2002.129868.

[4] B. J. Elmunzer *et al.*, “ACG Clinical Guideline: Diagnosis and Management of Biliary Strictures,” *Am. J. Gastroenterol.*, vol. 118, no. 3, pp. 405–426, Mar. 2023, doi: 10.14309/ajg.0000000000002190.

[5] W. H. Paik *et al.*, “EUS-Guided Biliary Drainage Versus ERCP for the Primary Palliation of Malignant Biliary Obstruction: A Multicenter Randomized Clinical Trial,” *Am. J. Gastroenterol.*, vol. 113, no. 7, pp. 987–997, Jul. 2018, doi: 10.1038/s41395-018-0122-8.

[6] A. Y. B. Teoh *et al.*, “EUS-Guided Choledocho-duodenostomy Using Lumen Apposing Stent Versus ERCP With Covered Metallic Stents in Patients With Unresectable Malignant Distal Biliary Obstruction: A Multicenter Randomized Controlled Trial (DRA-MBO Trial),” *Gastroenterology*, vol. 165, no. 2, pp. 473-482.e2, Aug. 2023, doi: 10.1053/j.gastro.2023.04.016.

[7] Y.-I. Chen *et al.*, “Endoscopic Ultrasound-Guided Biliary Drainage of First Intent With a Lumen-Apposing Metal Stent vs Endoscopic Retrograde Cholangiopancreatography in Malignant Distal Biliary Obstruction: A Multicenter Randomized Controlled Study (ELEMENT Trial),” *Gastroenterology*, vol. 165, no. 5, pp. 1249-1261.e5, Nov. 2023, doi: 10.1053/j.gastro.2023.07.024.

[8] K. W. Lau, M. Rimbaș, G. Tripodi, and A. Larghi, “Endoscopic Ultrasound Biliary Drainage in Pancreatic Cancer,” *J. Gastrointestin. Liver Dis.*, vol. 32, no. 4, Art. no. 4, Dec. 2023, doi: 10.15403/jgld-4922.

[9] Y.-I. Chen *et al.*, “EUS-guided gastroenterostomy is comparable to enteral stenting with fewer re-interventions in malignant gastric outlet obstruction,” *Surg. Endosc.*, vol. 31, no. 7, pp. 2946–2952, Jul. 2017, doi: 10.1007/s00464-016-5311-1.

[10] S.-B. Bian, W.-S. Shen, H.-Q. Xi, B. Wei, and L. Chen, “Palliative Therapy for Gastric Outlet Obstruction Caused by Unresectable Gastric Cancer: A Meta-analysis Comparison of Gastrojejunostomy with Endoscopic Stenting,” *Chin. Med. J. (Engl.)*, vol. 129, no. 9, pp. 1113–1121, May 2016, doi: 10.4103/0366-6999.180530.

[11] S. L. H. Cheung and A. Y. B. Teoh, “Optimal Management of Gastric Outlet Obstruction in Unresectable Malignancies,” *Gut Liver*, vol. 16, no. 2, pp. 190–197, Mar. 2022, doi: 10.5009/gnl210010.

[12] T. Itoi *et al.*, “Technical review of endoscopic ultrasonography-guided gastroenterostomy in 2017,” *Dig. Endosc.*, vol. 29, no. 4, pp. 495–502, 2017, doi: 10.1111/den.12794.

[13] A. Dormann, S. Meisner, N. Verin, and A. Wenk Lang, “Self-expanding metal stents for gastroduodenal malignancies: systematic review of their clinical effectiveness,” *Endoscopy*, vol. 36, no. 6, pp. 543–550, Jun. 2004, doi: 10.1055/s-2004-814434.

[14] M. Khashab *et al.*, "Enteral stenting versus gastrojejunostomy for palliation of malignant gastric outlet obstruction," *Surg. Endosc.*, vol. 27, no. 6, pp. 2068–2075, Jun. 2013, doi: 10.1007/s00464-012-2712-7.
[15] C. Miller *et al.*, "EUS-guided gastroenterostomy vs. surgical gastrojejunostomy and enteral stenting for malignant gastric outlet obstruction: a meta-analysis," *Endosc. Int. Open*, vol. 11, no. 7, pp. E660–E672, Jul. 2023, doi: 10.1055/a-2098-2570.
[16] Y.-I. Chen *et al.*, "EUS-guided gastroenterostomy: a multicenter study comparing the direct and balloon-assisted techniques," *Gastrointest. Endosc.*, vol. 87, no. 5, pp. 1215–1221, May 2018, doi: 10.1016/j.gie.2017.07.030.
[17] A. Singh, A. Gelrud, and B. Agarwal, "Biliary strictures: diagnostic considerations and approach," *Gastroenterol. Rep.*, vol. 3, no. 1, pp. 22–31, Feb. 2015, doi: 10.1093/gastro/gou072.
[18] T. Hennedige, W. Neo, and S. Venkatesh, "Imaging of malignancies of the biliary tract-an update," *Cancer Imaging*, vol. 14, Apr. 2014, doi: 10.1186/1470-7330-14-14.
[19] L. Rahib, B. D. Smith, R. Aizenberg, A. B. Rosenzweig, J. M. Fleshman, and L. M. Matrisian, "Projecting cancer incidence and deaths to 2030: the unexpected burden of thyroid, liver, and pancreas cancers in the United States," *Cancer Res.*, vol. 74, no. 11, pp. 2913–2921, Jun. 2014, doi: 10.1158/0008-5472.CAN-14-0155.
[20] S. I. Ilyas, S. A. Khan, C. L. Hallemeier, R. K. Kelley, and G. J. Gores, "Cholangiocarcinoma — evolving concepts and therapeutic strategies," *Nat. Rev. Clin. Oncol.*, vol. 15, no. 2, pp. 95–111, Feb. 2018, doi: 10.1038/nrclinonc.2017.157.
[21] B. I. Choi, J. K. Han, S. T. Hong, and K. H. Lee, "Clonorchiasis and Cholangiocarcinoma: Etiologic Relationship and Imaging Diagnosis," *Clin. Microbiol. Rev.*, vol. 17, no. 3, pp. 540–552, Jul. 2004, doi: 10.1128/CMR.17.3.540-552.2004.
[22] Y. Shaib and H. B. El-Serag, "The epidemiology of cholangiocarcinoma," *Semin. Liver Dis.*, vol. 24, no. 2, pp. 115–125, May 2004, doi: 10.1055/s-2004-828889.
[23] R. Hundal and E. A. Shaffer, "Gallbladder cancer: epidemiology and outcome," *Clin. Epidemiol.*, vol. 6, pp. 99–109, Mar. 2014, doi: 10.2147/CLEP.S37357.
[24] A. Sharma, K. L. Sharma, A. Gupta, A. Yadav, and A. Kumar, "Gallbladder cancer epidemiology, pathogenesis and molecular genetics: Recent update," *World J. Gastroenterol.*, vol. 23, no. 22, pp. 3978–3998, Jun. 2017, doi: 10.3748/wjg.v23.i22.3978.
[25] A. Duffy *et al.*, "Gallbladder cancer (GBC): 10-year experience at Memorial Sloan-Kettering Cancer Centre (MSKCC)," *J. Surg. Oncol.*, vol. 98, no. 7, pp. 485–489, Dec. 2008, doi: 10.1002/jso.21141.
[26] D. H. Ahn and T. Bekaii-Saab, "Ampullary Cancer: An Overview," *Am. Soc. Clin. Oncol. Educ. Book ASCO Am. Soc. Clin. Oncol. Meet.*, pp. 112–115, 2014, doi: 10.14694/EdBook_AM.2014.34.112.
[27] W.-C. Liao *et al.*, "Adjuvant treatments for resected pancreatic adenocarcinoma: a systematic review and network meta-analysis," *Lancet Oncol.*, vol. 14, no. 11, pp. 1095–1103, Oct. 2013, doi: 10.1016/S1470-2045(13)70388-7.
[28] R. A. Kozarek, "The Past, Present, and Future of Endoscopic Retrograde Cholangiopancreatography," *Gastroenterol. Hepatol.*, vol. 13, no. 10, p. 620, Oct. 2017.
[29] A. Canakis and M. Kahaleh, "Endoscopic palliation of malignant biliary obstruction," *World J. Gastrointest. Endosc.*, vol. 14, no. 10, pp. 581–596, Oct. 2022, doi: 10.4253/wjge.v14.i10.581.

