

## Role of preoperative palliation of jaundice in pancreatic cancer

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### Abstract

**Background/purpose** Recent studies suggest that there is no significant benefit and that there may be significantly higher morbidity rates in pancreatic cancer patients who undergo preoperative plastic stent placement for obstructive jaundice. This review attempts to define the role of stenting in patients with pancreatic cancer and malignant obstructive jaundice. The latter includes patients unresectable for cure, those who are too frail to withstand an operation, the occasional patient who presents with cholangitis, and those patients who will have a significant delay in surgery because of preoperative neoadjuvant therapy.

**Methods** Literature review. A therapeutic endoscopy team member of a multidisciplinary team which evaluates and treats >250 pancreatic cancer patients yearly.

**Results** There are 5 historical randomized controlled trials (RCTs) and 1 current RCT demonstrating no significant benefit in preoperatively decompressing jaundiced patients with pancreatic malignancy with percutaneously placed tubes or endoscopically inserted plastic stents. There are 5 RCTs defining a longer patency rate with self-expandable metal stents (SEMS) compared to plastic prostheses suggesting that in the setting of palliation as well as the use of neoadjuvant therapy for resectable or borderline resectable patients, SEMS placement is preferable.

**Conclusions** Despite data demonstrating lack of efficacy and potential harm in decompressing the biliary tree as opposed to early surgery in jaundiced patients with pancreatic malignancy, endoscopic retrograde cholangiopancreatography with SEMS insertion remains an invaluable

palliative modality in non-resectable patients as well as those in whom contemplated resection is delayed in order to give neoadjuvant therapy.

**Keywords** Pancreatic cancer · Jaundice · ERCP

### Background

Endoscopic intervention in pancreatic cancer antedated computed tomography (CT) and magnetic resonance (MR) imaging and consisted primarily of diagnostic brush cytology and fluoroscopic-facilitated biopsy and placement of small caliber (7-French) plastic prostheses at time of endoscopic retrograde cholangiopancreatography (ERCP). The latter was predicated on significant surgical morbidity and mortality for patients undergoing curative resection at the time and the knowledge that only 10–15 % of these patients were medically fit for surgery or resectable for cure [1]. Moreover, previous studies in the radiologic literature had demonstrated comparable patient survival in non-resectable jaundiced patients treated with percutaneous transhepatic biliary drainage (PTBD) as opposed to surgical biliary bypass. This same literature demonstrated that in patients who subsequently underwent exploration and resection, that jaundice could be resolved preoperatively [2, 3]. Based upon Whipple's original description of radical pancreaticoduodenectomy (PD) as a two-stage procedure, the assumption was that improved sepsis, lower rates of endotoxemia and disseminated intravascular coagulation, as well as improvements in coagulopathy and immune function by palliation of jaundice noted in laboratory animals, would translate into improvement in operative morbidity and mortality [4].

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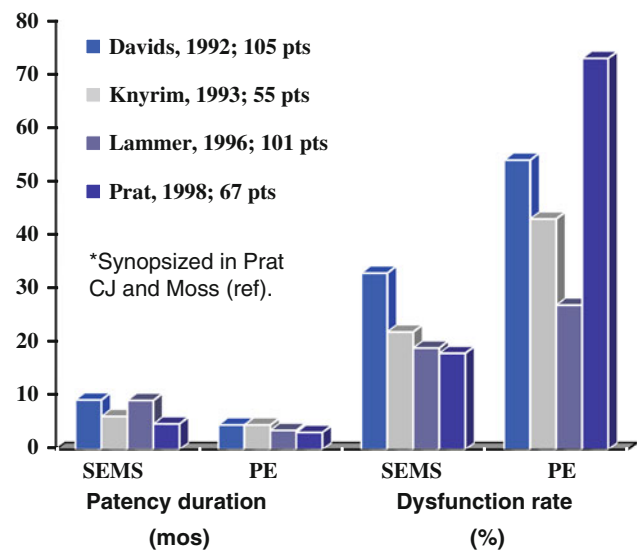
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There were several things wrong with these practice patterns, some of which have been abandoned as technology and additional endoscopic techniques have been introduced. On the one hand, noninvasive imaging has improved dramatically, allowing better definition of the tumor, not only its size and evidence of metastatic disease, but also its relationship to vascular structures. As such, this information allows us to define individuals who have local anatomic factors rendering them unresectable but also helping to define a subset of patients who can be potentially downstaged with preoperative chemoradiation.

