



Navajo saddle throw, c. 1875. From the Fred Harvey Company. Courtesy of the Heard Museum, Phoenix, Arizona.

*Endoscopic therapy facilitates palliation of obstructive jaundice, duodenal obstruction, and pain caused by pancreatic cancer.*

# Endoscopic Palliation for Inoperable Pancreatic Cancer

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**Background:** *The majority of patients with pancreatic cancer are not candidates for surgical resection. Palliative therapy remains the cornerstone of management of this population.*

**Methods:** *We reviewed recent clinical and experimental studies on endoscopic palliative therapy of inoperable pancreatic cancer.*

**Results:** *Endoscopic placement of a biliary stent is the preferred mode of palliation of obstructive jaundice in patients with pancreatic cancer. The techniques of endoscopic stent insertion are briefly described. Episodic recurrence of jaundice and cholangitis due to stent occlusion is a major drawback of biliary polyethylene stents. Self-expandable metal stents with large diameters have lower rates of stent occlusion and are cost effective in patients who are expected to survive beyond 3 months. Palliation of duodenal obstruction with self-expandable enteral stents and endosonography-guided celiac plexus neurolysis are emerging options for the treatment of patients with advanced pancreatic cancer.*

**Conclusions:** *Endoscopic therapy offers safe and effective management options for palliation of major symptoms associated with inoperable pancreatic cancer.*

## Introduction

Approximately 28,000 new cases of pancreatic cancer occur every year in the United States, and almost all of these patients eventually die of this disease.<sup>1</sup> The majority of these tumors are unresectable at presentation. When curative surgical resection is attempted, the median survival is only 18 to 20 months, and only 10% of patients survive beyond 5 years.<sup>2</sup> Because of this dismal natural history, palliative treatment remains the cornerstone of management of patients with pancreatic

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Table 1. — Summary of Results of Randomized Controlled Trials Comparing Endoscopic Therapy vs Surgical Bypass in Patients With Malignant Biliary Obstruction

	Shepherd et al <sup>7</sup>		Andersen et al <sup>8</sup>		Dowsett et al <sup>9</sup>		Smith et al <sup>10</sup>	
	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

cancer. Palliative intervention is primarily directed at relief of obstructive jaundice, pain, and nausea and vomiting due to duodenal obstruction. Endoscopic therapy offers a noninvasive management option for all three symptoms. For obstructive jaundice, endoscopic therapy is the preferred mode of palliation.

## Palliation of Obstructive Jaundice

Obstructive jaundice occurs in many patients with unresectable pancreatic cancer at presentation. Prolonged biliary obstruction usually results in malabsorption and consequent progressive malnutrition, pruritus, recurrent attacks of cholangitis, and hepatic dysfunction. In a review of surgery-related publications, Sarr and Cameron<sup>3</sup> observed that biliary bypass was associated with a longer survival and a higher quality of life compared to diagnostic laparotomy alone. In a study of patients with malignant bile duct obstruction, Ballinger et al<sup>4</sup> found that stent insertion provided complete relief of jaundice and itching, reduced dyspeptic symptoms, and improved appetite. Moreover, relief of jaundice provides a much needed psychological boost to the patient and family members.

Biliary obstruction can be relieved by surgery and by stent insertion (percutaneous or endoscopic). Before considering either a surgical or endoscopic drainage procedure, 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 extensive intrahepatic metastasis along with absence of significant biliary dilatation by non-invasive imaging studies should alert the clinician to this possibility. Surgical options for relief of obstructive jaundice include internal bypass by means of choledochoduodenostomy, choledochojejunostomy, or hepaticojejunostomy. In addition to endoscopic therapy, percutaneous trans-

hepatic drainage of the biliary tree is another option.<sup>5</sup> Relative contraindications to the transhepatic approach include gross ascites, major hepatic metastases, and coagulopathy. Simple external biliary drainage is useful only for short-term decompression. Permanent palliation involves crossing the obstruction, which should be possible in most cases using appropriate guidewire techniques. In a meta-analysis<sup>6</sup> of nearly 2,000 patients with malignant obstructive jaundice, the success rates were similar for all three modalities of decompression, but short-term morbidity, mortality, and length of hospital stay were higher in the surgical bypass group.

## Surgical vs Endoscopic Palliation

Several randomized trials<sup>7-10</sup> 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. Endoscopic stent placement significantly reduces the length of hospital stay and is associated with lower procedure-related morbidity and mortality.

Episodic recurrence of jaundice and cholangitis due to stent occlusion requiring repeated hospital visits is a drawback of endoscopic palliation. However, with the availability of expandable metal stents, such episodes occur less frequently. Another disadvantage of stent treatment is the potential for gastric outlet obstruction caused by tumor growth. In the study by Smith et al,<sup>10</sup> prophylactic gastroenterostomy reduced the number of late operations for late symptoms and did not increase mortality.

The major factors that determine the appropriate approach to biliary drainage are tumor stage and the

patient's general health status.<sup>11</sup> 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 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 is higher risk, invasive, and more expensive but more effective on 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.