[30] J.-M. Dumonceau *et al.*, “Endoscopic biliary stenting: Indications, choice of stents, and results: European Society of Gastrointestinal Endoscopy (ESGE) Clinical Guideline - Updated October 2017,” *Endoscopy*, vol. 50, no. 9, pp. 910–930, 2018, doi: 10.1055/a-0659-9864.
[31] H. Isayama *et al.*, “A prospective randomised study of ‘covered’ versus ‘uncovered’ diamond stents for the management of distal malignant biliary obstruction,” *Gut*, vol. 53, no. 5, pp. 729–734, 2004, doi: 10.1136/gut.2003.018945.
[32] J. J. Telford *et al.*, “A randomized trial comparing uncovered and partially covered self-expandable metal stents in the palliation of distal malignant biliary obstruction,” *Gastrointest. Endosc.*, vol. 72, no. 5, pp. 907–914, Nov. 2010, doi: 10.1016/j.gie.2010.08.021.
[33] E. Kullman *et al.*, “Covered versus uncovered self-expandable nitinol stents in the palliative treatment of malignant distal biliary obstruction: results from a randomized, multicenter study,” *Gastrointest. Endosc.*, vol. 72, no. 5, pp. 915–923, Nov. 2010, doi: 10.1016/j.gie.2010.07.036.
[34] M. Kitano *et al.*, “Covered Self-Expandable Metal Stents With an Anti-Migration System Improve Patency Duration Without Increased Complications Compared With Uncovered Stents for Distal Biliary Obstruction Caused by Pancreatic Carcinoma: A Randomized Multicenter Trial,” *Off. J. Am. Coll. Gastroenterol. ACG*, vol. 108, no. 11, p. 1713, Nov. 2013, doi: 10.1038/ajg.2013.305.
[35] M. L. Freeman *et al.*, “Complications of endoscopic biliary sphincterotomy,” *N. Engl. J. Med.*, vol. 335, no. 13, pp. 909–918, Sep. 1996, doi: 10.1056/NEJM199609263351301.
[36] B. Kochar *et al.*, “Incidence, severity, and mortality of post-ERCP pancreatitis: a systematic review by using randomized, controlled trials,” *Gastrointest. Endosc.*, vol. 81, no. 1, pp. 143-149.e9, Jan. 2015, doi: 10.1016/j.gie.2014.06.045.
[37] M. A. Almadi, A. Barkun, and M. Martel, “Self-expandable metal stents versus plastic stents for malignant biliary obstruction,” *Gastrointest. Endosc.*, vol. 83, no. 4, pp. 852–853, Apr. 2016, doi: 10.1016/j.gie.2015.10.035.
[38] M. A. Almadi, J. S. Barkun, and A. N. Barkun, “Stenting in Malignant Biliary Obstruction,” *Gastrointest. Endosc. Clin. N. Am.*, vol. 25, no. 4, pp. 691–711, Oct. 2015, doi: 10.1016/j.giec.2015.06.002.
[39] T. B. Gardner *et al.*, “Cost-effectiveness and clinical efficacy of biliary stents in patients undergoing neoadjuvant therapy for pancreatic adenocarcinoma in a randomized controlled trial,” *Gastrointest. Endosc.*, vol. 84, no. 3, pp. 460–466, Sep. 2016, doi: 10.1016/j.gie.2016.02.047.
[40] A. N. Barkun, V. Adam, M. Martel, K. AlNaamani, and P. L. Moses, “Partially covered self-expandable metal stents versus polyethylene stents for malignant biliary obstruction: a cost-effectiveness analysis,” *Can. J. Gastroenterol. Hepatol.*, vol. 29, no. 7, pp. 377–383, Oct. 2015, doi: 10.1155/2015/743417.
[41] S. E. Park *et al.*, “Effectiveness of ultrasound-guided percutaneous transhepatic biliary drainage to reduce radiation exposure: A single-center experience,” *PloS One*, vol. 17, no. 11, p. e0277272, 2022, doi: 10.1371/journal.pone.0277272.
[42] F. Glenn, J. A. Evans, Z. Mujahed, and B. Thorbjarnarson, “Percutaneous Transhepatic Cholangiography,” *Ann. Surg.*, vol. 156, no. 3, pp. 451–460, Sep. 1962.
[43] W. E. A. Saad, M. J. Wallace, J. C. Wojak, S. Kundu, and J. F. Cardella, “Quality improvement guidelines for percutaneous transhepatic cholangiography, biliary drainage, and

percutaneous cholecystostomy," *J. Vasc. Interv. Radiol. JVIR*, vol. 21, no. 6, pp. 789–795, Jun. 2010, doi: 10.1016/j.jvir.2010.01.012.
[44] V. Piñol *et al.*, "Percutaneous self-expanding metal stents versus endoscopic polyethylene endoprostheses for treating malignant biliary obstruction: randomized clinical trial," *Radiology*, vol. 225, no. 1, pp. 27–34, Oct. 2002, doi: 10.1148/radiol.2243011517.
[45] J. S. Laméris *et al.*, "Malignant biliary obstruction: percutaneous use of self-expandable stents," *Radiology*, vol. 179, no. 3, pp. 703–707, Jun. 1991, doi: 10.1148/radiology.179.3.2027978.
[46] E. L. A. Artifon *et al.*, "Surgery or Endoscopy for Palliation of Biliary Obstruction Due to Metastatic Pancreatic Cancer," *Off. J. Am. Coll. Gastroenterol. ACG*, vol. 101, no. 9, p. 2031, Sep. 2006.
[47] H. Asadi *et al.*, "A review of percutaneous transhepatic biliary drainage at a tertiary referral centre," *Clin. Radiol.*, vol. 71, no. 12, p. 1312.e7-1312.e11, Dec. 2016, doi: 10.1016/j.crad.2016.05.013.
[48] M. Sut, R. Kennedy, J. McNamee, A. Collins, and B. Clements, "Long-Term Results of Percutaneous Transhepatic Cholangiographic Drainage for Palliation of Malignant Biliary Obstruction," *J. Palliat. Med.*, vol. 13, no. 11, pp. 1311–1313, Nov. 2010, doi: 10.1089/jpm.2010.0205.
[49] P. A. Heedman, E. Åstradsson, K. Blomquist, and R. Sjödahl, "Palliation of Malignant Biliary Obstruction: Adverse Events are Common after Percutaneous Transhepatic Biliary Drainage," *Scand. J. Surg.*, vol. 107, no. 1, pp. 48–53, Mar. 2018, doi: 10.1177/1457496917731192.
[50] R. Uberoi, N. Das, J. Moss, and I. Robertson, "British Society of Interventional Radiology: Biliary Drainage and Stenting Registry (BDSR)," *Cardiovasc. Intervent. Radiol.*, vol. 35, no. 1, pp. 127–138, Feb. 2012, doi: 10.1007/s00270-011-0103-4.
[51] M. Giovannini, V. Moutardier, C. Pesenti, E. Bories, B. Lelong, and J. R. Delpero, "Endoscopic ultrasound-guided bilioduodenal anastomosis: a new technique for biliary drainage," *Endoscopy*, vol. 33, no. 10, pp. 898–900, Oct. 2001, doi: 10.1055/s-2001-17324.
[52] M. A. Khashab and J. Dewitt, "EUS-guided biliary drainage: is it ready for prime time? Yes!," *Gastrointest. Endosc.*, vol. 78, no. 1, pp. 102–105, Jul. 2013, doi: 10.1016/j.gie.2013.03.004.
[53] U. Hayat *et al.*, "EUS-guided versus percutaneous transhepatic cholangiography biliary drainage for obstructed distal malignant biliary strictures in patients who have failed endoscopic retrograde cholangiopancreatography: A systematic review and meta-analysis," *Endosc. Ultrasound*, vol. 11, no. 1, p. 4, Feb. 2022, doi: 10.4103/EUS-D-21-00009.
[54] H. Moole *et al.*, "Endoscopic versus Percutaneous Biliary Drainage in Palliation of Advanced Malignant Hilar Obstruction: A Meta-Analysis and Systematic Review," *Can. J. Gastroenterol. Hepatol.*, vol. 2016, no. 1, p. 4726078, 2016, doi: 10.1155/2016/4726078.
[55] G. Dell'Anna, T. Ogura, G. Vanella, H. Nishikawa, S. Lakhtakia, and P. G. Arcidiacono, "Endoscopic ultrasound guided biliary interventions," *Best Pract. Res. Clin. Gastroenterol.*, vol. 60–61, p. 101810, Sep. 2022, doi: 10.1016/j.bpg.2022.101810.
[56] R. Kunda *et al.*, "EUS-guided choledochoduodenostomy for malignant distal biliary obstruction using a lumen-apposing fully covered metal stent after failed ERCP," *Surg. Endosc.*, vol. 30, no. 11, pp. 5002–5008, Nov. 2016, doi: 10.1007/s00464-016-4845-6.

