Malignant jaundice

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Diagnosis

The appropriate management of malignant obstructive jaundice is contingent upon both the tumour site and accurate staging of the disease. As such, more than 50% of pancreatic carcinoma patients have distant metastases at presentation and only 20-30% will have localised disease amenable to surgical resection [1–4]. Extrahepatic cholangiocarcinoma, with the exception of incidental gallbladder cancer found at time of cholecystectomy in a patient with symptomatic cholelithiasis, has been reported to be potentially resectable in less than half of symptomatic patients [5–7]. Patients with significant intrahepatic extension, however (Bismuth III–IV lesions), have considerably lower rates of resectability, in part because of major vascular involvement, in part related to concomitant porta hepatis spread, and in part related to lobar atrophy and insufficient liver mass for post-hepatectomy recovery. On either end of the resectability spectrum is ampullary malignancy, potentially resectable for cure in up to two-third of patients who present with jaundice, and metastatic disease, which with the exception of rare instances, will be palliated non-operatively [8]. Table 1 defines common malignancies causing malignant obstructive jaundice.

Table 1
Major causes of malignant obstructive jaundice

- Duodenal/ampullary carcinoma
- Pancreatic cancer*
  - exocrine
  - islet cell
  - cystic
  - intrapapillary mucus secreting neoplasm (IPMN)
- Biliary malignancy
  - gallbladder
  - bile duct
    - extrahepatic
    - intrahepatic
- Metastatic disease
  - ± duodenum/papilla (e.g., hypernephroma)
  - porta hepatis adenopathy
  - intrahepatic

*Pancreatic cancer is the most frequent cause of malignant obstructive jaundice.

Clinically, 70-80% of pancreatic and 90% of bile duct malignancies present with obstructive jaundice [1, 2,5]. Pain is variable and its absence is often ominous at time of presentation. Constitutional symptoms include fatigue, nausea and weight loss, and neuropsychiatric complaints are common. Klatskin tumours, accounting for approximately 70% of cholangiocarcinomas in the western world, may obstruct only one side of the liver and present with isolated liver function test elevations, particularly alkaline phosphatase [5]. Pruritus is variable and cholangitis is unusual in my experience, unless the patient has ampullary malignancy, concomitant stones, or has had their biliary tree manipulated. Chronic gastrointestinal (GI) bleeding is not unusual in ampullary or duodenal malignancy or with metastases to the C-loop, most commonly from a hypernephroma metastatic to the periampullary area. Exocrine pancreatic malignancy may present with steatorrhea, and glucose intolerance or frank diabetes are not uncommon.

Physical examination and lab data are variably helpful in defining the approach to patients with malignant obstructive jaundice unless examination clearly shows signs of non-resectability such as ascites, portal hypertension, or malignant adenopathy such as an umbilical metastasis. Although marked elevations in CEA and CA19-9 are thought to confer poor survival statistics in duodenal and pancreatic cancer, respectively, exceptions are common. Painless jaundice and a palpable gall bladder, while usually implying a malignant obstruction distal to the cystic duct, does little to define the therapeutic approach but does help us define the imaging sequencing [9]. Thus, although there is now a plethora of diagnostic tests (Table 2) to define the presence and location of biliary obstruction (ultrasound [US], abdominal computed tomography [CT], magnetic resonance imaging [MRI] in conjunction with magnetic resonance cholangiopancreatography

Table 2
Diagnostic imaging modalities in malignant obstructive jaundice

- Ultrasound*
- Abdominal CT*
- MRI-MRCP
- ERCP*
- EUS*
- Laparoscopy*
- ± PET scan
- ± Abdominal angiography

*Modalities that can be used in conjunction with biopsy, brush cytology or fine needle aspiration to acquire tissue at time of procedure. See text for abbreviations.

