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Palliation of Pancreatic Cancer: A History

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Abstract

Pancreatic cancer has long been associated with profound morbidity and mortality, much of which stems from its anatomic location and the resultant complications such as biliary obstruction and gastric outlet obstruction. Due to the insidious nature of the disease, up to 80-85% of individuals diagnosed with this either have metastatic or unresectable disease. As such, palliation of the disease remains central in its care. Moreover, as advances in systemic chemotherapy have led to meaningful prolongation of survival, optimizing functional status and even quality of life have become increasingly imperative.

This article traces the historical evolution of palliative interventions for pancreatic cancer, beginning with the highly morbid surgical procedure of the 19th century, such as cholecystocolonic anastomoses and the original Roux-en-Y reconstruction, progressing to contemporary surgical approaches such as the laparoscopic loop gastrojejunostomy or hepaticojejunostomy. These surgical strategies are contrasted with the rapidly growing field of advanced endoscopy, highlighting novel, minimally-invasive techniques for palliation, including endoscopic retrograde cholangiopancreatography with stenting, duodenal stenting, endoscopic ultrasound-guided gastrojejunostomy or hepaticojejunostomy.

Keywords: Pancreatic cancer; Hepaticojejunostomy; Gastrojejunostomy; Endoscopic ultrasound; Endoscopic retrograde cholangiopancreatography; Whipple; Biliary obstruction; Gastric outlet obstruction; Endoscopic stenting

Definitions of abbreviations:

GOO: Gastric outlet obstruction; **PJ:** Pancreaticojejunostomy; **HJ:** – Hepaticojejunostomy **GJ:** Gastrojejunostomy; **ERCP:** Endoscopic retrograde cholangiopancreatography; **EUS-BD:** Endoscopic ultrasound-guided biliary drainage; **EUS-GE:** Endoscopic ultrasound-guided gastroenterostomy; **EUS-GJ:** Endoscopic ultrasound-guided gastrojejunostomy; **EUS-HJ:** Endoscopic ultrasound-guided hepaticogastrostomy; **SEMS:** Self expanding metal stents; **LAMS:** – Lumen opposing metal stent

Introduction

Pancreatic cancer is the 4th leading cause of cancer-related death in the United States, a statistic that can be much attributed to late diagnosis. The dismal five-year survival rate of approximately 5% is a direct consequence of the fact that 80−85% of patients already have unresectable or metastatic disease at presentation. Even for the minority who are candidates for surgical resection, five-year survival rate is only 17% [1].

Much of the disease's morbidity arises from the tumor's anatomic location. As the head of the pancreas encases the common bile duct and lies

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adjacent to the duodenum, a growing mass frequently causes mechanical obstruction of these structures, leading to two primary complications: biliary obstruction and gastric outlet obstruction [2].

Biliary obstruction is the more common complication, affecting up to 70% of patients and leading to the classic presentation of painless jaundice [3]. This blockage leads to progressive hyperbilirubinemia, in turn causing symptoms like malaise, nausea, and pruritus. Critically, significant elevations of bilirubin can also preclude patients from receiving systemic chemotherapy, delaying essential treatment [4].

Historically, gastric outlet obstruction (GOO) occurs in 10−25% of patients. As advances in chemoradiation allow patients with unresectable disease to live longer, they are now developing late-stage duodenal obstructions at higher rates, with some studies reporting an incidence of up to 50−60% [5].

Due to the significant morbidity associated with the complications associated with pancreatic cancer, surgical and procedural techniques to palliate the disease and manage these complications have developed over the past 150 years.

Historical surgical procedures

The first surgeries developed for pancreatic cancer were palliative in nature. To manage biliary obstruction, early surgeons connected the gallbladder to various parts of the GI tract to create a biliary bypass. The first documented surgical intervention for pancreatic disease was performed by Alexander Winiwarter in 1880. He attempted the first bilioenteric bypass by anastomosing the gallbladder to the colon. Due to anastomotic complications, this was later revised to a cholecystojejunostomy [6]. As surgical techniques and anatomical understanding progressed, so did the complexity of intraabdominal procedures.

In 1904, Ambrose Monprofit introduced the Roux-en-Y reconstruction, a technique that would become a cornerstone of the modern pancreaticoduodenectomy, now know as the Whipple [7].

The procedure involves dividing the jejunum and creating a Y-shaped anastomosis: the proximal end of the divided jejunum (the Roux limb) is brought up and anastomosed to a proximal gastrointestinal structure (such as the stomach, esophagus, or bile duct), while the distal end is reconnected to the jejunum further downstream, forming a jejunojejunostomy. This configuration diverts the flow of bile and pancreatic secretions away from the proximal anastomosis, reducing reflux and allowing for effective drainage or bypass of the upper gastrointestinal tract.