[57] J. Jacques *et al.*, “Endoscopic ultrasound-guided choledochoduodenostomy with electrocautery-enhanced lumen-apposing stents: a retrospective analysis,” *Endoscopy*, vol. 51, no. 6, pp. 540–547, Jun. 2019, doi: 10.1055/a-0735-9137.
[58] J. Rees, J. Mytton, F. Evison, K. S. Mangat, P. Patel, and N. Trudgill, “The outcomes of biliary drainage by percutaneous transhepatic cholangiography for the palliation of malignant biliary obstruction in England between 2001 and 2014: a retrospective cohort study,” *BMJ Open*, vol. 10, no. 1, p. e033576, Jan. 2020, doi: 10.1136/bmjopen-2019-033576.
[59] A. Tavakkoli *et al.*, “Survival analysis among unresectable pancreatic adenocarcinoma patients undergoing endoscopic or percutaneous interventions,” *Gastrointest. Endosc.*, vol. 93, no. 1, pp. 154-162.e5, Jan. 2021, doi: 10.1016/j.gie.2020.05.061.
[60] P. Huang, H. Zhang, X.-F. Zhang, W. Lv, and S. Lou, “Comparison of Endoscopic Ultrasonography Guided Biliary Drainage and Percutaneous Transhepatic Biliary Drainage in the Management of Malignant Obstructive Jaundice After Failed ERCP,” *Surg. Laparosc. Endosc. Percutan. Tech.*, vol. 27, no. 6, pp. e127–e131, Dec. 2017, doi: 10.1097/SLE.0000000000000485.
[61] E. Troncone *et al.*, “Malignant gastric outlet obstruction: Which is the best therapeutic option?,” *World J. Gastroenterol.*, vol. 26, no. 16, pp. 1847–1860, Apr. 2020, doi: 10.3748/wjg.v26.i16.1847.
[62] J. Klose, U. Ronellenfitsch, and J. Kleeff, “Management problems in patients with pancreatic cancer from a surgeon’s perspective,” *Semin. Oncol.*, vol. 48, no. 1, pp. 76–83, Feb. 2021, doi: 10.1053/j.seminoncol.2021.02.008.
[63] I. S. Papanikolaou and P. D. Siersema, “Gastric Outlet Obstruction: Current Status and Future Directions,” *Gut Liver*, vol. 16, no. 5, pp. 667–675, Sep. 2022, doi: 10.5009/gnl210327.
[64] A. Shah, A. Fehmi, and T. J. Savides, “Increased rates of duodenal obstruction in pancreatic cancer patients receiving modern medical management,” *Dig. Dis. Sci.*, vol. 59, no. 9, pp. 2294–2298, Sep. 2014, doi: 10.1007/s10620-014-3170-y.
[65] B. Brimhall and D. G. Adler, “Enteral Stents for Malignant Gastric Outlet Obstruction,” *Gastrointest. Endosc. Clin. N. Am.*, vol. 21, no. 3, pp. 389–403, Jul. 2011, doi: 10.1016/j.giec.2011.04.002.
[66] A. Kouanda, K. Binmoeller, C. Hamerski, A. Nett, J. Bernabe, and R. Watson, “Endoscopic ultrasound-guided gastroenterostomy versus open surgical gastrojejunostomy: clinical outcomes and cost effectiveness analysis,” *Surg. Endosc.*, vol. 35, no. 12, pp. 7058–7067, Dec. 2021, doi: 10.1007/s00464-020-08221-z.
[67] A. Jaroenlapnopparat, C. Jani, H. Singh, D. C. Marshall, J. D. Salciccioli, and J. Shalhoub, “An estimate of the burden of pancreatic cancer globally and its comparison with different WHO regions using Global Burden of Disease Database: A retrospective population-based analysis.,” *J. Clin. Oncol.*, May 2023, doi: 10.1200/JCO.2023.41.16_suppl.e16321.
[68] G. Lippi and C. Mattiuzzi, “The global burden of pancreatic cancer,” *Arch. Med. Sci. AMS*, vol. 16, no. 4, pp. 820–824, May 2020, doi: 10.5114/aoms.2020.94845.
[69] I. Mintziras, M. Miligkos, S. Wächter, J. Manoharan, and D. K. Bartsch, “Palliative surgical bypass is superior to palliative endoscopic stenting in patients with malignant gastric outlet obstruction: systematic review and meta-analysis,” *Surg. Endosc.*, vol. 33, no. 10, pp. 3153–3164, Oct. 2019, doi: 10.1007/s00464-019-06955-z.

[70] "Gastrojejunostomy - What is Laparoscopic Gastrojejunostomy?" Accessed: May 15, 2024. [Online]. Available: https://www.drrpadmakumar.com/blog/laparoscopic-gastrojejunostomy/
[71] J. L. Salluzzo and K. E. Roberts, "Laparoscopic Gastrojejunostomy," in *Operative Dictations in General and Vascular Surgery*, J. J. Hoballah, C. E. H. Scott-Conner, and H. S. Chong, Eds., Cham: Springer International Publishing, 2017, pp. 75–76. doi: 10.1007/978-3-319-44797-1_21.
[72] D. F. Sigmon and P. P. Lopez, "Gastrojejunostomy," in *StatPearls*, Treasure Island (FL): StatPearls Publishing, 2024. Accessed: May 15, 2024. [Online]. Available: http://www.ncbi.nlm.nih.gov/books/NBK560493/
[73] S. M. Singh, W. P. Longmire, and H. A. Reber, "Surgical palliation for pancreatic cancer. The UCLA experience.," *Ann. Surg.*, vol. 212, no. 2, pp. 132–139, Aug. 1990.
[74] E. Upchurch, M. Ragusa, and R. Cirocchi, "Stent placement versus surgical palliation for adults with malignant gastric outlet obstruction," *Cochrane Database Syst. Rev.*, vol. 5, no. 5, p. CD012506, May 2018, doi: 10.1002/14651858.CD012506.pub2.
[75] U. F. O. Themes, "Intervention for Gastric Outlet and Duodenal Obstruction," Radiology Key. Accessed: May 15, 2024. [Online]. Available: https://radiologykey.com/intervention-for-gastric-outlet-and-duodenal-obstruction/
[76] J. Hong *et al.*, "Comparison of gastrojejunostomy to endoscopic stenting for gastric outlet obstruction: An updated Systematic Review and Meta-analysis," *Am. J. Surg.*, vol. 223, no. 6, pp. 1067–1078, Jun. 2022, doi: 10.1016/j.amjsurg.2021.10.038.
[77] S. M. Jeurnink *et al.*, "Surgical gastrojejunostomy or endoscopic stent placement for the palliation of malignant gastric outlet obstruction (SUSTENT study): a multicenter randomized trial," *Gastrointest. Endosc.*, vol. 71, no. 3, pp. 490–499, Mar. 2010, doi: 10.1016/j.gie.2009.09.042.
[78] O. Ahmed, J. H. Lee, C. C. Thompson, and A. Faulx, "AGA Clinical Practice Update on the Optimal Management of the Malignant Alimentary Tract Obstruction: Expert Review," *Clin. Gastroenterol. Hepatol. Off. Clin. Pract. J. Am. Gastroenterol. Assoc.*, vol. 19, no. 9, pp. 1780–1788, Sep. 2021, doi: 10.1016/j.cgh.2021.03.046.
[79] S. R. Friedberg and J. Lachter, "Endoscopic ultrasound: Current roles and future directions," *World J. Gastrointest. Endosc.*, vol. 9, no. 10, pp. 499–505, Oct. 2017, doi: 10.4253/wjge.v9.i10.499.
[80] P. Vilmann, G. K. Jacobsen, F. W. Henriksen, and S. Hancke, "Endoscopic ultrasonography with guided fine needle aspiration biopsy in pancreatic disease," *Gastrointest. Endosc.*, vol. 38, no. 2, pp. 172–173, Mar. 1992, doi: 10.1016/S0016-5107(92)70385-X.
[81] G. Vanella *et al.*, "Current landscape of therapeutic EUS: Changing paradigms in gastroenterology practice," *Endosc. Ultrasound*, vol. 12, no. 1, pp. 16–28, Sep. 2022, doi: 10.4103/EUS-D-21-00177.
[82] T. Itoi *et al.*, "Prospective evaluation of endoscopic ultrasonography-guided double-balloon-occluded gastrojejunostomy bypass (EPASS) for malignant gastric outlet obstruction," *Gut*, vol. 65, no. 2, pp. 193–195, Feb. 2016, doi: 10.1136/gutjnl-2015-310348.
[83] A. Fritscher-Ravens, C. A. Mosse, D. Mukherjee, T. Mills, P.-O. Park, and C. P. Swain, "Transluminal endosurgery: single lumen access anastomotic device for flexible endoscopy," *Gastrointest. Endosc.*, vol. 58, no. 4, pp. 585–591, Oct. 2003, doi: 10.1016/s0016-5107(03)02006-6.

[84] K. F. Binmoeller and J. N. Shah, “Endoscopic ultrasound-guided gastroenterostomy using novel tools designed for transluminal therapy: a porcine study,” *Endoscopy*, vol. 44, no. 5, pp. 499–503, May 2012, doi: 10.1055/s-0032-1309382.
[85] M. Rimbaș, K. W. Lau, G. Tripodi, G. Rizzatti, and A. Larghi, “The Role of Luminal Apposing Metal Stents on the Treatment of Malignant and Benign Gastric Outlet Obstruction,” *Diagnostics*, vol. 13, no. 21, Art. no. 21, Jan. 2023, doi: 10.3390/diagnostics13213308.
[86] T. R. McCarty, R. Garg, C. C. Thompson, and T. Rustagi, “Efficacy and safety of EUS-guided gastroenterostomy for benign and malignant gastric outlet obstruction: a systematic review and meta-analysis,” *Endosc. Int. Open*, vol. 7, no. 11, pp. E1474–E1482, Nov. 2019, doi: 10.1055/a-0996-8178.
[87] A. Y. B. Teoh *et al.*, “Endoscopic ultrasonography-guided gastroenterostomy versus uncovered duodenal metal stenting for unresectable malignant gastric outlet obstruction (DRA-GOO): a multicentre randomised controlled trial,” *Lancet Gastroenterol. Hepatol.*, vol. 9, no. 2, pp. 124–132, Feb. 2024, doi: 10.1016/S2468-1253(23)00242-X.
[88] D. Moher *et al.*, “Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement,” *Syst. Rev.*, vol. 4, no. 1, p. 1, Jan. 2015, doi: 10.1186/2046-4053-4-1.
[89] L. A. Stewart *et al.*, “Preferred Reporting Items for Systematic Review and Meta-Analyses of individual participant data: the PRISMA-IPD Statement,” *JAMA*, vol. 313, no. 16, pp. 1657–1665, Apr. 2015, doi: 10.1001/jama.2015.3656.
[90] “Cochrane Handbook for Systematic Reviews of Interventions.” Accessed: Jul. 09, 2024. [Online]. Available: https://training.cochrane.org/handbook
[91] G. H. Guyatt *et al.*, “GRADE: an emerging consensus on rating quality of evidence and strength of recommendations,” *BMJ*, vol. 336, no. 7650, pp. 924–926, Apr. 2008, doi: 10.1136/bmj.39489.470347.AD.
[92] P. B. Cotton *et al.*, “A lexicon for endoscopic adverse events: report of an ASGE workshop,” *Gastrointest. Endosc.*, vol. 71, no. 3, pp. 446–454, Mar. 2010, doi: 10.1016/j.gie.2009.10.027.
[93] J. Y. Bang, U. Navaneethan, M. Hasan, R. Hawes, and S. Varadarajulu, “Stent placement by EUS or ERCP for primary biliary decompression in pancreatic cancer: a randomized trial (with videos),” *Gastrointest. Endosc.*, vol. 88, no. 1, pp. 9–17, Jul. 2018, doi: 10.1016/j.gie.2018.03.012.
[94] M. A. Almadi, A. Barkun, and M. Martel, “Plastic vs. Self-Expandable Metal Stents for Palliation in Malignant Biliary Obstruction: A Series of Meta-Analyses,” *Am. J. Gastroenterol.*, vol. 112, no. 2, pp. 260–273, Feb. 2017, doi: 10.1038/ajg.2016.512.
[95] S. Kiriyama *et al.*, “Tokyo Guidelines 2018: diagnostic criteria and severity grading of acute cholangitis (with videos),” *J. Hepato-Biliary-Pancreat. Sci.*, vol. 25, no. 1, pp. 17–30, Jan. 2018, doi: 10.1002/jhbp.512.
[96] G. B. Stewart, D. G. Altman, L. M. Askie, L. Duley, M. C. Simmonds, and L. A. Stewart, “Statistical analysis of individual participant data meta-analyses: a comparison of methods and recommendations for practice,” *PloS One*, vol. 7, no. 10, p. e46042, 2012, doi: 10.1371/journal.pone.0046042.
[97] B. A. Holt *et al.*, “Biliary drainage: role of EUS guidance,” *Gastrointest. Endosc.*, vol. 83, no. 1, pp. 160–165, Jan. 2016, doi: 10.1016/j.gie.2015.06.019.