[MRCP], endoscopic retrograde cholangiopancreatography [ERCP], percutaneous transhepatic cholangiography [PTC], and endoscopic ultrasound [EUS]), most centres use US as a screening modality only to define the presence or absence of gallstones or ductal dilation [10–13]. Although ultrasound can define liver metastases and some abdominal masses, pancreas protocol CT has become the staging modality of choice and is predictive of non-resectability (encasement of major vessels, liver and/or distant lymph node metastases, peritoneal studding) in up to two-thirds of patients at baseline (Fig. 1). [13]. Moreover, findings allow targeted CT- or ultrasound-directed, fine needle aspirate or biopsy for tissue diagnosis, in the same or subsequent imaging session. Whether CT documentation of duodenal involvement defines non-resectability in a patient with pancreatic cancer has been hotly debated as pylorus preserving Whipple or radical pancreaticoduodenectomy removes this tissue [14]. In this setting, however, the tumour has invaded tissue planes to include lymph and vascular channels and the rate of resection *for cure* is extremely low in my experience.

Most authors relegate MRI/MRCP to a backup role with respect to staging of malignant obstructive jaundice [13]. Not only is the technology more expensive, but also tissue acquisition at time of the scan is impossible (Fig. 1). However, in patients in whom intravenous CT contrast cannot be used due to allergy or severe renal impairment, MRI/MRCP is a

Fig. 1. MRCP in divisum patient with pancreatic malignancy. Arrow demonstrates high-grade stricture. Note normal biliary tree.

Table 3
Staging modalities in malignant obstructive jaundice

Pancreas protocol CT*	± CT angiography
MRI-MRCP	± MR angiography
EUS	
Staging laparoscopy	

useful technique. The ability to obtain high quality cholangiograms is also useful in planning appropriate interventions in patients with cholangiocarcinoma.

The application of EUS in the staging of malignant obstructive jaundice is highly contentious [11–13]. There are authors who feel that EUS is the most sensitive tool to define vascular involvement in pancreatic malignancy. Likewise, intraductal ultrasound (IDUS) is quite helpful in defining the aetiology of biliary strictures in whom brush cytology or biopsy is non-diagnostic. There are others who feel that the primary role of EUS is tissue acquisition when percutaneous attempts are impossible or non-diagnostic or when adenopathy is suspicious.

In our own institution (Virginia Mason Medical Center), a pancreatic cancer patient who is potentially resectable by pancreas protocol CT will undergo diagnostic laparoscopically and peritoneal lavage if no peritoneal or miliary liver lesions are noted. Popularised by Warsaw et al. [15], 15-20% of patients resectable by CT scan are deemed non-operative candidates post-laparoscopy. Table 2 outlines diagnostic imaging, and Table 3 staging modalities in routine use for malignant obstructive jaundice.

Indications for biliary drainage in malignant obstructive jaundice

After initial staging procedures, surgically fit patients with the potential for surgical cure (20-30% of patients with pancreatic and <30% of all patients with biliary carcinoma) should be offered surgery. Unfortunately, with the exception of a few reports looking at aggressive post-operative chemoirradiation, the 5-year survival rates for pancreatic cancer approximate 5-8% and those for hilar cholangiocarcinoma in whom up to three-quarters are found unresectable for cure at time of exploration, are relatively comparable [1–7]. In contrast, 5–year survival rates for ampullary cancer approach 50-69% if patients are properly selected [8]. A number of studies have looked at preoperative biliary drainage as a bridge for surgery. Although some centres place bilateral percutaneous transhepatic

biliary drainage (PTBD) catheters routinely prior to attempted resection of Klatskin tumours, there are no data to suggest that stenting prior to planned Whipple procedure for pancreatic or periampullary cancer improves outcomes [8,13,16]. Rather, there are contradictory studies suggesting that patients who have undergone stenting prior to attempted Whipple or surgical bypass have an increased incidence of perioperative sepsis and/or wound infections.