### *Endoscopic Placement*

Before endoscopic placement of a biliary endoprosthesis, endoscopic retrograde cholangiopancreatography is performed to evaluate the biliary tree and the pancreatic duct. Preceding the procedure, antibiotics should be administered prophylactically, and coagulopathy should be treated if present. The location and length of the biliary stricture must be determined accurately, and the proximal biliary tree also must be opacified to correctly assess the proximal extent of the stricture and to exclude the presence of additional proximal strictures. Deep cannulation of the biliary system is performed, and a guidewire is manipulated across the stricture to maintain access. At this stage, an endoscopic transpapillary wire-guided brush cytologic specimen or forceps biopsy may be obtained from the area of the stricture, if indicated. Several techniques have been described for stent placement, but the easiest and most commonly used procedure involves placing a stiff polyethylene 6-Fr inner catheter with radio-opaque markers (guide catheter) over the guidewire. The biliary stent is then pushed into position using an outer larger-diameter catheter (pusher) device as a three-layer system. The guidewire and the guide catheter are withdrawn, leaving the biliary stent in position. This procedure is performed under fluoroscopic guidance. The stent is placed through a "therapeutic duodenoscope" that has an accessory channel diameter of at least 4 mm. A single-assembly stent delivery system, the One-Action Stent Insertion Set (OASIS, Wilson-Cook

Medical, Winston-Salem, NC) is also available. In a randomized trial<sup>12</sup> involving 20 patients, stent insertion appeared to be easier and faster with the OASIS system compared with the standard three-layer system. In most cases, dilation of the strictures is not required but may be accomplished if needed using stepped dilators (bougies) before placement of the stent. Hydrophilic-coated guidewires can expedite passage through tight and tortuous strictures.

### *Types of Biliary Stents*

Broadly, two different types of biliary stents are available for endoscopic palliation of malignant obstructive jaundice. 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 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, one of which will be suitable in most cases. With experience, the length of stent required can be accurately estimated from the fluoroscopic images, although more precise methods have been described.<sup>13</sup>

The main causes of failure to place a biliary stent endoscopically include obstruction of the duodenum and the inability to cannulate the common bile duct or pass a guidewire through the stricture. In these cases, a combined percutaneous endoscopic "rendezvous" technique is useful to access the biliary system and place a stent across the biliary stricture. An interventional radiologist passes a guidewire transhepatically down the bile duct and into the duodenum (through a small catheter to protect the liver from laceration). By means of any of several different devices (eg, snare), the endoscopist then grasps the wire, pulls it up through the instrument channel, and uses it for stent placement. A particularly long wire (at least 400 cm) is required. This combined procedure is safer than placing a large-bore polyethylene stent directly through the liver substance.

### *Complications of Stent Placement*

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

or distally) is unusual, it may impair biliary drainage or injure the duodenum. In most cases, proximally migrated plastic stents can be recovered by endoscopic methods, viz, 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.<sup>14</sup> Fracture of indwelling plastic biliary stents is a rare complication that usually occurs when the stents are left in the bile duct for prolonged 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.<sup>15</sup> Electron microscopic studies of occluded stents have shown that the clogging material consists of bacterial cellular debris and microcolonies of bacteria in a matrix of extracellular anionic fibrillar material. In vitro studies suggest that formation of a protein biofilm is probably the initial event in stent clogging.<sup>16</sup> Once formed, it has been impossible to eliminate this biofilm from an indwelling stent, and subsequent bacterial adherence is certain to occur. Bacterial enzymes such as beta-glucuronidase and phospholipase deconjugate bilirubin and other substances present in bile with the resultant formation of calcium bilirubinate and calcium salts of fatty acids. Microscopic surface irregularities and imperfections that occur during the manufacture of stents probably facilitate bacterial colonization; sludge tends to accumulate mainly around side holes and at the ends of stents.<sup>17</sup> Various approaches to prolong stent patency (eg, modifying the stent surface by coating it with a polymer, orally administering antibiotics and choleric and mucolytic agents) have yielded promising results in vitro; however, none has been shown to consistently prolong stent life in clinical practice. Aspirin (to reduce mucin secretion) and doxycycline failed to improve stent patency in a clinical study.<sup>18</sup> In another study by Palmer and Ghosh,<sup>19</sup> the sequential administration of ampicillin, metronidazole, and ciprofloxacin plus ursodeoxycholic acid did not decrease stent clogging. In a randomized trial, Barrioz et al<sup>20</sup> found that the combination of norfloxacin and ursodeoxycholic acid significantly increased stent patency, although the results of this study are open to question because the median duration of patency in the control group was unusually short. Due to their bactericidal effect, bile salts have received considerable attention because of a potential role in increasing stent patency. They are often prescribed empirically after stent placement.

An in vitro study<sup>21</sup> has shown that insertion of a biliary stent completely into the bile duct, thus preserving the barrier function of the sphincter, decreases bacterial adherence to stents. However, this concept is not clinically attractive because complete insertion may be impossible with distal biliary obstruction and it makes stent exchange especially difficult.