[98] V. Palmieri *et al.*, “EUS-guided biliary drainage in malignant distal biliary obstruction: An international survey to identify barriers of technology implementation,” *Endosc. Ultrasound*, vol. 12, no. 1, pp. 104–110, 2023, doi: 10.4103/EUS-D-21-00137.
[99] J. S. Barkun *et al.*, “Evaluation and stages of surgical innovations,” *Lancet Lond. Engl.*, vol. 374, no. 9695, pp. 1089–1096, Sep. 2009, doi: 10.1016/S0140-6736(09)61083-7.
[100] M. Bronswijk *et al.*, “Same-session double EUS-guided bypass versus surgical gastroenterostomy and hepaticojejunostomy: an international multicenter comparison,” *Gastrointest. Endosc.*, vol. 98, no. 2, pp. 225-236.e1, Aug. 2023, doi: 10.1016/j.gie.2023.03.019.
[101] L. A. Stewart and J. F. Tierney, “To IPD or not to IPD?: Advantages and Disadvantages of Systematic Reviews Using Individual Patient Data,” *Eval. Health Prof.*, vol. 25, no. 1, pp. 76–97, Mar. 2002, doi: 10.1177/0163278702025001006.
[102] K. D. Lillemoe *et al.*, “Is prophylactic gastrojejunostomy indicated for unresectable periampullary cancer? A prospective randomized trial,” *Ann. Surg.*, vol. 230, no. 3, pp. 322–328; discussion 328-330, Sep. 1999, doi: 10.1097/00000658-199909000-00005.
[103] T. Conroy *et al.*, “FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer,” *N. Engl. J. Med.*, vol. 364, no. 19, pp. 1817–1825, May 2011, doi: 10.1056/NEJMoa1011923.
[104] S. Gourgou-Bourgade *et al.*, “Impact of FOLFIRINOX Compared With Gemcitabine on Quality of Life in Patients With Metastatic Pancreatic Cancer: Results From the PRODIGE 4/ACCORD 11 Randomized Trial,” *J. Clin. Oncol.*, vol. 31, no. 1, pp. 23–29, Jan. 2013, doi: 10.1200/JCO.2012.44.4869.
[105] N. T. van Heek, “Palliative treatment in ‘peri’-pancreatic carcinoma : stenting or surgical therapy ?,” 2002.
[106] J. Espinel, S. Vivas, F. Muñoz, F. Jorquera, and J. L. Olcoz, “Palliative treatment of malignant obstruction of gastric outlet using an endoscopically placed enteral Wallstent,” *Dig. Dis. Sci.*, vol. 46, no. 11, pp. 2322–2324, Nov. 2001, doi: 10.1023/a:1012378509762.
[107] S. Y. Oh *et al.*, “Survival and clinical outcome after endoscopic duodenal stent placement for malignant gastric outlet obstruction: comparison of pancreatic cancer and nonpancreatic cancer,” *Gastrointest. Endosc.*, vol. 82, no. 3, pp. 460-468.e2, Sep. 2015, doi: 10.1016/j.gie.2015.01.026.

3. Chapter 3: Discussion and Conclusions

3.1. Summary

This concluding chapter integrates the findings from the original research manuscripts, which investigate innovative endoscopic procedures for managing complications in periampullary cancers. The chapter summarizes and discusses the results, addresses study limitations, outlines future research directions, and presents conclusions.

Our IPD and aggregate meta-analysis of RCTs highlights the advantages of EUS-guided choledochoduodenostomy (EUS-CDSL) using a lumen apposing metal stent (LAMS) over the conventional endoscopic retrograde cholangiopancreatography (ERCP) for patients with malignant distal biliary obstruction (MDBO). The data demonstrates that EUS-CDSL has higher rates of technical success and shorter procedure times compared to ERCP, while maintaining a comparable level of safety. This suggests that EUS-CDSL could be considered as the preferred initial treatment option.[6], [7][1, 2]

Our retrospective study addresses the occurrence of malignant gastric outlet obstruction (MGOO) in patients with unresectable pancreatic head cancer who underwent FOLFIRINOX chemotherapy. The prevalence of MGOO in this population is significant (36%), and it had a notable effect on patient morbidity[9], [65], [103][3-5] and the length of hospital stays. This study underlines the importance of implementing efficient management strategies, such as prophylactic surgical gastrojejunostomy or endoscopic stenting, to reduce the negative impact of MGOO[9], [65][4, 5] and improve patient outcomes.

3.2. Discussion

The findings of these studies have significant implications for the treatment of biliary and gastric outlet obstructions in patients with advanced peri-ampullary cancers.

The findings of our IPD and aggregate meta-analysis of RCTs highlight the capacity of EUS-CDSL as an initial therapeutic approach for MDBO. The procedure's superior technical success rates and shorter procedure times in comparison to ERCP establish it as a practical alternative, particularly for patients who are incapable of undergoing immediate curative surgery. This shift could lead to improved patient outcomes in clinical settings.

The results of our single-center retrospective study demonstrate an increased risk of MGOO in patients with pancreatic head cancer who received FOLFIRINOX chemotherapy. This highlights the importance of implementing preventive management strategies. Prophylactic measures could significantly reduce the morbidity and healthcare burden associated with this complication, improving the quality of life for these patients.

3.3. Limitations

Both studies have limitations that need to be considered. Our IPD and aggregate meta-analyses is limited by the fact that it only includes two randomized controlled trials (RCTs) and has a low occurrence of severe or fatal adverse events, which limit the robustness and precision of the findings. Although the American Society of Gastrointestinal Endoscopy (ASGE) recognized EUS-biliary drainage as a research priority in 2008, it has not been widely adopted in clinical practice outside of specialized centers in the last 15 years.[97][6] The absence of particular equipment has made EUS-biliary drainage technically challenging, while the limited availability of reliable data has additionally restricted its widespread adoption.[98][7] The cost of LAMS has been identified as

a major barrier to the widespread clinical adoption of EUS-CDSL.[98][7] Currently, there is a lack of cost-effectiveness data to determine if the increased efficiency and technical success of EUS-CDSL can compensate for the higher initial cost of LAMS. The presence of this significant barrier is expected to persist and restrict the clinical application of EUS-CDSL, emphasizing the necessity for alternative device choices in order to decrease expenses. Additionally, it is important to note that the studies included in the meta-analysis did not involve patients who showed clinical signs of malignant gastric outlet obstruction (MGOO) and patients with resectable cancers. Although there are limitations, both studies have significant strengths. High-quality RCTs and IPD and aggregate meta-analytical methods strengthen our meta-analysis. IPD enabled a homogenous endpoint definition, improving data precision, directness, and certainty. When possible, an IPD meta-analysis is the gold standard for systematic reviews. Undoubtedly, an IPD meta-analysis is widely regarded as the most reliable method for conducting systematic reviews, whenever it is practicable to perform one.[101][8] Our data on location, patient demographics, and health care systems is more generalizable due to the two trials' multicenter design across continents. Inclusion of operators with limited EUS-CDSL experience greatly improves generalizability. Only two RCTs were found in our IPD meta-analysis, preventing a hierarchical study level analysis. A wide confidence interval was due to the low event rate of the primary endpoint of severe or fatal adverse events. However, the consistent findings across both trials make it unlikely that other RCTs will be conducted, making the current analysis the most authoritative data-driven conclusions to inform EUS-CDSL guidelines for MDBO patients who are not candidates for upfront pancreaticoduodenectomy.

Our single-center retrospective study, conducted at MUHC, is susceptible to biases and has a limited focus on patients with unresectable pancreatic head cancer. The study was conducted at a

single center, which may potentially restrict the applicability of the results to different contexts, particularly smaller or community-oriented healthcare institutions. Furthermore, our study employed a retrospective design, which inherently entails certain limitations and potential biases. In order to reduce selection bias, we opted to include consecutive patients, but this does not eliminate risk. Furthermore, our research specifically targeted individuals with unresectable pancreatic head cancer, which limits the relevance of the results to different groups of patients or cancer types. Although this study has limitations, it offers contemporary data, which is a strong point, regarding the occurrence of MGOO in patients receiving FOLFIRINOX chemotherapy. It emphasizes the significance of early intervention and preventative management strategies.

