Special Article

Endoscopic Management of Pancreatic Cancer

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Endoscopic treatment of pancreatic malignancy can be considered as an alternative treatment option in inoperable patients. Endoscopic retrograde cholangio-pancreatography (ERCP) plays a key role, allowing diagnosis, collection of cytologic, biopsy specimens, and insertion of biliary and pancreatic stents. A major problem is the patency of plastic stents that will eventually clog on average after 3 to 4 months. Self-expandable metallic stents have longer patency, but they can also become occluded by tumor ingrowth or overgrowth. Furthermore, metallic stents are much more expensive and their uses may be considered in patients with longer life expectancy. ERCP can be performed on an outpatient basis in selected patients, reducing costs related to hospitalization. A team approach is mandatory to obtain the best results.

Keywords: *Endoscopic management, Pancreatic cancer*

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Ductal adenocarcinoma of the pancreas, which accounts for 90% of pancreatic cancer, has the lowest five-year survival rate (1-3%) compared to any other [1]. Because of this dismal natural history, palliative treatment remains the cornerstone of management of patients with pancreatic cancer. Palliative intervention is primarily directed at relief of obstructive jaundice, pain, nausea and vomiting due to duodenal obstruction. Endoscopic therapy offers a noninvasive management option for all these symptoms. Endoscopic manipulation in patients with pancreatic cancer focuses mainly on the biliary tree since most patients present with obstructive jaundice. Pancreatic ductal manipulation is rarely necessary. It may be appropriate to obtain cytology specimens from the pancreatic duct and to place a pancreatic stent in some patients with intractable pancreatic pain that may be due to obstruction.

Palliation of Obstructive Jaundice *(Surgical vs Endoscopic Palliation)*

Prolonged biliary obstruction usually results in malabsorption and consequent progressive malnutrition, pruritus, recurrent attacks of cholangitis, and hepatic dysfunction. Biliary obstruction can be relieved by surgery or endoscopy. It is important to establish that jaundice is caused by obstruction of the biliary ductal system rather than by extensive intrahepatic tumor deposit leading to functional liver failure. The presence of significant biliary dilatation without significant intrahepatic metastasis by non-invasive imaging studies should alert the clinician to this possibility.

Several randomized trials [2-5] have compared surgical vs endoscopic palliation of malignant obstructive jaundice (Table 1). The majority of the patients studied had unresectable pancreatic cancer. Overall, both endoscopic stent insertion and surgical bypass appear to be effective palliative treatments, with the former having fewer early treatment-related complications and the latter having fewer late complications. The major factors that determine the appropriate approach to biliary drainage are tumor stage and the patient's general health status. Attempts at curative resection with surgical bypass as a fallback measure should be considered in relatively young and otherwise healthy patients when imaging studies show no definite evidence of unresectability. However, placement of a biliary stent should be used in patients with a large tumor burden, substantial comorbid illnesses and absence of duodenal obstruction. Whether the

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Table 1. Randomized controlled trials comparing endoscopic therapy vs surgical bypass in patients with malignant biliary obstruction

	Shepherd et al[2]		Andersen et al[3]		Dowsett et al[4]		Smith et al[5]	
	Stent	Surgery	Stent	Surgery	Stent	Surgery	Stent	Surgery
Number of Patients	23	25	25	25	65	62	101	103
Success	82%	92%	96%	88%	94%	94%	92%	92%
Complication	30%	56%	36%	20%	23%	50%	11%	29%
30-Day Mortality	9%	20%	20%	24%	6%	15%	8%	15%
Length of Hospital Stay (days)	5	13	26	27	11	15	19	26
Recurrent Jaundice/Cholangitis	30%	0%	0%	0%	17%	3%	36%	2%
Survival (weeks)	22	18	12	14	22	16	21	26

approach will be endoscopic or percutaneous will be determined by the relative levels of expertise available locally. The endoscopic method is generally preferred because it is quicker, equally effective, and probably safer. For those patients in the intermediate category in terms of tumor stage and general health status, the decision-making process is more complex. The patient may have to choose between a surgical approach, which has a higher risk, is more, invasive, and more expensive but more effective in the long-term, or the quicker, safer method of endoscopic stent placement, which may need to be repeated frequently. Although at present the balance is somewhat tilted in favor of the endoscopic approach, the surgical option may become more competitive as expertise with laparoscopic drainage procedures continues to develop.

Type of Biliary Stents *(Plastic vs. Metal)*

Before endoscopic placement of a biliary endoprosthesis, endoscopic retrograde cholangiopancreatography (ERCP) should be performed to evaluate the biliary tree and the pancreatic duct. Antibiotics should be administered prophylactically before the procedure, and coagulopathy should be corrected if present. The location and length of the biliary stricture must be demonstrated as well as the proximal biliary tree in order to assess the proximal extent of the stricture and to exclude the presence of concomitant proximal strictures.