The evolution of the Whipple procedure is credited to several pioneering surgeons included Walter Kausch and Allen O. Whipple [8]. It was Whipple in 1940 who refined the operation into a single-stage resection, significantly improving its feasibility and outcomes [9]. The modern Whipple procedure involves a complex resection, including partial gastrectomy, cholecystectomy, removal of the distal common bile duct, head of the pancreas, duodenum, proximal jejunum, and regional lymph nodes. Reconstruction is achieved via pancreaticojejunostomy (PJ), hepaticojejunostomy (HJ), and gastrojejunostomy (GJ) [10].

Initially, the procedure was performed infrequently due to high perioperative mortality rates, which initially exceeded 20% [11]. However, improvements in surgical technique and perioperative care in the mid-20th century led to a steady decline in mortality [11, 12]. Today, perioperative mortality rates at high-volume centers are reported to be as low as 1.6% [13].

Current approaches to palliation

Currently, most surgical interventions for advanced pancreatic cancer are aimed at relieving biliary or gastric outlet obstruction, particularly in patients with a life expectancy greater than six months. When surgery is indicated for malignant biliary obstruction, bypass is typically achieved via either HJ or cholecystojejunostomy, with evidence suggesting that HJs are generally more successful than cholecystojejunostomies [14].

Surgical management of biliary obstruction in this setting is generally effective, with a low reintervention rate of approximately 1.5% [15]. However, given the frailty and advanced disease status of this patient population, both morbidity and mortality remain significant. Major complications occur in roughly 17-23% of cases, and the 30-day postoperative mortality rate is approximately 17% [16]. As a result, with advances in endoscopic techniques, surgical bypass for biliary obstruction is generally not recommended as the first-line approach.

Endoscopic approaches to palliation: ERCP

Endoscopic bile duct drainage via ERCP with transpapillary placement of a 7 French pigtail catheter was first described in 1980 [17]. The procedure was particularly innovative as it provided a less invasive way to manage biliary obstruction when compared to surgery. Originally, plastic stents were used primarily for their low cost, but they were more prone to clogging and recurrent obstruction due to bacterial biofilm formation [17,18]. Plastic stent occlusion usually develops after 3-5 months, then requiring reintervention [19].

The development of self-expanding metal stents (SEMS) provided a more durable solution. SEMS, with their larger diameter have double the length of stent patency when compared with their plastic counterparts [20, 21]. As a result, guidelines and major medical societies such as The American

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Gastroenterological Association (AGA) and the American Society of Clinical Oncology (ASCO) recommend the use of SEMS for management of malignant biliary obstruction as SEMS provide significantly longer stent patency and reduce cholangitis events, leading to fewer interruptions in chemotherapy and lower rates of hospitalization, thereby improving quality of life [22, 23].

EUS-biliary drainage (EUS-BD)

Endoscopic ultrasound-guided biliary drainage (EUS-BD) was first described in the early 2000s. Initially used only as a salvage for failed ERCP, inaccessible papilla (duodenal obstruction), or to avoid percutaneous drainage. It is now increasingly used as first-line drainage over ERCP. EUS-BD had a lower reintervention rate than ERCP and EUS-BD with lumen apposing metal stent (LAMS) had a higher technical success rate than ERCP [24].

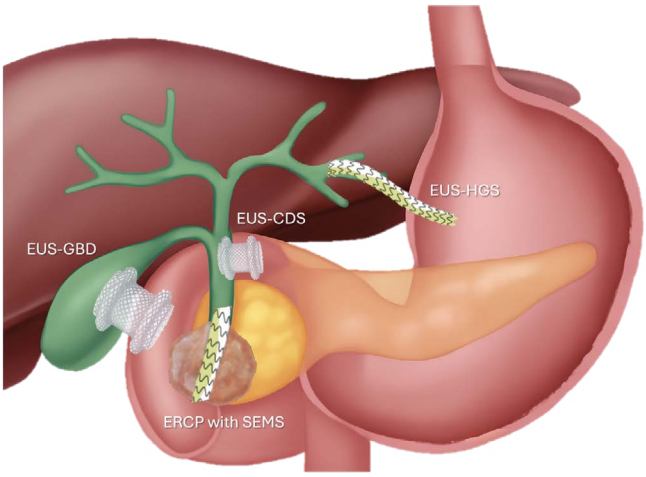

Figure 1: Endoscopic approach to palliation of pancreatic cancer. [25]