3.4. Future Directions

Future investigations need to focus on expanding the scope and scale of these studies to validate findings across diverse patient populations and healthcare settings. Cost-effectiveness analyses are needed to evaluate the economic viability of adopting EUS-CDSL as a first-line therapy for malignant distal biliary obstruction (MDBO). Establishing predictive models to identify high-risk patients for MGOO at an early stage of their treatment could provide valuable information to apply prophylactic interventions. Prospective studies should examine the long-term effects and assess how these interventions affect patient quality of life and overall survival.

3.5.Conclusions

In conclusion, our IPD and aggregate meta-analyses of RCTs have indicated that EUS-CDSL is a safe, efficient, and technically superior first-line alternative to ERCP for managing patients with malignant distal biliary obstruction who are unable to have upfront curative surgical resection. This evidence strongly supports the implementation of EUS-CDSL. Additionally, the high rate of malignant gastric outlet obstruction in pancreatic cancer patients undergoing FOLFIRINOX in our

retrospective study emphasizes the need for preventive treatment to reduce morbidity and improve outcomes. These findings recommend early intervention and comprehensive treatment strategies for cancer patients with biliary and gastric outlet obstructions to improve patient care and quality of life.

References

[1] A. Y. B. Teoh *et al.*, "EUS-Guided Choledocho-duodenostomy Using Lumen Apposing Stent Versus ERCP With Covered Metallic Stents in Patients With Unresectable Malignant Distal Biliary Obstruction: A Multicenter Randomized Controlled Trial (DRA-MBO Trial)," *Gastroenterology*, vol. 165, no. 2, pp. 473-482.e2, Aug. 2023, doi: 10.1053/j.gastro.2023.04.016.

[2] Y.-I. Chen *et al.*, "Endoscopic Ultrasound-Guided Biliary Drainage of First Intent With a Lumen-Apposing Metal Stent vs Endoscopic Retrograde Cholangiopancreatography in Malignant Distal Biliary Obstruction: A Multicenter Randomized Controlled Study (ELEMENT Trial)," *Gastroenterology*, vol. 165, no. 5, pp. 1249-1261.e5, Nov. 2023, doi: 10.1053/j.gastro.2023.07.024.

[3] T. Conroy *et al.*, "FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer," *N Engl J Med*, vol. 364, no. 19, pp. 1817–1825, May 2011, doi: 10.1056/NEJMoa1011923.

[4] Y.-I. Chen *et al.*, "EUS-guided gastroenterostomy is comparable to enteral stenting with fewer re-interventions in malignant gastric outlet obstruction," *Surg Endosc*, vol. 31, no. 7, pp. 2946–2952, Jul. 2017, doi: 10.1007/s00464-016-5311-1.

[5] B. Brimhall and D. G. Adler, "Enteral Stents for Malignant Gastric Outlet Obstruction," *Gastrointestinal Endoscopy Clinics of North America*, vol. 21, no. 3, pp. 389–403, Jul. 2011, doi: 10.1016/j.giec.2011.04.002.

[6] B. A. Holt *et al.*, "Biliary drainage: role of EUS guidance," *Gastrointest Endosc*, vol. 83, no. 1, pp. 160–165, Jan. 2016, doi: 10.1016/j.gie.2015.06.019.

[7] V. Palmieri *et al.*, "EUS-guided biliary drainage in malignant distal biliary obstruction: An international survey to identify barriers of technology implementation," *Endosc Ultrasound*, vol. 12, no. 1, pp. 104–110, 2023, doi: 10.4103/EUS-D-21-00137.

[8] L. A. Stewart and J. F. Tierney, "To IPD or not to IPD?: Advantages and Disadvantages of Systematic Reviews Using Individual Patient Data," *Eval Health Prof*, vol. 25, no. 1, pp. 76–97, Mar. 2002, doi: 10.1177/0163278702025001006.

Master Reference List

[1] M. Porta *et al.*, “Exocrine pancreatic cancer: symptoms at presentation and their relation to tumour site and stage,” *Clin. Transl. Oncol. Off. Publ. Fed. Span. Oncol. Soc. Natl. Cancer Inst. Mex.*, vol. 7, no. 5, pp. 189–197, Jun. 2005, doi: 10.1007/BF02712816.

[2] M. Fernandez Y Viesca and M. Arvanitakis, “Early Diagnosis And Management Of Malignant Distal Biliary Obstruction: A Review On Current Recommendations And Guidelines,” *Clin. Exp. Gastroenterol.*, vol. 12, pp. 415–432, Nov. 2019, doi: 10.2147/CEG.S195714.

[3] N. S. Abraham, J. S. Barkun, and A. N. Barkun, “Palliation of malignant biliary obstruction: a prospective trial examining impact on quality of life,” *Gastrointest. Endosc.*, vol. 56, no. 6, pp. 835–841, Dec. 2002, doi: 10.1067/mge.2002.129868.

[4] B. J. Elmunzer *et al.*, “ACG Clinical Guideline: Diagnosis and Management of Biliary Strictures,” *Am. J. Gastroenterol.*, vol. 118, no. 3, pp. 405–426, Mar. 2023, doi: 10.14309/ajg.0000000000002190.

[5] W. H. Paik *et al.*, “EUS-Guided Biliary Drainage Versus ERCP for the Primary Palliation of Malignant Biliary Obstruction: A Multicenter Randomized Clinical Trial,” *Am. J. Gastroenterol.*, vol. 113, no. 7, pp. 987–997, Jul. 2018, doi: 10.1038/s41395-018-0122-8.

[6] A. Y. B. Teoh *et al.*, “EUS-Guided Choledocho-duodenostomy Using Lumen Apposing Stent Versus ERCP With Covered Metallic Stents in Patients With Unresectable Malignant Distal Biliary Obstruction: A Multicenter Randomized Controlled Trial (DRA-MBO Trial),” *Gastroenterology*, vol. 165, no. 2, pp. 473-482.e2, Aug. 2023, doi: 10.1053/j.gastro.2023.04.016.

[7] Y.-I. Chen *et al.*, “Endoscopic Ultrasound-Guided Biliary Drainage of First Intent With a Lumen-Apposing Metal Stent vs Endoscopic Retrograde Cholangiopancreatography in Malignant Distal Biliary Obstruction: A Multicenter Randomized Controlled Study (ELEMENT Trial),” *Gastroenterology*, vol. 165, no. 5, pp. 1249-1261.e5, Nov. 2023, doi: 10.1053/j.gastro.2023.07.024.

[8] K. W. Lau, M. Rimbaș, G. Tripodi, and A. Larghi, “Endoscopic Ultrasound Biliary Drainage in Pancreatic Cancer,” *J. Gastrointestin. Liver Dis.*, vol. 32, no. 4, Art. no. 4, Dec. 2023, doi: 10.15403/jgld-4922.

[9] Y.-I. Chen *et al.*, “EUS-guided gastroenterostomy is comparable to enteral stenting with fewer re-interventions in malignant gastric outlet obstruction,” *Surg. Endosc.*, vol. 31, no. 7, pp. 2946–2952, Jul. 2017, doi: 10.1007/s00464-016-5311-1.

[10] S.-B. Bian, W.-S. Shen, H.-Q. Xi, B. Wei, and L. Chen, “Palliative Therapy for Gastric Outlet Obstruction Caused by Unresectable Gastric Cancer: A Meta-analysis Comparison of Gastrojejunostomy with Endoscopic Stenting,” *Chin. Med. J. (Engl.)*, vol. 129, no. 9, pp. 1113–1121, May 2016, doi: 10.4103/0366-6999.180530.

[11] S. L. H. Cheung and A. Y. B. Teoh, “Optimal Management of Gastric Outlet Obstruction in Unresectable Malignancies,” *Gut Liver*, vol. 16, no. 2, pp. 190–197, Mar. 2022, doi: 10.5009/gnl210010.

[12] T. Itoi *et al.*, “Technical review of endoscopic ultrasonography-guided gastroenterostomy in 2017,” *Dig. Endosc.*, vol. 29, no. 4, pp. 495–502, 2017, doi: 10.1111/den.12794.

[13] A. Dormann, S. Meisner, N. Verin, and A. Wenk Lang, “Self-expanding metal stents for gastroduodenal malignancies: systematic review of their clinical effectiveness,” *Endoscopy*, vol. 36, no. 6, pp. 543–550, Jun. 2004, doi: 10.1055/s-2004-814434.