Nevertheless, the endoscopist often sees these patients early in their workup and there is little controversy that symptomatic patients with cholangitis, jaundice, refractory pruritus, or those with obstructive pain should be considered for endoscopic stenting if surgery is not imminent. Stenting should also be proffered in patients in whom chemoirradiation is being used in an attempt to downstage a patient for ultimate resection, and drainage is mandatory once contrast has been injected into an obstructed biliary tree because of the risk of iatrogenic cholangitis. Finally, even in asymptomatic patients, stenting is frequently used in the 70-80% of patients with malignant obstructive jaundice to forestall symptoms of pruritus and improve body image.

Palliative techniques: Percutaneous vs. endoscopic vs. surgical

Distal obstruction

Although technically successful in up to 95% of unresectable patients, PTBD complications including bile leak, bleeding, and cholangitis, have limited its application currently to surgically unfit patients in whom therapeutic ERCP proves unsuccessful [5,7,13, 17–23]. With the improvement in imaging modalities, endoscopic palliation has replaced biliary-enteric bypass in many centres. For instance, in a meta-analysis of 856 patients treated with plastic prostheses, Nagger et al. [24] noted successful stent placement and relief of jaundice in approximately 90% of patients, with a mean survival of 5 months. These results are quite comparable to historical surgical data. Since then, there have been five prospective studies randomising surgical therapy to plastic prostheses for malignant obstructive jaundice (Table 4) [24–31]. Procedural success rates, 30-day mortality and mean survival have all been comparable between the two treatment arms although up to 50% of stented patients developed recurrent jaundice as a consequence of stent occlusion and there was a lower incidence of gastric outlet obstruction in surgical patients who had a concomitant gastric bypass. In contrast, our group has documented

Table 4
Randomized, prospective trials of SEMS vs. plastic (PE) stents in distal malignant obstructive jaundice

Author/year	No. of patients	Duration patency (mos)		% Dysfunction	
		SEMS	PE	SEMS	PE
Kaassis et al., 2003 [26]	118	>1 year	5.5	20	63
Prat et al., 1998 [29]	67	4.8	3.2	18	73
Lammer et al., 1996 [28]	101	9.2	3.6	19	27
Knyrim et al., 1993 [27]	55	6.2	4.6	22	43
Davids et al., 1992 [25]	105	9.3	4.6	33	54

that endoscopically treated patients utilise <50% of dollars spent on surgically treated patients, from diagnosis to death [32].

Proximal obstructive jaundice

As noted above, many centres initially place unilateral or bilateral PTBDs in types II–III cholangiocarcinoma patients being considered for surgical cure [5]. However, as preoperative imaging has improved, the number of patients undergoing exploration has declined significantly, as has surgical palliation. Prior to the development of self-expandable metal stents (SEMS), the interventional radiologic approach was commonly used preferentially to endoscopy. Not only could isolated areas of ductal obstruction be readily accessed under ultrasound or CT guidance, the resources required to change a malfunctioning tube were less than those required for a repeat ERCP. In addition, data were clear that a single endoscopically-placed plastic prosthesis into a bifurcation lesion predisposed patients to contralateral cholangitis if contrast was instilled into an undrained segment at time of ERCP. Deviere [33], for instance, reviewed 48 patients with Bismuth II and III strictures demonstrating significantly improved median survival (176 vs. 119 days), 30-day mortality (8% vs. 29%), and early cholangitis (17% vs. 38%) in patients who underwent bilateral as opposed to unilateral stenting [33].