Moreover, ERCP has proven to be notoriously inadequate in making a tissue diagnosis of pancreatic malignancy with brush cytology alone, even when combined with finding chromosomal aneuploidy using fluorescence in situ hybridization. These techniques demonstrated the ability to diagnose malignancy in <50 % of jaundiced patients. Other techniques, including directed forceps biopsy, ERCP-directed fine-needle aspiration (FNA), and cytological aspiration of occluded biliary stent material have resulted in incremental improvements in diagnostic yield, but are still inferior to the >90 % diagnostic accuracy currently available by the use of FNA at time of endoscopic ultrasound (EUS) [5–7]. The latter has become the gold standard for tissue acquisition prior to palliative chemoradiation or neoadjuvant therapy and many practitioners now combine both diagnostic EUS-FNA and ERCP-stenting as a single diagnostic and palliative procedure. For instance, Camus et al. [6] reviewed their experience in 122 patients who underwent combined EUS-FNA stenting and a control group of 68 patients who underwent stenting alone. There was histologic proof of cancer in 89 % of patients at index, and 95 % after a second EUS-FNA. Successful biliary stenting was undertaken in 98 % of the initial EUS as well as 98 % in the control group. There was no difference in procedural morbidity or length of hospital stay, and the authors suggest that these two complementary procedures should be combined.

From a therapeutic standpoint, ERCP has become an entrenched modality to palliate malignant obstructive jaundice both prior to and following the 3 prospective trials randomizing endoscopic stent placement versus biliary bypass for distal malignant obstructive jaundice [8]. These studies showed comparable initial palliation [109/117 (93 %) success, stent placement vs 102/112 (91 %) surgical bypass], complications (23–36 vs 20–56 %), 30-day mortality [12 (6–20) vs 17 (5–32) %], and median survival in days [130 (84–152) vs 112 (100–125)]. Patients undergoing plastic prosthesis placement had a higher incidence of recurrent jaundice prior to death.

There has been a single trial randomizing stage IV pancreatic cancer patients to self-expandable metal stents



**Fig. 1** Randomized, controlled trials comparing stent dysfunction and patency in 10-Fr. plastic vs. 10 mm Wallstents™

(SEMS) versus surgery to palliate malignant obstructive jaundice [9]. This study demonstrated significant benefit including costs, hospitalization time, and procedural morbidity for patients palliated with SEMS. To date, there are no trials randomizing patients deemed locally unresectable because of vascular involvement to SEMS or surgery. There are, however, multiple randomized and controlled trials consisting of 466 patients demonstrating improved stent patency (4.8–10 months) compared to plastic prostheses (3.2–4.6 months) as well as individual studies and meta-analyses that suggest increased stent patency but perhaps slightly higher complication rates with covered versus uncovered SEMS to palliate jaundice in patients with pancreatic malignancy [10–13] (Fig. 1). No survival advantage has been demonstrated with either prosthesis [3, 8, 14].

### Does preoperative resolution of jaundice improve surgical outcomes?

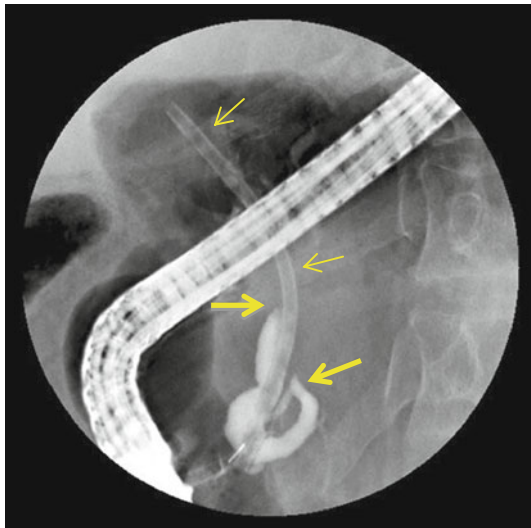
Prior to the mid-1990s, there were 5 randomized controlled trials looking at preoperative biliary drainage for malignant obstructive jaundice [15–17]. Together, 326 patients were randomized to biliary drainage, 75 % of whom had palliation by PTBD. Eighty percent of the studies showed no difference in subsequent patient outcomes, although there were multiple limitations including treating patients with cholangiocarcinoma as well as pancreatic cancer, multiple different types of surgical procedures performed, and a marked inter-series discordance in fistula and infection rates. There have been multiple subsequent non-randomized series published with discordant results related to

preoperative biliary drainage complications, survival, and resources utilized [18–27].