Biofilm formation or the adherence of bacteria may in theory be prevented by using ultrasoft materials to make stents, by impregnating stents with bactericidal agents, and by designing stents that resist adherence. Teflon-coated (cross-linked polymers of urea and poly-N-vinylpyrrolidone- PVP) and silver-coated stents have been shown to decrease bacterial adherence in vitro.<sup>22-25</sup> Stents have been designed without the rough edges and side holes that enhance adherence of bacteria. However, such changes in design resulted in structural weakening that increases the chance of migration and fracture. In at least one clinical trial,<sup>26</sup> design modifications did not decrease stent clogging.

The most direct approach to prolonging patency is to increase the diameter of the stent. Larger stents are associated with higher bile flow rates and lower rates of clogging, particularly 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.

The risk of occlusion of standard polyethylene stents appears to increase progressively after approximately 3 months. Stents should be changed immediately if signs of cholangitis develop because life-threatening sepsis can quickly occur. Elective stent exchange at 3 to 6 months appears reasonable if the general condition of the patient remains good. The standard technique for changing a stent is to grasp the distal tip in the duodenum using a basket or snare and then pull it out through the mouth by removing the duodenoscope, which is then reinserted for bile duct cannulation and stent replacement. Occasionally, difficulty in recannulating the papilla (or stricture) may be encountered. This has led to the development of techniques for exchanging stents over a guidewire so that access is not lost.

To obviate the problem of plastic stent occlusion, large-diameter, self-expandable metal stents have been developed and marketed by several commercial manufacturers: Wallstent (Schneider Stent, Minneapolis, Minn), Ultraflex Diamond (Boston Scientific, Natick, Mass), Endocoil (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.<sup>27</sup> Follow-up studies have shown a low incidence of stent clogging by the usual bacteria/bile salt process, but stents have become obstructed by tumor (or tissue) ingrowth through the interstices of the metal mesh or by overgrowth at either end of the stent. O'Brien et al<sup>28</sup> reported 13 of 22 patients with a variety of malignant tumors developed stent obstruction due to tumor ingrowth (median follow-up = 14.6 months). In a retrospective review, van Berkel et al<sup>29</sup> found that 13 of 28 patients with metastatic malignant biliary obstruction developed symptoms of recurrent obstruction. Retrograde cholangiography in 10 patients demonstrated tumor overgrowth in 3 and ingrowth in 7. Blocked stents can be reopened by debulking with diathermic devices, by brachytherapy, by 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 through the blocked stent.

### Metal vs Plastic Stents

Three randomized controlled trials<sup>30-32</sup> have been reported that compare self-expandable metallic stents and plastic stents (Table 2). In general, plastic stents were associated with a higher rate of cholangitis and occlusion and a longer rate of hospitalization compared with metallic stents. In the randomized trial of Davids et al,<sup>30</sup> metal expandable stents were cost effective in patients who survived beyond a few months because the overall number of endoscopic retrograde cholangiopancreatography procedures required for stent exchange was reduced by 28%. In the randomized trial of Knyrim et al,<sup>32</sup> more endoscopic interventions subsequent to initial stent placement were required in the plastic stent group. There were also significant differences in the number of days in hospital as well as the cost of treatment of stent-related complications. Although the total overall cost of treatment was higher using plastic stents, the difference was not

Table 2. — Results of Three Controlled Trials Comparing Metal Stents With Plastic Stents

	Davids et al <sup>30</sup>		Carr-Locke et al <sup>31</sup>		Knyrim et al <sup>32</sup>	
	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

significant. The results of other studies suggest that self-expandable metal stents have longer patency, but their initial costs are higher and patency curves of metal and plastic stents run parallel during the first 3 months. Thus, patients in whom life expectancy is thought to be short should receive plastic stents, whereas metal expandable stents would be more cost effective in patients who are expected to survive beyond 3 months.

### Palliation of Duodenal Obstruction

Approximately 10%-20% of patients with advanced pancreatic cancer develop duodenal obstruction at some point before death. Although surgical gastrojejunostomy remains the standard treatment for duodenal obstruction, it has a mortality rate up to 10% as well as associated morbidity, additional high cost, and prolonged hospitalization. Preliminary data from small case series suggest that self-expandable enteral stents can effectively relieve duodenal obstruction in selected patients with advanced pancreatic cancer.<sup>33</sup>

### Palliation of Pain

Palliation of pain in patients with advanced pancreatic cancer is often difficult; narcotics may be ineffective in providing relief. Pain in up to 15% of patients with inoperable pancreatic cancer may have an obstructive quality characterized by postprandial occurrence and a dilated pancreatic duct upstream from the malignant stricture. Pain may be relieved in these patients after placing a pancreatic stent in the main pancreatic duct across the obstructing tumor.<sup>34</sup>

Endosonography-guided celiac plexus neurolysis has recently emerged as a safe and effective technique for palliation of uncontrolled pain due to advanced pancreatic cancer. A curvilinear array echoendoscope and a needle catheter are used to inject bupivacaine and 98% dehydrated absolute alcohol around the celiac plexus through the transgastric route. Endoscopic

ultrasound-guided celiac plexus neurolysis can be performed as an outpatient procedure often in the same session as an endoscopic ultrasound staging examination, and it is associated with persistent analgesia in more than 80% patients.<sup>35</sup>

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