Since the advent of SEMS, there are numerous series to suggest that Bismuth II, III, and IV lesions are better palliated, develop a lesser incidence of cholangitis, and demonstrate prolonged stent patency, whether prostheses are inserted percutaneously or endoscopically (Fig. 2) [5,16,20–22,34,35]. While intuitively, multiple SEMS would seem to confer survival and decreased infection advantage comparable to studies using plastic stents, study results are contradictory. In the only prospective, randomised trial published to date, De Palma et al. [36] randomised

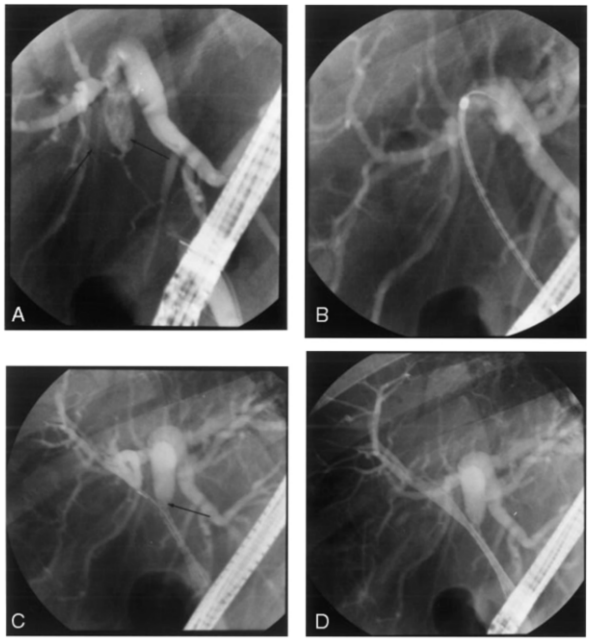

Fig. 2. Type 3 cholangiocarcinoma: (A) Arrows demonstrate right and left intrahepatic duct strictures treated with (B) left and (C,D) right ductal expandable stents.

patients with Bismuth I–III lesions for unilateral or bilateral SEMS. There was a higher success rate in the unilaterally stented group (89% vs. 77%, $p = 0.04$), adequate drainage (81% vs. 73%, $p = 0.05$) and a significantly lower complication rate (19% vs. 27%; $p = 0.03$). Procedure-related and 30-day mortality were comparable as was survival (140 vs. 142 days).

Comparable recent data have been published by Freeman and Overby [37], using MR and CT studies prior to ERCP to allow selection of a dominant duct and minimise injection into obstructed ducts in which drainage was not planned.

In contrast with extrinsic lesions by obstructive adenopathy at the porta hepatis, in which SEMS alone are used (Fig. 3), several other palliative manoeuvres have been described for cholangiocarcinoma. They include intraluminal brachytherapy, most commonly performed by utilising iridium-92 seeds passed through a PTBD catheter [38,39]. For instance, Gerhards et al. [40] retrospectively looked at brachytherapy as a possible adjunct to surgery (Group I: surgery no brachytherapy; Group II: surgery followed by external beam irradiation; Group III: surgery followed by brachytherapy). Mean survival was significantly improved in patients undergoing adjuvant radiation (I: 8 months; 2: 21 months; 3: 30 months) although the brachytherapy group had a higher rate of procedural cholangitis. Photodynamic therapy using sodium porfimer and a

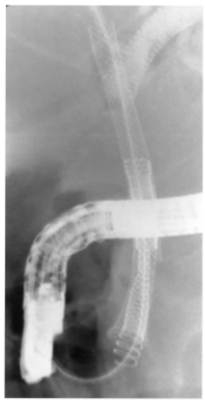

Fig. 3. Widely metastatic colon cancer causing obstructive jaundice treated with right and left duct Wallstents and common duct biliary EndoCoil.

variety of lasers has also been used, primarily endoscopically [41]. In the sole prospective, randomised trial, Ortner et al. [42] demonstrated significantly longer median survival (493 vs. 98 days, $p < 0.001$) in patients undergoing PDT in conjunction with stenting when compared to stenting alone. Finally, localised ablation using high-intensity ultrasound has been described in a small number of patients treated at time of ERCP [5]. Results are preliminary but decreased tumour bulk was noted in 3 of 6 patients in one study.