[14] M. Khashab *et al.*, “Enteral stenting versus gastrojejunostomy for palliation of malignant gastric outlet obstruction,” *Surg. Endosc.*, vol. 27, no. 6, pp. 2068–2075, Jun. 2013, doi: 10.1007/s00464-012-2712-7.
[15] C. Miller *et al.*, “EUS-guided gastroenterostomy vs. surgical gastrojejunostomy and enteral stenting for malignant gastric outlet obstruction: a meta-analysis,” *Endosc. Int. Open*, vol. 11, no. 7, pp. E660–E672, Jul. 2023, doi: 10.1055/a-2098-2570.
[16] Y.-I. Chen *et al.*, “EUS-guided gastroenterostomy: a multicenter study comparing the direct and balloon-assisted techniques,” *Gastrointest. Endosc.*, vol. 87, no. 5, pp. 1215–1221, May 2018, doi: 10.1016/j.gie.2017.07.030.
[17] A. Singh, A. Gelrud, and B. Agarwal, “Biliary strictures: diagnostic considerations and approach,” *Gastroenterol. Rep.*, vol. 3, no. 1, pp. 22–31, Feb. 2015, doi: 10.1093/gastro/gou072.
[18] T. Hennedige, W. Neo, and S. Venkatesh, “Imaging of malignancies of the biliary tract-an update,” *Cancer Imaging*, vol. 14, Apr. 2014, doi: 10.1186/1470-7330-14-14.
[19] L. Rahib, B. D. Smith, R. Aizenberg, A. B. Rosenzweig, J. M. Fleshman, and L. M. Matrisian, “Projecting cancer incidence and deaths to 2030: the unexpected burden of thyroid, liver, and pancreas cancers in the United States,” *Cancer Res.*, vol. 74, no. 11, pp. 2913–2921, Jun. 2014, doi: 10.1158/0008-5472.CAN-14-0155.
[20] S. I. Ilyas, S. A. Khan, C. L. Hallemeier, R. K. Kelley, and G. J. Gores, “Cholangiocarcinoma — evolving concepts and therapeutic strategies,” *Nat. Rev. Clin. Oncol.*, vol. 15, no. 2, pp. 95–111, Feb. 2018, doi: 10.1038/nrclinonc.2017.157.
[21] B. I. Choi, J. K. Han, S. T. Hong, and K. H. Lee, “Clonorchiasis and Cholangiocarcinoma: Etiologic Relationship and Imaging Diagnosis,” *Clin. Microbiol. Rev.*, vol. 17, no. 3, pp. 540–552, Jul. 2004, doi: 10.1128/CMR.17.3.540-552.2004.
[22] Y. Shaib and H. B. El-Serag, “The epidemiology of cholangiocarcinoma,” *Semin. Liver Dis.*, vol. 24, no. 2, pp. 115–125, May 2004, doi: 10.1055/s-2004-828889.
[23] R. Hundal and E. A. Shaffer, “Gallbladder cancer: epidemiology and outcome,” *Clin. Epidemiol.*, vol. 6, pp. 99–109, Mar. 2014, doi: 10.2147/CLEP.S37357.
[24] A. Sharma, K. L. Sharma, A. Gupta, A. Yadav, and A. Kumar, “Gallbladder cancer epidemiology, pathogenesis and molecular genetics: Recent update,” *World J. Gastroenterol.*, vol. 23, no. 22, pp. 3978–3998, Jun. 2017, doi: 10.3748/wjg.v23.i22.3978.
[25] A. Duffy *et al.*, “Gallbladder cancer (GBC): 10-year experience at Memorial Sloan-Kettering Cancer Centre (MSKCC),” *J. Surg. Oncol.*, vol. 98, no. 7, pp. 485–489, Dec. 2008, doi: 10.1002/jso.21141.
[26] D. H. Ahn and T. Bekaii-Saab, “Ampullary Cancer: An Overview,” *Am. Soc. Clin. Oncol. Educ. Book ASCO Am. Soc. Clin. Oncol. Meet.*, pp. 112–115, 2014, doi: 10.14694/EdBook_AM.2014.34.112.
[27] W.-C. Liao *et al.*, “Adjuvant treatments for resected pancreatic adenocarcinoma: a systematic review and network meta-analysis,” *Lancet Oncol.*, vol. 14, no. 11, pp. 1095–1103, Oct. 2013, doi: 10.1016/S1470-2045(13)70388-7.
[28] R. A. Kozarek, “The Past, Present, and Future of Endoscopic Retrograde Cholangiopancreatography,” *Gastroenterol. Hepatol.*, vol. 13, no. 10, p. 620, Oct. 2017.
[29] A. Canakis and M. Kahaleh, “Endoscopic palliation of malignant biliary obstruction,” *World J. Gastrointest. Endosc.*, vol. 14, no. 10, pp. 581–596, Oct. 2022, doi: 10.4253/wjge.v14.i10.581.

[30] J.-M. Dumonceau *et al.*, “Endoscopic biliary stenting: Indications, choice of stents, and results: European Society of Gastrointestinal Endoscopy (ESGE) Clinical Guideline - Updated October 2017,” *Endoscopy*, vol. 50, no. 9, pp. 910–930, 2018, doi: 10.1055/a-0659-9864.
[31] H. Isayama *et al.*, “A prospective randomised study of ‘covered’ versus ‘uncovered’ diamond stents for the management of distal malignant biliary obstruction,” *Gut*, vol. 53, no. 5, pp. 729–734, 2004, doi: 10.1136/gut.2003.018945.
[32] J. J. Telford *et al.*, “A randomized trial comparing uncovered and partially covered self-expandable metal stents in the palliation of distal malignant biliary obstruction,” *Gastrointest. Endosc.*, vol. 72, no. 5, pp. 907–914, Nov. 2010, doi: 10.1016/j.gie.2010.08.021.
[33] E. Kullman *et al.*, “Covered versus uncovered self-expandable nitinol stents in the palliative treatment of malignant distal biliary obstruction: results from a randomized, multicenter study,” *Gastrointest. Endosc.*, vol. 72, no. 5, pp. 915–923, Nov. 2010, doi: 10.1016/j.gie.2010.07.036.
[34] M. Kitano *et al.*, “Covered Self-Expandable Metal Stents With an Anti-Migration System Improve Patency Duration Without Increased Complications Compared With Uncovered Stents for Distal Biliary Obstruction Caused by Pancreatic Carcinoma: A Randomized Multicenter Trial,” *Off. J. Am. Coll. Gastroenterol. ACG*, vol. 108, no. 11, p. 1713, Nov. 2013, doi: 10.1038/ajg.2013.305.
[35] M. L. Freeman *et al.*, “Complications of endoscopic biliary sphincterotomy,” *N. Engl. J. Med.*, vol. 335, no. 13, pp. 909–918, Sep. 1996, doi: 10.1056/NEJM199609263351301.
[36] B. Kochar *et al.*, “Incidence, severity, and mortality of post-ERCP pancreatitis: a systematic review by using randomized, controlled trials,” *Gastrointest. Endosc.*, vol. 81, no. 1, pp. 143-149.e9, Jan. 2015, doi: 10.1016/j.gie.2014.06.045.
[37] M. A. Almadi, A. Barkun, and M. Martel, “Self-expandable metal stents versus plastic stents for malignant biliary obstruction,” *Gastrointest. Endosc.*, vol. 83, no. 4, pp. 852–853, Apr. 2016, doi: 10.1016/j.gie.2015.10.035.
[38] M. A. Almadi, J. S. Barkun, and A. N. Barkun, “Stenting in Malignant Biliary Obstruction,” *Gastrointest. Endosc. Clin. N. Am.*, vol. 25, no. 4, pp. 691–711, Oct. 2015, doi: 10.1016/j.giec.2015.06.002.
[39] T. B. Gardner *et al.*, “Cost-effectiveness and clinical efficacy of biliary stents in patients undergoing neoadjuvant therapy for pancreatic adenocarcinoma in a randomized controlled trial,” *Gastrointest. Endosc.*, vol. 84, no. 3, pp. 460–466, Sep. 2016, doi: 10.1016/j.gie.2016.02.047.
[40] A. N. Barkun, V. Adam, M. Martel, K. AlNaamani, and P. L. Moses, “Partially covered self-expandable metal stents versus polyethylene stents for malignant biliary obstruction: a cost-effectiveness analysis,” *Can. J. Gastroenterol. Hepatol.*, vol. 29, no. 7, pp. 377–383, Oct. 2015, doi: 10.1155/2015/743417.
[41] S. E. Park *et al.*, “Effectiveness of ultrasound-guided percutaneous transhepatic biliary drainage to reduce radiation exposure: A single-center experience,” *PloS One*, vol. 17, no. 11, p. e0277272, 2022, doi: 10.1371/journal.pone.0277272.
[42] F. Glenn, J. A. Evans, Z. Mujahed, and B. Thorbjarnarson, “Percutaneous Transhepatic Cholangiography,” *Ann. Surg.*, vol. 156, no. 3, pp. 451–460, Sep. 1962.
[43] W. E. A. Saad, M. J. Wallace, J. C. Wojak, S. Kundu, and J. F. Cardella, “Quality improvement guidelines for percutaneous transhepatic cholangiography, biliary drainage, and