The most commonly used biliary stents are straight or slightly curved polyethylene stents with side flaps (Amsterdam-type) at each end to reduce the chance of stent migration. These stents are available in different lengths and different inner diameters. The largest stent that can be passed through the accessory channel of a duodenoscope has a 12-Fr inner diameter. The length of the stent chosen is such that the distance between the flaps is approximately 1 cm greater than the distance between the proximal margin of the stricture and the duodenal papilla. Stents are available in lengths of 5, 7, 9, and 12 cm, which will be suitable in most cases. With approximation, the length of stent required can be estimated from the fluoroscopic images, although more precise methods have been described [6].

Plastic stents are indicated for both malignant and benign obstructions. All plastic stents eventually become obstructed with a bacterial biofilm and biliary sludge. The duration of stent patency greatly influences their cost-effectiveness. Larger stents (>10F) remain patent significantly longer (3–6 months) than smaller (5-7 F) stents (6 weeks). A variety of interventions have not proven useful for extending stent patency, including chronic use of antibiotics, aspirin, and ursodiol. The most efficacious means of extending stent patency is to maximize the caliber of the lumen. This is achieved with self-expanding metal stents (SEMS), which can remain patent for 9–12 months or longer. Three randomized controlled trials [7-9] have been reported that compare self-expandable metallic stents and plastic stents (Table 2). The overall results suggest that SEMS have longer patency, but their initial costs are higher and patency curves of metal and plastic stents run parallel during the first 3 months. Due to their expense, SEMS are usually reserved for inoperable malignant obstruction in patients with anticipated longevity beyond 3 to 6 months. Plastic stents are most appropriate and SEMS are generally avoided in patients going to surgery for malignant obstruction and in those with known hepatic metastasis, malignant ascites, or widespread intra-abdominal disease.

Complications of Stent Placement

Complications of stent placement include short-term complications related to ERCP (eg, pancreatitis, cholangitis, perforation) and delayed complications related to stent placement (eg, stent migration, stent fracture, stent occlusion). Although stent migra-

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Table 2. Results of controlled trials comparing metal stents with plastic stents

	Davids et al[7]		Carr-Locke et al[8]		Knyrim et al[9]	
	Plastic	Metal	Plastic	Metal	Plastic	Metal
Number of Patients	56	49	78	86	31	31
Drainage	95	96	95	98	100	100
Occlusion	54	33	13	13	22	43
30-Day Mortality	4	14	5	5	9	13
Patency (days)	126	273	62	111	43	22

tion (proximally or distally) is unusual, it may impair biliary drainage or cause injury to the duodenum. In most cases, proximally migrated plastic stents can be recovered by endoscopic methods by inserting a guidewire through the stent for removal by means of an over-the-wire extraction device, grasping with a forceps or basket, or extracting with a catheter balloon placed next to the stent. Surgery is rarely necessary [10]. Fracture of indwelling plastic biliary stents is a rare complication that usually occurs when the stents are left in the bile duct for long periods of time, an unlikely situation in patients with malignant bile duct obstruction. Stent occlusion with subsequent development of cholangitis remains the most significant problem with the biliary endoprosthesis. Bile is ordinarily sterile. However, with the loss of the barrier function of the sphincter of Oddi, as occurs with stent placement, the biliary system is rapidly colonized with gut bacteria [11]. Various approaches to prolong stent patency (eg, modifying the stent surface by coating it with a polymer, orally administering antibiotics and choleretic and mucolytic agents) have yielded promising results in vitro; however, none has been shown to consistently prolong stent life in clinical practice [12-14].