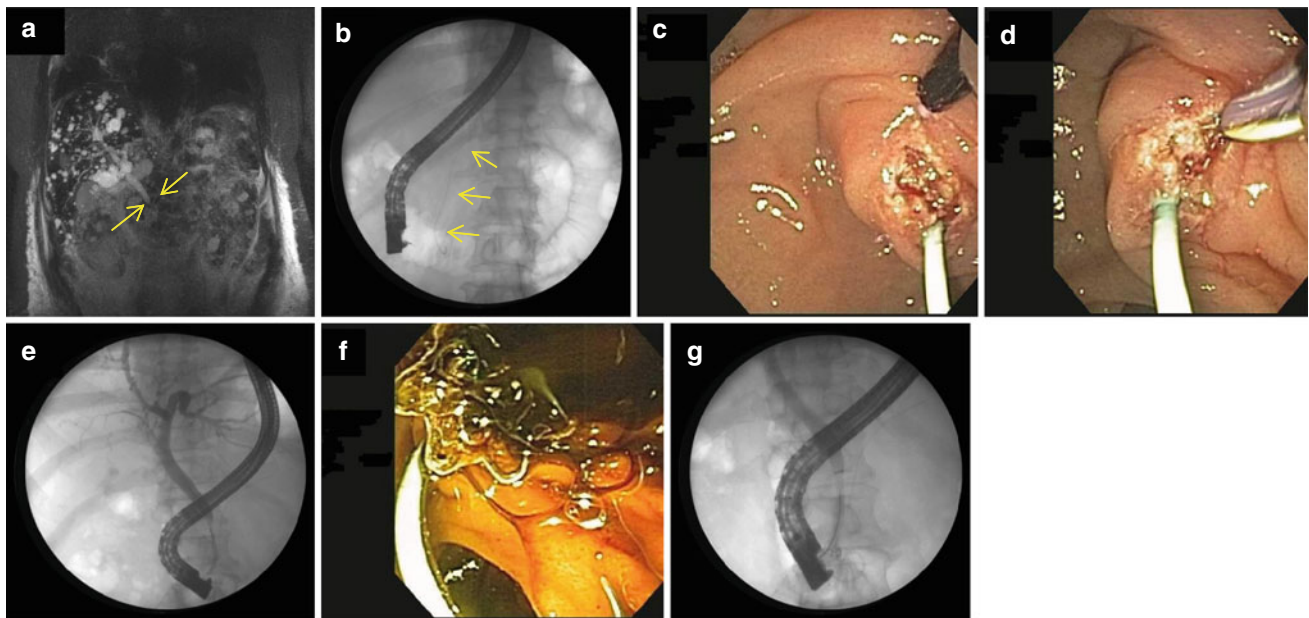
A more recent multicenter Dutch study published in 2010 was supposed to have definitively answered the advisability of preoperative biliary drainage insofar as improving or worsening patient outcomes in jaundiced patients with presumptive pancreatic malignancy [28]. In this study, 202 patients were initially enrolled, 96 in an early surgery arm (within 1 week of diagnosis), and 106 who underwent

preoperative biliary drainage with placement of a 10-French plastic stent (Fig. 2). Excluding 6 patients from analysis, there was almost a two-fold rate of serious complications in the stented group (74 vs 37 %,  $p < 0.001$ ). Surgery-related complications occurred in 47 and 37 %, respectively, but were not statistically significant. The authors concluded that preoperative biliary drainage should not be performed routinely in patients undergoing surgery for jaundiced patients with presumptive pancreatic cancer. Moreover, they concluded that a delay in surgery neither impaired nor benefited subsequent patient survival. Mortality and length of hospitalization did not differ between the 2 groups.

In an editorial accompanying the New England Journal of Medicine publication, Baron and I commended the authors on an excellent study design that was unfortunately hindered by suboptimal ERCP expertise [4]. As such, <75 % of ERCPs were successful initially and there was an extraordinarily high rate of cholangitis, in part from unsuccessful ERCPs but more commonly related to early occlusion of the 10-French prostheses. Because previous studies have demonstrated that short SEMS not only stay open longer than plastic prostheses but do not interfere in a subsequent pancreatectomy, our practice for years has been to place SEMS for documented distal malignant obstructive jaundice (Fig. 3). The rationale for this is threefold—(1) 80 % of patients are either unfit for surgery or surgically unresectable at time of diagnosis. These patients will have prolonged palliation with SEMS placement; (2) the incidence of cholangitis in patients who undergo decompression of the biliary tree with SEMS and have surgery