percutaneous cholecystostomy," *J. Vasc. Interv. Radiol. JVIR*, vol. 21, no. 6, pp. 789–795, Jun. 2010, doi: 10.1016/j.jvir.2010.01.012.
[44] V. Piñol *et al.*, "Percutaneous self-expanding metal stents versus endoscopic polyethylene endoprostheses for treating malignant biliary obstruction: randomized clinical trial," *Radiology*, vol. 225, no. 1, pp. 27–34, Oct. 2002, doi: 10.1148/radiol.2243011517.
[45] J. S. Laméris *et al.*, "Malignant biliary obstruction: percutaneous use of self-expandable stents," *Radiology*, vol. 179, no. 3, pp. 703–707, Jun. 1991, doi: 10.1148/radiology.179.3.2027978.
[46] E. L. A. Artifon *et al.*, "Surgery or Endoscopy for Palliation of Biliary Obstruction Due to Metastatic Pancreatic Cancer," *Off. J. Am. Coll. Gastroenterol. ACG*, vol. 101, no. 9, p. 2031, Sep. 2006.
[47] H. Asadi *et al.*, "A review of percutaneous transhepatic biliary drainage at a tertiary referral centre," *Clin. Radiol.*, vol. 71, no. 12, p. 1312.e7-1312.e11, Dec. 2016, doi: 10.1016/j.crad.2016.05.013.
[48] M. Sut, R. Kennedy, J. McNamee, A. Collins, and B. Clements, "Long-Term Results of Percutaneous Transhepatic Cholangiographic Drainage for Palliation of Malignant Biliary Obstruction," *J. Palliat. Med.*, vol. 13, no. 11, pp. 1311–1313, Nov. 2010, doi: 10.1089/jpm.2010.0205.
[49] P. A. Heedman, E. Åstradsson, K. Blomquist, and R. Sjödahl, "Palliation of Malignant Biliary Obstruction: Adverse Events are Common after Percutaneous Transhepatic Biliary Drainage," *Scand. J. Surg.*, vol. 107, no. 1, pp. 48–53, Mar. 2018, doi: 10.1177/1457496917731192.
[50] R. Uberoi, N. Das, J. Moss, and I. Robertson, "British Society of Interventional Radiology: Biliary Drainage and Stenting Registry (BDSR)," *Cardiovasc. Intervent. Radiol.*, vol. 35, no. 1, pp. 127–138, Feb. 2012, doi: 10.1007/s00270-011-0103-4.
[51] M. Giovannini, V. Moutardier, C. Pesenti, E. Bories, B. Lelong, and J. R. Delpero, "Endoscopic ultrasound-guided bilioduodenal anastomosis: a new technique for biliary drainage," *Endoscopy*, vol. 33, no. 10, pp. 898–900, Oct. 2001, doi: 10.1055/s-2001-17324.
[52] M. A. Khashab and J. Dewitt, "EUS-guided biliary drainage: is it ready for prime time? Yes!," *Gastrointest. Endosc.*, vol. 78, no. 1, pp. 102–105, Jul. 2013, doi: 10.1016/j.gie.2013.03.004.
[53] U. Hayat *et al.*, "EUS-guided versus percutaneous transhepatic cholangiography biliary drainage for obstructed distal malignant biliary strictures in patients who have failed endoscopic retrograde cholangiopancreatography: A systematic review and meta-analysis," *Endosc. Ultrasound*, vol. 11, no. 1, p. 4, Feb. 2022, doi: 10.4103/EUS-D-21-00009.
[54] H. Moole *et al.*, "Endoscopic versus Percutaneous Biliary Drainage in Palliation of Advanced Malignant Hilar Obstruction: A Meta-Analysis and Systematic Review," *Can. J. Gastroenterol. Hepatol.*, vol. 2016, no. 1, p. 4726078, 2016, doi: 10.1155/2016/4726078.
[55] G. Dell'Anna, T. Ogura, G. Vanella, H. Nishikawa, S. Lakhtakia, and P. G. Arcidiacono, "Endoscopic ultrasound guided biliary interventions," *Best Pract. Res. Clin. Gastroenterol.*, vol. 60–61, p. 101810, Sep. 2022, doi: 10.1016/j.bpg.2022.101810.
[56] R. Kunda *et al.*, "EUS-guided choledochoduodenostomy for malignant distal biliary obstruction using a lumen-apposing fully covered metal stent after failed ERCP," *Surg. Endosc.*, vol. 30, no. 11, pp. 5002–5008, Nov. 2016, doi: 10.1007/s00464-016-4845-6.

[57] J. Jacques *et al.*, “Endoscopic ultrasound-guided choledochoduodenostomy with electrocautery-enhanced lumen-apposing stents: a retrospective analysis,” *Endoscopy*, vol. 51, no. 6, pp. 540–547, Jun. 2019, doi: 10.1055/a-0735-9137.
[58] J. Rees, J. Mytton, F. Evison, K. S. Mangat, P. Patel, and N. Trudgill, “The outcomes of biliary drainage by percutaneous transhepatic cholangiography for the palliation of malignant biliary obstruction in England between 2001 and 2014: a retrospective cohort study,” *BMJ Open*, vol. 10, no. 1, p. e033576, Jan. 2020, doi: 10.1136/bmjopen-2019-033576.
[59] A. Tavakkoli *et al.*, “Survival analysis among unresectable pancreatic adenocarcinoma patients undergoing endoscopic or percutaneous interventions,” *Gastrointest. Endosc.*, vol. 93, no. 1, pp. 154-162.e5, Jan. 2021, doi: 10.1016/j.gie.2020.05.061.
[60] P. Huang, H. Zhang, X.-F. Zhang, W. Lv, and S. Lou, “Comparison of Endoscopic Ultrasonography Guided Biliary Drainage and Percutaneous Transhepatic Biliary Drainage in the Management of Malignant Obstructive Jaundice After Failed ERCP,” *Surg. Laparosc. Endosc. Percutan. Tech.*, vol. 27, no. 6, pp. e127–e131, Dec. 2017, doi: 10.1097/SLE.0000000000000485.
[61] E. Troncone *et al.*, “Malignant gastric outlet obstruction: Which is the best therapeutic option?,” *World J. Gastroenterol.*, vol. 26, no. 16, pp. 1847–1860, Apr. 2020, doi: 10.3748/wjg.v26.i16.1847.
[62] J. Klose, U. Ronellenfitsch, and J. Kleeff, “Management problems in patients with pancreatic cancer from a surgeon’s perspective,” *Semin. Oncol.*, vol. 48, no. 1, pp. 76–83, Feb. 2021, doi: 10.1053/j.seminoncol.2021.02.008.
[63] I. S. Papanikolaou and P. D. Siersema, “Gastric Outlet Obstruction: Current Status and Future Directions,” *Gut Liver*, vol. 16, no. 5, pp. 667–675, Sep. 2022, doi: 10.5009/gnl210327.
[64] A. Shah, A. Fehmi, and T. J. Savides, “Increased rates of duodenal obstruction in pancreatic cancer patients receiving modern medical management,” *Dig. Dis. Sci.*, vol. 59, no. 9, pp. 2294–2298, Sep. 2014, doi: 10.1007/s10620-014-3170-y.
[65] B. Brimhall and D. G. Adler, “Enteral Stents for Malignant Gastric Outlet Obstruction,” *Gastrointest. Endosc. Clin. N. Am.*, vol. 21, no. 3, pp. 389–403, Jul. 2011, doi: 10.1016/j.giec.2011.04.002.
[66] A. Kouanda, K. Binmoeller, C. Hamerski, A. Nett, J. Bernabe, and R. Watson, “Endoscopic ultrasound-guided gastroenterostomy versus open surgical gastrojejunostomy: clinical outcomes and cost effectiveness analysis,” *Surg. Endosc.*, vol. 35, no. 12, pp. 7058–7067, Dec. 2021, doi: 10.1007/s00464-020-08221-z.
[67] A. Jaroenlapnopparat, C. Jani, H. Singh, D. C. Marshall, J. D. Salciccioli, and J. Shalhoub, “An estimate of the burden of pancreatic cancer globally and its comparison with different WHO regions using Global Burden of Disease Database: A retrospective population-based analysis.,” *J. Clin. Oncol.*, May 2023, doi: 10.1200/JCO.2023.41.16_suppl.e16321.
[68] G. Lippi and C. Mattiuzzi, “The global burden of pancreatic cancer,” *Arch. Med. Sci. AMS*, vol. 16, no. 4, pp. 820–824, May 2020, doi: 10.5114/aoms.2020.94845.
[69] I. Mintziras, M. Miligkos, S. Wächter, J. Manoharan, and D. K. Bartsch, “Palliative surgical bypass is superior to palliative endoscopic stenting in patients with malignant gastric outlet obstruction: systematic review and meta-analysis,” *Surg. Endosc.*, vol. 33, no. 10, pp. 3153–3164, Oct. 2019, doi: 10.1007/s00464-019-06955-z.

