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REVIEW ARTICLE

Pancreatic carcinoma: Palliative surgical and endoscopic treatment[*]

D.J. GOUMA, O.R.C. BUSCH & T.M. VAN GULIK

Department of Surgery, Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands

Abstract

The majority of patients with pancreatic carcinoma (hepaticojejunostomy) unfortunately will have palliative treatment and palliation of symptoms is important to improve Quality of Life. The most common symptoms that require palliation are jaundice, gastric outlet obstruction and pain. Obstructive jaundice should be treated with a biliary bypass, the optimal palliation in relatively fit patients and endoscopic stenting is preferred in patients with short survival (3–6 months). To prevent gastric outlet obstruction a prophylactic gastroenterostomy should be performed routinely during bypass surgery. Symptomatic patients after earlier stenting of the bile duct can be treated nowadays by duodenal stenting. Pain management is according to the progressive analgesic ladder but a (percutaneous) neurolytic celiac plexus block may be indicated. Currently a R1 (palliative) resection is acceptable in high volume centres but so far there is a very limited role for planned R2 palliative resections.

Key Words: *pancreatic carcinoma, palliative treatment, jaundice, gastric outlet obstruction, pain management*

Introduction

Pancreatic tumors are the fifth most common cause of cancer-related death in the Western world [1,2]. The incidence in the US is around 10 per 100 000 per year. The majority of these tumors are pancreatic adenocarcinomas and the survival is poor [1–4]. Despite surgical treatment with or without radiotherapy and chemotherapy, the overall 5-year survival is around 4% and has hardly improved during recent decades [3]. Unfortunately the majority of patients will present with 'incurable' disease due to extensive local disease or metastases at the time of diagnosis. There is confusion about the terminology, as the terms 'incurable', 'inoperable', and 'unresectable' have a variety of interpretations. The term unresectable is also partly dependent on the local surgical philosophy, for example, including a resection of the mesenteric or portal vein, as well as the acceptance of macroscopically nonradical resections. This surgical philosophy is not only a country-related pattern or 'part of the world'-related pattern but may also be influenced by the experience per center as well as local tradition of surgeons. The strong relation between outcome and mortality may play a role in the indication for resection and acceptance of palliative resections [5–7]. It has even been questioned whether cure is possible at all in patients with pancreatic cancer [3]. There is, however, consensus that patients who undergo resection have the best chance for long-term survival [3,4,8].

Thus overall the majority of patients will have palliative treatment and therefore palliation of symptoms will still be an important focus. The three most important symptoms that should be treated in advanced pancreatic cancer are obstructive jaundice, duodenal obstruction, and pain.

The decision to aim for palliative treatment can be made at two different time points during the disease. The first point is generally after the staging procedures and a selection is made for potential curative surgery, palliative surgery or nonsurgical (endoscopic) palliation. A second time point for selection of a treatment strategy is during surgical exploration and a decision can be made for a curative resection, a resection for optimal palliation or other surgical procedures for palliative treatment.

Thus, accurate initial staging remains the crucial step for the selection of surgical and nonsurgical

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(palliative) treatment. Contrast-enhanced spiral computed tomography (CT), magnetic resonance imaging (MRI), and endoscopic ultrasonography have enhanced the accuracy of radiological imaging, and noninvasive staging procedures are currently first choice [9–11]. Patients who are found to have a resectable tumor at preoperative noninvasive diagnostic work-up (dependent on local philosophy) should undergo an exploratory laparotomy directly. Patients with unresectable or incurable disease found during exploration (11–50%) are generally considered to be best treated with surgical palliation [12–14].

The current knowledge of different aspects of surgical and endoscopic palliative treatment for the above-mentioned symptoms (i.e. obstructive jaundice, duodenal obstruction, and pain) will be summarized in this review.