Malignant gastric outlet obstruction

The surgical management of malignant gastric outlet obstruction (GOO) has evolved significantly, with the traditional open GJ of the 20th century being succeeded by the minimally invasive laparoscopic approach developed in the 1990s by Cuschieri and colleagues (Figure 1). Laparoscopic GJ was just as effective as open GJ, although with key advantages, including short hospitalization and quicker return to diet. Open GJ poses an increased risk of post-operative delayed gastric emptying when compared to its laparoscopic counterpart, with the open procedure having a 10-30% risk and the laparoscopic procedure having a 0-15% risk [26, 27]. Modern laparoscopic GJ carries an operative mortality under 2.5–4.5% [28] and restores oral intake in more than 85–90% [29, 30] of appropriately selected patients.

Prophylactic gastrojejunostomy is however, a controversial topic. Studies from the 1990's and 2000's showed strong evidence supporting the use of a prophylactic GJ for patients with unresectable cancer at high risk of developing a future obstruction. Seminal studies and a subsequent meta-analysis have shown that this preventative surgery dramatically reduces the risk of gastric outlet obstruction (odds ratio 0.06, [95% confidence interval; $p<0.001$]) [31].

While early landmark studies supported prophylactic GJ for the prevention of GOO in high-risk patients without increasing morbidity [32-34], more recent data has challenged this approach. Newer evidence, which emerged alongside new, advanced systemic therapies as well as endoscopic stenting, suggests that prophylactic surgical bypass may actually increase perioperative complications, prolong hospital stays, and potentially shorten survival without improving symptom control [35]. Although the utility of prophylactic GJ is now debated, surgical GJ remains a durable palliative treatment for patients who have already developed an obstruction, providing long-term luminal patency in the majority of patients who receive one [36].

Endoscopic management of GOO

Endoscopic duodenal stenting for malignant GOO was first described in the 1990s and has since become a standard minimally invasive palliative option for patients with unresectable malignancies causing GOO.

The technique involves the endoscopic deployment of a self-expandable metal stent (SEMS) across the obstructed duodenum to restore luminal patency and allow resumption of oral intake. Compared to surgical GJ, it offers more rapid symptom relief, shorter hospital stays, and faster return to oral intake [37, 38]. However, these stents have high rates of symptom recurrence and reintervention due to migration, caused by insufficient radial force and the duodenum's natural curvature [39], and tumor ingrowth through the mesh of uncovered stents or overgrowth at the stent ends [40].

2015 brough the emergence of endoscopic ultrasound-guided gastroenterostomy (EUS-GE) as an alternative (Figure 1). EUS-GE achieves clinical success in approximately 90% of cases, with adverse event rates comparable to duodenal stenting, though stent misdeployment, which can lead to perforation, is a unique risk for EUS-GE. EUS-GE provides more durable palliation, especially in patients with longer life expectancy, and is recommended to be performed at centers with expertise in training. Duodenal stenting remains appropriate for those with a limited prognosis due to its rapid symptom relief and minimally invasive nature.

Combination biliary obstruction and GOO

For patients with advanced pancreatic cancer causing simultaneous biliary and gastric outlet obstruction, palliative management has traditionally involved a surgical double bypass. This technically complex open procedure combines

a gastrojejunostomy with a bilioenteric anastomosis. The surgery is highly effective, with recurrence rates of either obstruction being less than 5% [41]. Advancements in therapeutic endoscopy have opened newer, less-invasive options for management of combined obstruction. Through single session EUS-guided double-bypass (consisting of a hepaticogastrostomy and gastrojejunostomy) simultaneous obstructions can be palliated. A recent study showed technical success was 100% for EUS-HG and 95.6% for EUS-GJ. All patients tolerated a soft diet, 72.7% had ≥50% bilirubin reduction, and the median hospital stay was two days [42].

Conclusion

For patients with advanced pancreatic cancer, the management of malignant biliary and gastric outlet obstruction has shifted from surgery to less invasive endoscopic solutions. Initially, this involved endoscopic stenting, which reduced post-procedural morbidity compared to surgery but often required re-intervention due to stent occlusion.

More recently, EUS-guided therapies have become the forefront of care for these complex obstructions. These advanced techniques, combining stenting with EUS-guided anastomoses, provide higher rates of technical succ17ess and improved long-term patency compared to traditional stenting. In challenging scenarios, such as severe duodenal obstruction, an EUS-guided hepaticogastrostomy has a far superior success rate (93.3%) than a conventional ERCP approach (22.2%) [43]. As patient life expectancies increase with better systemic therapies, these durable EUS procedures are vital alternatives to surgery or percutaneous drainage.

Disclosures:

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