[70] "Gastrojejunostomy - What is Laparoscopic Gastrojejunostomy?" Accessed: May 15, 2024. [Online]. Available: https://www.drrpadmakumar.com/blog/laparoscopic-gastrojejunostomy/
[71] J. L. Salluzzo and K. E. Roberts, "Laparoscopic Gastrojejunostomy," in *Operative Dictations in General and Vascular Surgery*, J. J. Hoballah, C. E. H. Scott-Conner, and H. S. Chong, Eds., Cham: Springer International Publishing, 2017, pp. 75–76. doi: 10.1007/978-3-319-44797-1_21.
[72] D. F. Sigmon and P. P. Lopez, "Gastrojejunostomy," in *StatPearls*, Treasure Island (FL): StatPearls Publishing, 2024. Accessed: May 15, 2024. [Online]. Available: http://www.ncbi.nlm.nih.gov/books/NBK560493/
[73] S. M. Singh, W. P. Longmire, and H. A. Reber, "Surgical palliation for pancreatic cancer. The UCLA experience.," *Ann. Surg.*, vol. 212, no. 2, pp. 132–139, Aug. 1990.
[74] E. Upchurch, M. Ragusa, and R. Cirocchi, "Stent placement versus surgical palliation for adults with malignant gastric outlet obstruction," *Cochrane Database Syst. Rev.*, vol. 5, no. 5, p. CD012506, May 2018, doi: 10.1002/14651858.CD012506.pub2.
[75] U. F. O. Themes, "Intervention for Gastric Outlet and Duodenal Obstruction," Radiology Key. Accessed: May 15, 2024. [Online]. Available: https://radiologykey.com/intervention-for-gastric-outlet-and-duodenal-obstruction/
[76] J. Hong *et al.*, "Comparison of gastrojejunostomy to endoscopic stenting for gastric outlet obstruction: An updated Systematic Review and Meta-analysis," *Am. J. Surg.*, vol. 223, no. 6, pp. 1067–1078, Jun. 2022, doi: 10.1016/j.amjsurg.2021.10.038.
[77] S. M. Jeurnink *et al.*, "Surgical gastrojejunostomy or endoscopic stent placement for the palliation of malignant gastric outlet obstruction (SUSTENT study): a multicenter randomized trial," *Gastrointest. Endosc.*, vol. 71, no. 3, pp. 490–499, Mar. 2010, doi: 10.1016/j.gie.2009.09.042.
[78] O. Ahmed, J. H. Lee, C. C. Thompson, and A. Faulx, "AGA Clinical Practice Update on the Optimal Management of the Malignant Alimentary Tract Obstruction: Expert Review," *Clin. Gastroenterol. Hepatol. Off. Clin. Pract. J. Am. Gastroenterol. Assoc.*, vol. 19, no. 9, pp. 1780–1788, Sep. 2021, doi: 10.1016/j.cgh.2021.03.046.
[79] S. R. Friedberg and J. Lachter, "Endoscopic ultrasound: Current roles and future directions," *World J. Gastrointest. Endosc.*, vol. 9, no. 10, pp. 499–505, Oct. 2017, doi: 10.4253/wjge.v9.i10.499.
[80] P. Vilmann, G. K. Jacobsen, F. W. Henriksen, and S. Hancke, "Endoscopic ultrasonography with guided fine needle aspiration biopsy in pancreatic disease," *Gastrointest. Endosc.*, vol. 38, no. 2, pp. 172–173, Mar. 1992, doi: 10.1016/S0016-5107(92)70385-X.
[81] G. Vanella *et al.*, "Current landscape of therapeutic EUS: Changing paradigms in gastroenterology practice," *Endosc. Ultrasound*, vol. 12, no. 1, pp. 16–28, Sep. 2022, doi: 10.4103/EUS-D-21-00177.
[82] T. Itoi *et al.*, "Prospective evaluation of endoscopic ultrasonography-guided double-balloon-occluded gastrojejunostomy bypass (EPASS) for malignant gastric outlet obstruction," *Gut*, vol. 65, no. 2, pp. 193–195, Feb. 2016, doi: 10.1136/gutjnl-2015-310348.
[83] A. Fritscher-Ravens, C. A. Mosse, D. Mukherjee, T. Mills, P.-O. Park, and C. P. Swain, "Transluminal endosurgery: single lumen access anastomotic device for flexible endoscopy," *Gastrointest. Endosc.*, vol. 58, no. 4, pp. 585–591, Oct. 2003, doi: 10.1016/s0016-5107(03)02006-6.

[84] K. F. Binmoeller and J. N. Shah, “Endoscopic ultrasound-guided gastroenterostomy using novel tools designed for transluminal therapy: a porcine study,” *Endoscopy*, vol. 44, no. 5, pp. 499–503, May 2012, doi: 10.1055/s-0032-1309382.
[85] M. Rimbaș, K. W. Lau, G. Tripodi, G. Rizzatti, and A. Larghi, “The Role of Luminal Apposing Metal Stents on the Treatment of Malignant and Benign Gastric Outlet Obstruction,” *Diagnostics*, vol. 13, no. 21, Art. no. 21, Jan. 2023, doi: 10.3390/diagnostics13213308.
[86] T. R. McCarty, R. Garg, C. C. Thompson, and T. Rustagi, “Efficacy and safety of EUS-guided gastroenterostomy for benign and malignant gastric outlet obstruction: a systematic review and meta-analysis,” *Endosc. Int. Open*, vol. 7, no. 11, pp. E1474–E1482, Nov. 2019, doi: 10.1055/a-0996-8178.
[87] A. Y. B. Teoh *et al.*, “Endoscopic ultrasonography-guided gastroenterostomy versus uncovered duodenal metal stenting for unresectable malignant gastric outlet obstruction (DRA-GOO): a multicentre randomised controlled trial,” *Lancet Gastroenterol. Hepatol.*, vol. 9, no. 2, pp. 124–132, Feb. 2024, doi: 10.1016/S2468-1253(23)00242-X.
[88] D. Moher *et al.*, “Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement,” *Syst. Rev.*, vol. 4, no. 1, p. 1, Jan. 2015, doi: 10.1186/2046-4053-4-1.
[89] L. A. Stewart *et al.*, “Preferred Reporting Items for Systematic Review and Meta-Analyses of individual participant data: the PRISMA-IPD Statement,” *JAMA*, vol. 313, no. 16, pp. 1657–1665, Apr. 2015, doi: 10.1001/jama.2015.3656.
[90] “Cochrane Handbook for Systematic Reviews of Interventions.” Accessed: Jul. 09, 2024. [Online]. Available: https://training.cochrane.org/handbook
[91] G. H. Guyatt *et al.*, “GRADE: an emerging consensus on rating quality of evidence and strength of recommendations,” *BMJ*, vol. 336, no. 7650, pp. 924–926, Apr. 2008, doi: 10.1136/bmj.39489.470347.AD.
[92] P. B. Cotton *et al.*, “A lexicon for endoscopic adverse events: report of an ASGE workshop,” *Gastrointest. Endosc.*, vol. 71, no. 3, pp. 446–454, Mar. 2010, doi: 10.1016/j.gie.2009.10.027.
[93] J. Y. Bang, U. Navaneethan, M. Hasan, R. Hawes, and S. Varadarajulu, “Stent placement by EUS or ERCP for primary biliary decompression in pancreatic cancer: a randomized trial (with videos),” *Gastrointest. Endosc.*, vol. 88, no. 1, pp. 9–17, Jul. 2018, doi: 10.1016/j.gie.2018.03.012.
[94] M. A. Almadi, A. Barkun, and M. Martel, “Plastic vs. Self-Expandable Metal Stents for Palliation in Malignant Biliary Obstruction: A Series of Meta-Analyses,” *Am. J. Gastroenterol.*, vol. 112, no. 2, pp. 260–273, Feb. 2017, doi: 10.1038/ajg.2016.512.
[95] S. Kiriyama *et al.*, “Tokyo Guidelines 2018: diagnostic criteria and severity grading of acute cholangitis (with videos),” *J. Hepato-Biliary-Pancreat. Sci.*, vol. 25, no. 1, pp. 17–30, Jan. 2018, doi: 10.1002/jhbp.512.
[96] G. B. Stewart, D. G. Altman, L. M. Askie, L. Duley, M. C. Simmonds, and L. A. Stewart, “Statistical analysis of individual participant data meta-analyses: a comparison of methods and recommendations for practice,” *PloS One*, vol. 7, no. 10, p. e46042, 2012, doi: 10.1371/journal.pone.0046042.
[97] B. A. Holt *et al.*, “Biliary drainage: role of EUS guidance,” *Gastrointest. Endosc.*, vol. 83, no. 1, pp. 160–165, Jan. 2016, doi: 10.1016/j.gie.2015.06.019.

[98] V. Palmieri *et al.*, “EUS-guided biliary drainage in malignant distal biliary obstruction: An international survey to identify barriers of technology implementation,” *Endosc. Ultrasound*, vol. 12, no. 1, pp. 104–110, 2023, doi: 10.4103/EUS-D-21-00137.
[99] J. S. Barkun *et al.*, “Evaluation and stages of surgical innovations,” *Lancet Lond. Engl.*, vol. 374, no. 9695, pp. 1089–1096, Sep. 2009, doi: 10.1016/S0140-6736(09)61083-7.
[100] M. Bronswijk *et al.*, “Same-session double EUS-guided bypass versus surgical gastroenterostomy and hepaticojejunostomy: an international multicenter comparison,” *Gastrointest. Endosc.*, vol. 98, no. 2, pp. 225-236.e1, Aug. 2023, doi: 10.1016/j.gie.2023.03.019.
[101] L. A. Stewart and J. F. Tierney, “To IPD or not to IPD?: Advantages and Disadvantages of Systematic Reviews Using Individual Patient Data,” *Eval. Health Prof.*, vol. 25, no. 1, pp. 76–97, Mar. 2002, doi: 10.1177/0163278702025001006.
[102] K. D. Lillemoe *et al.*, “Is prophylactic gastrojejunostomy indicated for unresectable periampullary cancer? A prospective randomized trial,” *Ann. Surg.*, vol. 230, no. 3, pp. 322–328; discussion 328-330, Sep. 1999, doi: 10.1097/00000658-199909000-00005.
[103] T. Conroy *et al.*, “FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer,” *N. Engl. J. Med.*, vol. 364, no. 19, pp. 1817–1825, May 2011, doi: 10.1056/NEJMoa1011923.
[104] S. Gourgou-Bourgade *et al.*, “Impact of FOLFIRINOX Compared With Gemcitabine on Quality of Life in Patients With Metastatic Pancreatic Cancer: Results From the PRODIGE 4/ACCORD 11 Randomized Trial,” *J. Clin. Oncol.*, vol. 31, no. 1, pp. 23–29, Jan. 2013, doi: 10.1200/JCO.2012.44.4869.
[105] N. T. van Heek, “Palliative treatment in ‘peri’-pancreatic carcinoma : stenting or surgical therapy ?,” 2002.
[106] J. Espinel, S. Vivas, F. Muñoz, F. Jorquera, and J. L. Olcoz, “Palliative treatment of malignant obstruction of gastric outlet using an endoscopically placed enteral Wallstent,” *Dig. Dis. Sci.*, vol. 46, no. 11, pp. 2322–2324, Nov. 2001, doi: 10.1023/a:1012378509762.
[107] S. Y. Oh *et al.*, “Survival and clinical outcome after endoscopic duodenal stent placement for malignant gastric outlet obstruction: comparison of pancreatic cancer and nonpancreatic cancer,” *Gastrointest. Endosc.*, vol. 82, no. 3, pp. 460-468.e2, Sep. 2015, doi: 10.1016/j.gie.2015.01.026.