Obstructive jaundice

At the time of diagnosis up to 90% of patients with pancreatic tumors present with obstructive jaundice. More severe consequences are liver dysfunction and eventually hepatic failure due to bile stasis and cholangitis. Cholangitis is more frequently found in patients with ampullary lesions than in patients with pancreatic cancer. Relief of the obstructive jaundice causes a dramatic increase in the quality of life of patients and should therefore always be accomplished [15].

Biliary drainage can be achieved nonsurgically by placement of a biliary stent (endoscopic or percutaneous) or surgically by performing a biliary bypass. The success rate for short-term relief of biliary obstruction is comparable for both surgical and nonsurgical biliary drainage procedures and varies between 80 and 100%.

In the past, endoscopic biliary drainage was widely performed using plastic (Teflon and polyethylene) stents. Plastic stents can give rise to complications such as migration and occlusion, reported up to 40%. A new stent type for endoscopic treatment is the self-expandable (covered) metallic stent; occlusion will lead to cholangitis. Compared with plastic stents, expandable stents have a longer patency, but cannot be removed after placement [16,17].

Internal biliary drainage is generally preferred and performed by a cholecystojejunostomy, choledocho(hepatico)jejunostomy or choledochoduodenostomy [18]. In this extensive review the success rate of cholecystojejunostomy to relieve obstructive jaundice was lower than that for choledochojejunostomy. A randomized controlled trial (RCT) also confirmed that the technically more difficult choledochojejunostomy is preferred over a cholecystoenterostomy, due to the lower rate of recurrent jaundice and cholangitis and a better patency of the bypass [19].

A choledochoduodenostomy is not recommended because it is generally thought that this drainage procedure frequently results in recurrent jaundice due to local tumor ingrowth into the duodenum and the distal common bile duct.

In our institution (AMC, Amsterdam) a side-to-side Roux-en-Y hepaticojejunostomy is performed after removal of the gallbladder in case of detection of advanced disease or metastases. According to the extension of dissection and in an attempt to dissect locally advanced disease, the common bile duct may be transected in an early phase of the exploration and an end-to-side bilio-enteric anastomosis is made by a one layer running suture [20].

Results of surgical or endoscopic/percutaneous drainage

Five prospective RCTs have been performed, of which four compared surgical biliary drainage and endoscopic drainage [12,21–24]. In the first trial by Bornman et al. percutaneous biliary drainage was used and no differences were found between percutaneous and surgical palliation [22] (Table I). The other studies are relatively old studies and were performed between 1988 and 1994, except for the study by Nieveen et al. in which patients underwent a diagnostic laparoscopy as a final staging procedure and randomization for stent versus bypass was performed after proven metastasis [12]. The studies by Shepherd et al. [23] and Andersen et al. [21] were both hampered by the small number of patients that were randomized. Furthermore, the length of follow-up in both studies is unclear and the registration of complications and the re-admission rate are rather limited. In the study by Smith et al. [24] 201 patients were randomized. A higher procedure-related mortality was found after bypass compared with stenting (14% versus 3%, respectively). Interestingly, the 30-day mortality was not significantly different (15% versus 8%, respectively) but was still relatively high. Major complications after bypass versus stenting were significantly different, 29% versus 11%, respectively, and the minor complications rates were comparable, i.e. 29% versus 18%. The recurrence of jaundice and cholangitis during follow-up was significantly higher after stenting (36% versus 2%) and survival was comparable in both groups [24]. Taylor et al. [25] conducted a meta-analysis using the three above-mentioned studies and concluded that more treatment sessions were required after stent placement than after surgery, with a common odds ratio estimated to be 7.23.

The more recent randomized study by Nieveen et al. analysed the value of a diagnostic laparoscopy in 297 patients with a periampullary carcinoma [12]. A relatively small number of patients who were found to have uncurable disease due to metastases were allocated to either surgical (double bypass) or endoscopic palliation by a Wallstent. There was no difference in procedure-related morbidity or number of re-admitted patients between the surgically and

Table I. The prospectively randomized controlled trials comparing percutaneous or endoscopic with surgical biliary drainage.