SEMS vs. plastic prostheses

As noted above, data are clear that proximal cholangiocarcinomas as well as other neoplasms are better palliated by SEMS. In contrast to the studies randomising palliative surgical bypass to plastic stent placement in distal malignancy, however, no such studies have been performed with metal stents. There are several reasons for this. On the one hand, it was clear that individuals stented with conventional prostheses developed recurrent jaundice and often cholangitis 3–6 months post-placement. A consequence of bacterial biofilm development, attempts at changing materials (polyvinyl, Vivithane, Teflon), improving flow with ursodeoxycholic acid, or impregnating the stents with a variety of antibiotics, have all failed to prevent occlusion. SEMS, because of their larger diameter (8–10 mm vs. 10–11 Fr.), have now been shown to maintain patency approximately two-fold longer than plastic prostheses in five prospective, randomised trials (Table 4) [25–29]. While this increase in stent survival has not been shown to improve patient longevity, the development of stent-related ' flu' (cholangitis) has dramatically decreased prior to patient demise. Figure 4 demonstrates various currently marketed, plastic and self-expandable metal stents.

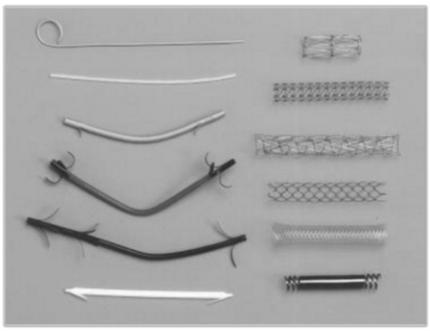

Fig. 4. Various plastic (left) and self-expandable metal stents (right) used to palliate malignant obstructive jaundice. See text for details.

A number of questions remain relative to SEMS. On the one hand, the cost of SEMS is approximately 20–40 fold higher than plastic prostheses. Although multiple studies have shown that SEMS are cost-effective in large populations because of the resources expended in repeat ERCP to replace plastic stents [43], there are clearly a subset of patients who die before stent dysfunction. Selection of these patients, if possible, would allow improved resource utilization. In an attempt to define which patient should receive which type of stent, Prat and his colleagues reviewed a variety of imaging, biochemical, and clinical criteria [29]. Patients with tumours <3 cm size, good performance status, and normal albumen were much more likely to live ⩾6 months, whereas those with low proteins, poor performance status, and larger tumours usually had survival of <3 months. They noted that the latter group should be considered for plastic prostheses, although I will usually insert a SEMS if the patient has had recurrent occlusion of a plastic stent or lives in a geographically remote area.

Other issues related to SEMS are their variable design and whether current data, almost all generated using endoscopically or radiographically placed Wallstents, can be generalised to other SEMS (Fig. 5). Currently, although there are a plethora of studies using a variety of commercially marketed SEMS, there is a single, randomised prospective multicentre trial comparing SEMS types [44–50]. Reported by Shah et al. [51], 145 patients were randomised either to a Wallstent or Spiral Z stent. Success rates were comparable, as were complication and reocclusion rates (median patency Z stent: 152 days; Wallstent: 154 days). In contrast to plastic prostheses [31,52–55], SEMS primarily occlude by tumour ingrowth or, more commonly, by mucosal hyperplasia at the site of the metallic struts [49]. An additional subset occlude by contralateral duodenal wall obstruction or local bile duct perforation as the stent straightens in an acutely angulated duct (Fig. 5). Attempts to minimise

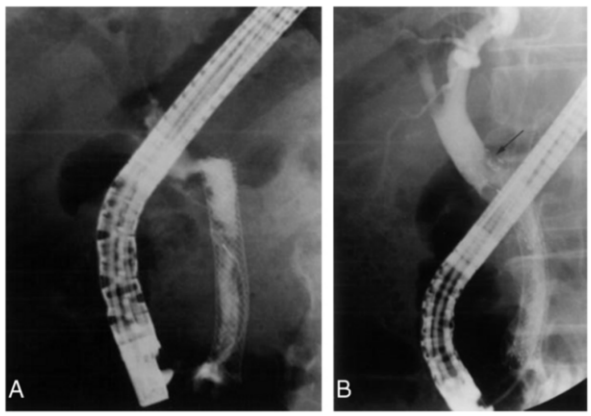

Fig. 5. (A) Biliary Wallstent in patient with pancreatic cancer (A). Note local perforation at proximal end in (A), treated with placement of subsequent Diamond stent (arrow) (B).