The most direct approach to prolonging patency is to increase the diameter of the stent. Larger stents are associated with higher bile flow rate and lower rate of clogging, as previously shown in, in-vitro studies. Currently, available duodenoscopes accept stents up to a maximum diameter of 12 Fr. However, the added increase in flow through 11.5 Fr and 12 Fr may not translate into clinically relevant improvement in stent patency, jaundice, and cholangitis. To obviate the problem of plastic stent occlusion, large-diameter, self-expandable metalic stents have been developed and marketed by several commercial manufacturers: Wallstent (Schneider Stent, Minneapolis, Minn), Ultraflex Diamond (Boston Scientific, Natick, (InStent, Eden Prairie, Minn) and Gianturco-Rosch Z (Wilson-Cook Medical, Winston Salem, NC). The Wallstent, one of the commonly used metallic stents, is a tubular mesh made from surgical-grade stainless steel alloy. The Wallstent is delivered in a collapsed configuration on an 8-Fr delivery system. When deployed, it expands to a final diameter of 30 Fr. Because of its inherent expansible properties, it can be shortened by approximately 30% to a designated length of 42, 68, or 90 mm. A sphincterotomy is usually not required. Wallstents cannot be removed once fully implanted, but additional stents can be placed through the indwelling stent lumen if necessary. Erosion of a biliary metal stent through the duodenal wall with resultant hemorrhage has been reported [15]. One study [16] reported 13 of 22 patients with a variety of malignant tumors developed stent obstruction due to tumor ingrowth (median follow-up = 14.6 months). Blocked stents can be reopened by debulking with diathermic devices, brachytherapy, dragging an extraction balloon through the obstructed segment or, preferably, by inserting a standard polyethylene stent or in some cases a second metal expandable stent is placed through the blocked stent.

Duodenal Obstruction

Approximately 15-20% of patients with pancreatic cancer will develop duodenal obstruction leading to gastric outlet obstruction, although it is typically not present at diagnosis [17]. Duodenal stenting using larger caliber SEMS of 20–22 mm diameter can be accomplished using fluoroscopy techniques. Duodenal strictures do not need to be traversed endoscopically, as this increases the risk of perforation. Many duodenal SEMS traverse the papilla, hence prior consideration should be given to whether biliary obstruction is imminent, and prophylactic biliary decompression may be useful. Rarely, duodenal stenting can precipitate sudden biliary occlusion by compressing adjacent periductal lesions. A study suggested that self-expandable enteral stents can effectively relieve duodenal obstruction in selected patients with advanced pancreatic cancer [18].

Pain Management

Pain can be a significant feature of advanced pancreatic cancer. Palliation of pain can be ineffectively

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achieved by narcotic analgesics alone. An increasingly used approach is celiac plexus neurolysis (CPN), a chemical splanchnicectomy of the celiac plexus, which ablates the afferent nerve fibers that transmit pain from intraabdominal viscera via local injection of absolute alcohol. CPN can be performed percutaneously, surgically, or under endosonographic guidance [19]. In the past, it has been most commonly performed intraoperatively or percutaneously with fluoroscopic or computed tomographic guidance. Recently experience has demonstrated that it can also be safely performed during endoscopic ultrasonography. CPN appears to be more effective than pharmacologic therapy. As an example, in a prospective, randomized double-blind trial involving 100 patients with locally advanced pancreatic cancer, CPN was associated with significantly better immediate and long-term relief of pain compared with the control group who received pharmacologic therapy and a sham injection [20]. However, patients undergoing CPN did not report less consumption of opioids or fewer opioid-related side effects.

Since the survival rate of pancreatic cancer is so poor, much pancreatic cancer treatment focuses on relieving pain and discomfort. Endoscopic therapy is an often used, noninvasive way to relieve jaundice and the pain and nausea caused by tumor blockages in the duodenum. Relieving jaundice symptoms facilitate patients' appetites and emotional well being. For some patients with resectable tumors or patients with jaundice and gastric outlet obstruction, surgical management is indicated. A team approach is mandatory to obtain the successful and best care for the patients.