Study	Bormann et al. 1986 [22] Percutaneous stent n=25	Bypass n=25	Shepherd et al. 1988 [23] Stent n=23	Bypass n=25	Andersen et al. 1989 [21] Stent n=25	Bypass n=25	Smith et al. 1994 [24] Stent n=100	Bypass n=101	Nieveen et al. 2003 [12] Wallstent n=14	Bypass n=13
Success (%)		76	80	92	96	88	95	93	100	100
Morbidity (%)	28	32	30	56	36	20	29	58	7	8
30-day mortality (%)	8	20	9	20	20	24	15	8	0	0
Hospital stay (days)	18	24	5	13	26	27	19	26	3	12
Re-admission(s) (%)			43	12	NS	NS	NS	NS	65	56
Recurrent jaundice/cholangitis (%)	38	16	30	0	0	0	36	2	NS	NS
Gastric outlet obstruction (%)	14	0	9	4	0	0	19	11	NS	NS
Survival (weeks)	19	15	22	18	12	14	21	26	17	27

NS, not stated in the article.

endoscopically palliated patients (Table I). The mean hospital-free survival was 164 days after surgical palliation and 94 days after endoscopic palliation. The survival was 192 and 116 days in the surgical and endoscopic group, respectively ($p = 0.05$). It must be kept in mind, however, that this concerns a selected group of patients who were thought to have a resectable tumor after conventional radiological staging.

So far a few general conclusions can be drawn from the available studies. Surgical treatment of biliary obstruction in unresectable pancreatic cancer is associated with higher early morbidity, longer hospital stay, and probably higher initial mortality rate, but long-term results are better. Endoscopic treatment is associated with a lower initial mortality and morbidity but more frequently leads to late biliary complications and re-interventions due to clotting of the stent, infection, and gastric outlet obstruction. The results for the newest development of a stent without a lumen are awaited [26].

Gastric outlet obstruction

Symptoms of gastric outlet obstruction (GOO) such as nausea and vomiting are reported in 11–50% of patients with pancreatic cancer at the time of diagnosis [1]. For the optimal palliative treatment, it is important to determine the origin of these symptoms. The first cause is motility dysfunction of the stomach and duodenum due to tumor infiltration of the celiac nerve plexus [27] or probably dysfunction of the small bowel due to tumor infiltration around the mesenteric artery. The second cause of GOO is mechanical obstruction of the duodenum due to direct tumor ingrowth into the duodenum or secondary to compression of the duodenum by a tumor in the direct vicinity. At presentation, mechanical obstruction is reported in around 5% of patients with pancreatic tumours. Approximately 3–20% of patients with unresectable pancreatic cancer will eventually develop mechanical GOO [14,28].

In the patients who are found to have an unresectable tumor at laparotomy, a gastrojejunostomy (in addition to a biliary bypass) can easily be performed without substantial morbidity.

On the other hand endoscopic duodenal stenting was recently introduced and also accepted as a nonsurgical palliative treatment of duodenal obstruction [29,30]. In a multicenter study the success rate after stent placement was 84% and oral intake in patients with succesful stent placement resumed for a median time of 146 days. So far no randomized trials have been performed to compare endoscopic duodenal stenting versus surgical gastroenterostomy.

Therefore, even between surgeons there remains a debate as to whether or not to perform a prophylactic gastrojejunostomy.