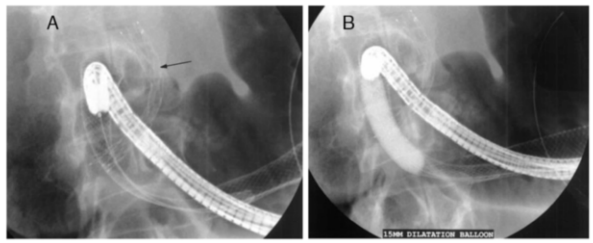

Fig. 6. Arrow demonstrates biliary Diamond stent. Note 2 interconnected C-loop Wallstents (A) dilated to complete expansion (B), dilated to complete expansion (C) in patient with pancreatic cancer, duodenal and biliary obstruction.

ingrowth or hyperplasia by use of a covered stent have been variably successful and data are conflicting over whether patency is prolonged [45,48]. Moreover, use of a coated stent has been associated with a higher migration rate as well as a subset of patients developing acute cholecystitis from cystic duct obstruction.

Most studies suggest that 5–10% of patients with pancreatic cancer and other forms of malignant obstructive jaundice develop gastric outlet obstruction (GOO), often as a preterminal event [32]. Historically, this has been treated surgically with a gastrojejunostomy or endoscopically-placed feeding jejunostomy in conjunction with decompressive gastrostomy in high surgical risk patients. There are now multiple series attesting to the high rate of successful duodenal SEMS insertion for GOO with survival and palliation statistics approximating surgical results (Fig. 6) [56–63]. While not strictly the focus of this article, endoscopists recognise the necessity of placing a biliary SEMS prior to, or in conjunction with, a duodenal SEMS because of the difficulty in accessing the biliary tree through the metal mesh after enteral stent placement. In a recent comparative study, Wong et al. [63] retrospectively reviewed 250 patients with

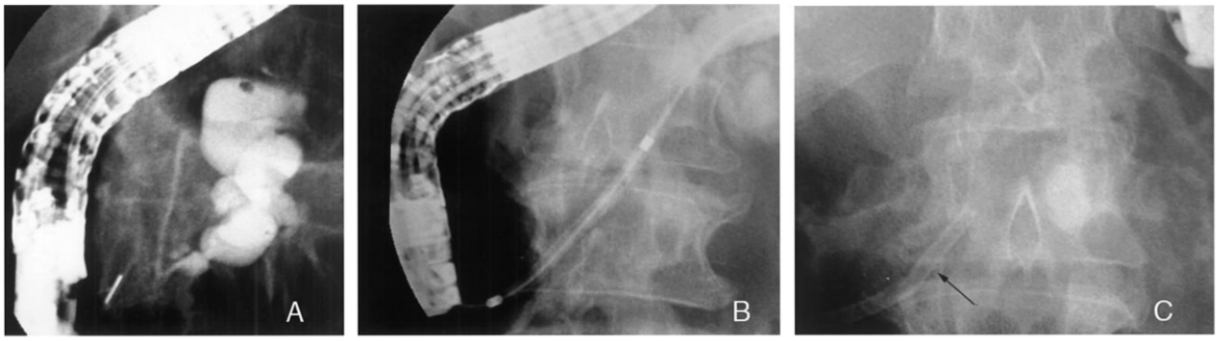

Fig. 7. Grossly, dilated pancreatic duct in patient with intractable post-prandial pain in non-surgical patient with ampullary cancer (A). Note ERCP (B) with subsequent pancreatic stent placement (C) (arrow) which resulted in complete pain relief.

pancreatic cancer. Of the 10% who developed GOO, 2/3 were bypassed or underwent palliative resection and 1/3 stenting. Median survival was two-fold longer (111 vs. 64 days) in the stented group and there was a decreased hospital stay (4 vs. 15 days) and 30-day mortality (0% vs. 17.6%).