References

1. Parker SL, Tong T, Bolden S, Wingo PA. Cancer statistics 1996. CA Cancer J Clin 1996;46:5.
2. Shepherd HA,Royle G, Ross AP. Endoscopic biliary endoprosthesis in the palliation of malignant obstruction of the distal common bile duct: a randomized trial. Br J Surg 1988;75:1166-8.
3. Andersen JR, Sorensen SM, Kruse A. Randomised trial of endoscopic endoprosthesis versus operative bypass in malignant obstructive jaundice. Gut 1989;30:1132-5.
4. Dowsett JF, Russell RCG, Hatfield ARW. Malignant obstructive jaundice: a prospective randomized trial of surgery vs. endoscopic stenting. Gastroenterology 1989;96:A128.
5. Smith AC, Dowsett JF, Russell RC. Randomised trial of endoscopic stenting versus surgical bypass in malignant low bile duct obstruction. Lancet 1994;344:1655-60.
6. Kendall BJ, Jutabha R, So L. Determining required stent length in endoscopic retrograde biliary stenting. Gastrointest Endosc 1995;41:242-3.
7. Davids PH, Groen AK, Rauws EA. Randomised trial of self-expanding metal stents versus polyethylene stents for distal malignant biliary obstruction. Lancet 1992;340:1488-92.
8. Carr-Locke DL, Ball TJ, Connors PJ. Multicenter randomized trial of Wallstent biliary endoprosthesis versus plastic stents. Gastrointest Endosc 1993;39:310-6.
9. Knyrim K,Wagner HJ, Pausch J. A prospective, randomized, controlled trial of metal stents for malignant obstruction of the common bile duct. Endoscopy 1993;25:207-12.
10. Tarnasky PR, Cotton PB, Baillie J. Proximal migration of biliary stents: attempted endoscopic retrieval in forty-one patients. Gastrointest Endosc 1995;42:513-20.
11. Sung JY,Leung JW,Shaffer EA. Ascending infection of the biliary tract after surgical sphincterotomy and biliary stenting. J Gastroenterol Hepatol 1992;7:240-5.
12. Smit JM, Out MM, Groen AK. A placebo-controlled study on the efficacy of aspirin and doxycycline in preventing clogging of biliary endoprostheses. Gastrointest Endosc 1989;35:485-9.
13. Ghosh S, Palmer KR. Prevention of biliary stent occlusion using cyclical antibiotics and ursodeoxycholic acid. Gut 1994;35:1757-9.
14. Barrioz T, Ingrand P, Besson I. Randomised trial of prevention of biliary stent occlusion by ursodeoxycholic acid plus norfloxacin. Lancet 1994;344: 581-2.
15. Marano BJ Jr, Bonanno CA. Metallic biliary endoprosthesis causing duodenal perforation and acute upper gastrointestinal bleeding. Gastrointest Endosc 1994;40:257-8.
16. O'Brien S, Hatfield AR, Craig PI. A three year follows up of self expanding metal stents in the endoscopic palliation of longterm survivors with malignant biliary obstruction. Gut 1995; 36: 618-21.
17. Singh SM, Longmire WP Jr, Reber HA. Surgical palliation for pancreatic cancer. The UCLA experience. Ann Surg 1990;212:132-9.
18. Feretis C, Benakis P,Dimpoulos C. Duodenal obstruction caused by pancreatic head carcinoma: palliation with self-expandable endoprostheses. Gastrointest Endosc 1997;46:161-5.

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19. de Leon-Casasola OA. Critical evaluation of chemical neurolysis of the sympathetic axis for cancer pain. Cancer Control 2000; 7:142-8.
20. Wong GY, Schroeder DR, Carns PE. Effect of neurolytic celiac plexus block on pain relief, quality of life, and survival in patients with unresectable pancreatic cancer: a randomized controlled trial. JAMA 2004; 291:1092-9.

การรักษามะเร็งตับอ่อนโดยการส่องกล้องระบบทางเดินอาหาร

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การรักษาโดยการส่องกล้องระบบทางเดินอาหารในผู้ป่วยมะเร็งตับอ่อนเป็นการรักษาตามอาการที่สำคัญยิ่ง โดยเฉพาะในรายที่ไม่สามารถผ่าตัดได้ การรักษาหลักมักผ่านการส่องกล้องระบบทางเดินน้ำดี (endoscopic retrograde cholangio-pancreatography (ERCP)) ซึ่งสามารถระบายท่อน้ำดีที่อุดตันโดยการใส่ท่อน้ำดีเทียมซึ่งมี 2 ชนิดคือ ชนิดพลาสติก (plastic stent) และชนิดที่เป็นเหล็กสังเคราะห์ (metallic stent) ผ่านทางกล้องส่องทางเดินอาหาร ซึ่งการเลือกชนิดของท่อน้ำดีเทียมขึ้นอยู่กับผู้ป่วยแต่ละราย โดยทั่วไปท่อน้ำดีเทียมชนิดพลาสติกมีราคาถูกกว่า แต่อายุการใช้งานมักสั้นเพียง 3-4 เดือนเท่านั้น สำหรับท่อน้ำดีเทียมชนิดเหล็กสังเคราะห์มักมีราคาค่อนข้างแพง แต่สามารถใช้งานได้นานกว่า นอกจากนี้การส่องกล้องระบบทางเดินน้ำดี ยังสามารถช่วยในการวินิจฉัยโรคได้โดยสามารถตัดชิ้นเนื้อส่วนที่ต้องการผ่านกล้องส่องทางเดินอาหารโดยตรง และส่งตรวจทางพยาธิวิทยาเพื่อยืนยันผลการวินิจฉัย ในปัจจุบันการส่องกล้องระบบทางเดินน้ำดีสามารถให้บริการแบบผู้ป่วยนอกได้ เพื่อประหยัดค่าใช้จ่ายสำหรับผู้ป่วย การทำงานร่วมกันเป็นทีมเป็นสิ่งสำคัญที่ทำให้การรักษาผู้ป่วยประสบความสำเร็จ

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