Two recent RCTs have evaluated the role of a prophylactic gastrojejunostomy in patients who were

Table II. Two prospectively randomized controlled trials analyzing a prophylactic gastrojejunostomy in patients who underwent a hepaticojejunostomy for unresectable periampullary cancer.

| | Lillemoe et al. 1999 [14] | | Van Heek et al. 2003 [31] | |
Study	Double bypass $n = 44$	Single bypass $n = 43$	Double bypass $n = 36$	Single bypass $n = 29$
Morbidity (%)	32	33	31	28
Mortality (%)	0	0	3	0
Hospital stay (days)	8.5	8	11	9
Late gastric outlet obstruction (%)	0	19	5.5	41.4
Survival (months)	8.3	8.3	7.2	8.4

found to have an unresectable periampullary or pancreatic tumour during explorative laparotomy [14,31]. The patients in both studies received either a prophylactic retrocolic gastrojejunostomy and a biliary bypass (double bypass) or a biliary bypass alone (single bypass) and also underwent a chemical splanchnicectomy during the laparotomy. The addition of a prophylactic gastrojejunostomy did not increase procedure-related mortality and morbidity rates and did not extend hospital stay (Table II). None of the patients who received a gastrojejunostomy in the study by Lillemoe et al. [14] developed late GOO during follow-up, compared with 19% of patients who did not undergo a gastrojejunostomy during the initial procedure. There was no significant difference in survival between both groups. Van Heek et al. also randomly assigned patients who were found to be unresectable during exploration to either a single or a double bypass in a multicenter trial [31]. Because the study by Lillemoe et al. was published shortly after the start of this study, an interim analysis was performed after 50% ($n = 70$) of the inclusion. Concerning mortality, morbidity, survival, and hospital stay, this study showed comparable results to the study by Lillemoe et al. (Table II). The study by van Heek et al. also longitudinally evaluated the quality of life using the EORTC-C30 and Pan 26 questionnaires and no major differences in the quality of life were found between the two surgical treatment groups [31]. After surgery most quality of life scores deteriorated temporarily and were restored to their pre-operative levels within 4 months. This pattern of a temporary deterioration of the different domains of quality of life score and restoration after a few months was recently also found in patients undergoing a Whipple procedure and comparable with the temporary deterioration of quality of life after bypass surgery [13]. From these trials it might be concluded that a prophylactic gastrojejunostomy is preferable to a biliary bypass alone, because of the significantly reduced risk of late GOO and the low morbidity and mortality rates. However, it has to be realized that in these two studies endoscopic stenting of duodenal obstruction during follow-up was not attempted and this might influence the outcome in the near future.

Pain management

At the time of diagnosis, approximately 40–80% of patients already report pain complaints. As the disease progresses, >90% of the patients will eventually have to deal with moderate to severe pain. The pain of advanced pancreatic cancer is most frequently located in the upper abdomen (epigastric region) and the back and is generally caused by tumor ingrowth into the mesenteric and celiac nerve plexus.

According to the World Health Organization (WHO) guidelines, the initial pain management should be pharmacological, and consists of analgesics such as nonsteroidal anti-inflammatory drugs (NSAIDs) and oral or transdermal narcotic analgesics [WHO 1986]. However, side effects of these drugs are reported frequently and eventually pharmaceutical pain management alone may not be sufficient in patients with pancreatic carcinoma [32]. The next step is a celiac plexus nerve block, which was first described by Kappis in 1914 [33]. It interrupts the innervation of the pancreas and prevents painful stimuli from reaching the brain. Currently the celiac plexus block can be performed percutaneously, endoscopically or during laparotomy.

The percutaneous route to block the celiac plexus has been investigated extensively. It can be performed under fluoroscopic, CT, or ultrasound guidance. In a meta-analysis of 24 publications that included 1145 patients treated with a percutaneous neurolytic celiac plexus block for cancer pain (63% pancreatic cancer), 70–80% of patients had a long-lasting benefit from the procedure [34].

There are only a few RCTs on percutaneous neurolytic celiac plexus blockade (NCPB) [35–37]. Best evidence is the recent study by Wong et al. [37]. They randomly assigned 100 patients with unresectable pancreatic cancer to receive either NCPB or a sham NCPB procedure. The major findings were that NCPB, as compared with optimized analgesic therapy, significantly improved pain relief in patients with pancreatic cancer, but did not affect the quality of life or survival. Furthermore, NCPB had no effect on the consumption of analgesics and significantly more patients needed a rescue NCPB in the analgesic therapy group (10 versus 3 patients, $p = 0.01$). These results suggest that the application of an aggressive

pain management protocol, regardless of NCPB, can control pain effectively, although NCPB can provide significantly better analgesia than optimized analgesic therapy alone.