**Fig. 2** Large arrows depict pancreaticobiliary obstruction palliated by 10-French plastic prosthesis (small arrows)



**Fig. 3** Arrows show obstruction of distal bile duct in patient with polycystic liver and kidney disease and potentially downstageable malignancy of the pancreatic head (a). Note cut-off of PD (arrows) (b) stented with a 3-French PD stent (c) to allow needle-knife access

into the biliary tree (d, e). A fully covered, self-expandable metal stent (f) is placed into the biliary tree (g) in an attempt to correct jaundice prior to neoadjuvant therapy

within 4–6 weeks is very low, possibly <5 %; and (3) marginally resectable patients treated with 4–6 months of neoadjuvant therapy may be potentially resectable, thus expanding our surgically treated pool of patients. This can only be performed safely in patients who have SEMS inserted initially or in whom plastic stents are traded out for SEMS prior to therapy initiation.

van der Gaag et al. reported on a subsequent study utilizing this same patient population in which Eshuis et al. [29] followed patients to median survival times [12.2 (9.1–15.4) vs 12.7 (8.9–16.6) months] for early surgery versus delayed surgery (stented) group, respectively. Survival times were equivalent suggesting that preoperative stenting with delay in surgical intervention did not impair survival; however, there was a slightly lower surgical mortality rate in the stented group when compared to patients who had early surgery.

### Do preoperative biliary SEMS change outcomes, allow for successful downstaging with neoadjuvant therapy in patients with pancreatic cancer?

To date, there are a number of studies that have addressed these issues but none in the form of randomized, controlled trials [30–35]. Singal et al. [36] reviewed 79 patients who underwent PD at a median of 120 days following insertion. There were no technical difficulties. There was a 33 % 30-day complication rate, not significantly different from their rate in PD patients without stenting and a median survival rate approximating 3 years. Similarly, Coates et al. [37] reviewed 90 patients undergoing PD, 62 % having undergone biliary drainage and 38 % who did not. Although these included plastic stents as well as SEMS, there were no significant differences in fluid or transfusion requirements or operative length between the 2 groups. Eighty-eight percent of patients had a positive bile culture in stented patients, and there was slightly higher blood loss in this group (625 vs 525 mL), but reoperation was significantly higher (15 vs 4 %) in the non-stented group ( $p = 0.02$ ). ICU stay, hospital stay, infectious complications, readmission rates, and 30- and 90-day mortality were comparable between the 2 groups.

There have been multiple retrospective studies and a recently published prospective study about the efficacy and safety of using SEMS in an attempt to downstage patients with neoadjuvant therapy for pancreatic cancer [38–40]. In the latter study from Milwaukee, 55 patients with resectable [23] and borderline resectable [32] cancers were recruited between March 2009 and December 2010 [41]. SEMS were placed in all patients. The median time for neoadjuvant therapy prior to surgery was 104 days (range 70–260 days) and the primary outcomes measured included SEMS patency, stent malfunction rate, and overall

complication rates. Information was also collected on stent-related difficulties at surgery. At a median of 104 days, 88 % of SEMS remained patent and by 260 days, 15 % of stents had malfunctioned to include 1 migration. Ultimately, 27 patients, including 3 (11 %) who developed stent dysfunction, had PD whereas 21 patients including 5 with stent dysfunction, ( $p = \text{NS}$ ) had disease progression. The presence of SEMS did not interfere with PD. The authors concluded that SEMS are safe and effective and durable in pancreatic cancer patients undergoing neoadjuvant therapy for pancreatic cancer.

Our oncology and pancreaticobiliary surgical groups have shown comparable findings in our first 39 patients using a 6-month course of gemcitabine and docetaxel as a neoadjuvant protocol. In this expanding and yet to be published series, 38 completed the protocol and 10 progressed on noninvasive imaging. Of the 28 people deemed surgical candidates, 24 underwent PD and the median survival has yet to be reached at 24 months. Patients sent from outside the institution with plastic prostheses had a dramatically higher incidence of stent-related occlusions than those who had SEMS in place at initiation of therapy.

### Conclusions (Table 1)

1. Biliary stent therapy for malignant obstructive jaundice remains the main method of biliary decompression in surgically unfit or unresectable patients. There should be SEMS placement in all but the most infirm in whom very short survival is anticipated.
2. Routine placement of plastic prostheses in patients with resectable pancreatic cancer within a week or 10 days is not indicated.
3. In resectable or potentially resectable patients in whom there will be a significant surgical delay, jaundice should be palliated with SEMS and all jaundiced patients undergoing neoadjuvant therapy should have initial SEMS placement or, if referred with a plastic stent in place, should have it exchanged for a metal stent prior to initiation of therapy.

**Table 1** Current indications for palliation of jaundice in pancreatic cancer

Surgically unfit patient
Surgically unresectable patient
Presentation/development of acute cholangitis
Resectable patient with significant delay in surgery
SEMS only
Borderline resectable patient treated with neoadjuvant therapy
SEMS only

**Conflict of interest** None.

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