Quality of life (QOL) data

Quality of life data are sparse in the palliation of malignant obstructive jaundice. Shinchi et al. [64] retrospectively reviewed 54 patients with unresectable cholangiocarcinoma treated with PTBD or SEMS, with or without external beam irradiation. The irradiated group had statistically significant longer survival (10.6 months vs. 4.4 months, PTBD) and higher average Karnofsky scores (75 vs. 68 with SEMS vs. 58 with PTBD).

Garcia Sanchez et al. [65] retrospectively analysed 30 patients with biliopancreatic malignancies palliated with endoscopic stent or surgery. Quality of life was defined by absence of jaundice, pruritus, and cholangitis after initial therapy. Although stented patients had a median survival of 9.6 months vs. 17 months for surgically treated patients, there was no significant difference in the ' comfort index' between the two groups.

Abraham et al. [66], in turn, looked at 50 inoperable or unresectable patients, 2/3 with a distal malignancy, 12.5% with a mid-ductal obstruction, and the remainder with more proximal lesions. Prior to stenting, 48% were jaundiced and 70% had pruritus. Elevated bilirubin and weight loss had the largest impact on baseline QOL whether defined by univariate or multivariate analysis. Following stent placement, improvement in bilirubin levels was associated with significant improvement in both mental health and social function. A baseline bilirubin of greater than 14, in turn, was associated with a lack of improvement in social function.

Finally, Van Laethem et al. [67] reviewed 35 patients with a variety of malignancies and obstructive metastases at the hilum. The overall success of endoscopic or rendezvous procedures was 86% and pruritus, jaundice, nausea, abdominal pain and anorexia improved significantly in 88, 86, 75, 66, and 50% of cases, respectively. Median survival was 4 months [6.5 versus 1.8 months ($p < 0.05$) in the group with complete versus incomplete resolution of jaundice].

A major determinant of QOL in some series was control of pain in patients undergoing palliative stenting, bypass, or resection of pancreaticobiliary cancer. Previous series suggest that 80% of patients with advanced malignant biliary obstruction experience severe pain [1]. While narcotics have been the mainstay of medical therapy, previous data by the Hopkins group has demonstrated that palliative resection of pancreatic cancer in conjunction with chemical splanchnicectomy using 20 ml of 50% alcohol on either side of the coeliac plexus, is associated with acute pain relief in 80% of the patients [4]. Moreover, pain relief persisted for up to 6 months and correlated with improved survival relative to patients without pain control.

More commonly coeliac neurolyses has been undertaken under CT or EUS guidance, the latter study offering the advantage of obtaining tissue for definitive diagnoses during the same procedure [11,68,69]. Regardless of methodology, however, coeliac block using alcohol ablation has been reported to offer significant pain relief and improved QOL in 85–95% of these unfortunate patients [11].

Additional studies demonstrate that some patients with pancreatic cancer develop relapsing attacks of pancreatitis or post-prandial pancreatic-type pain related to an obstructed pancreatic duct (Fig. 7) [54]. Popularised by Costamagna et al. [44], 60% of 55 patients who underwent PD stent placement at ERCP became symptom-free and another 20-25% had significant reduction in pain and analgesic requirements.

Conclusions

Malignant obstructive jaundice is ominous in metastatic disease and can be treated by resective surgery in only a subset of patients with pancreaticobiliary cancers. Although jaundice can be treated with bypass, percutaneous biliary drainage, or endoscopic stenting, patients are more than an obstructed bile duct. Proper palliation includes relief of pain, psychosocial support, and amelioration of gastric outlet obstruction in a patient subset.

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