More recently, endoscopic ultrasound-guided fine-needle injection therapy has been developed [38,39]. Different techniques have been described. Generally 5–10 ml xylocaïne 1% and then 15–20 ml alcohol 95% are injected at two areas of the celiac trunk. Results from non-randomized studies showed a significant reduction of pain in 85–90% of the patients; however, studies and follow-up are rather limited. Endoscopic pancreatic duct stenting has also been used successfully for relief of pain [40].

Celiac plexus block during surgery

Celiac plexus block during surgery has already been performed for many years. Lillemoe et al. performed a double-blinded RCT that compared a chemical splanchnicectomy during laparotomy with alcohol versus saline placebo [41]. Chemical splanchnicectomy was performed peroperatively by injection of 20 ml of either 50% alcohol or saline solution on each side of the aorta at the level of the celiac axis. Compared with the placebo group, alcohol injection significantly reduced the mean pain score for surviving patients at 2, 4, and 6 months. In the alcohol group, significantly more patients never reported pain until death (56% versus 34%). Interestingly, actuarial survival was improved in the subgroup of patients who reported significant preoperative pain and underwent a splanchnicectomy with alcohol ($p < 0.0001$). The authors suggested that the difference can be caused by the progressive physical deterioration due to persistent pain, which eventually leads to impaired survival.

Another strategy to palliate pain is thoracoscopic splanchnicectomy. This can be performed by a bilateral thoracoscopic splanchnicectomy or a unilateral left-sided thoracoscopic splanchnicectomy. Ihse et al. performed a prospective study analyzing the follow-up of patients with pancreatic cancer ($n = 23$) or chronic pancreatitis ($n = 21$) who underwent a bilateral thoracoscopic splanchnicectomy [42]. Within 1 week, the average pain scores reduced by >50% and remained stable throughout the follow-up period, which was 4 months for the patients with pancreatic cancer. More recently Leksowski showed adequate and consistent pain relief in 26 patients undergoing a unilateral splanchnicectomy [43].

Radiotherapy can also be applied to reduce pancreatic cancer pain. However, it may take several weeks before the relief of pain is achieved and side effects are common. Furthermore, due to the fractionated delivery of the radiotherapy, the treatment time for these patients with a short life expectancy is considerable. Most studies are limited due to small patient numbers and poor pain assessment methods; pain relief was experienced in 68% of patients, with a median duration of 6 months to pain progression [44,45].

Pancreaticoduodenectomy for palliation

Several reports have appeared which discussed the indications for performing a pancreaticoduodenectomy (PD) as a palliative treatment option [46–48]. This controversial question results from the observation in recent literature that morbidity and mortality rates after PD are decreasing. In early reports mortality after pancreatic resection was around 25%. In recent reports large series from specialized centres showed mortality rates below 5% [6,8,49–52]. This decreased mortality is partly due to improved management of severe complications [53,54] but is may also be due to a hospital-volume effect [5–7,50–52].

Frequently the term 'palliative resection' has been used incorrectly to describe this topic. In most patients in the above-mentioned studies the palliative resection was regarded as a macroscopically radical resection, which appeared to be microscopically irradical after pathological examination (a so-called R1 resection). Although the resection was undertaken with a curative intention, it can be considered as palliative. In this case the R1 resection is called 'palliative in retrospect'. It is debatable whether these patients should be included if the role of a palliative resection *per se* is discussed, because these patients underwent a resection with a curative intention. The term palliative resection should therefore only be used for R2 resections (resections with macroscopically residual tumor). There are a few of these situations, for example, when the tumor is found to be unresectable after a point of no return (e.g. transection of the pancreatic neck), or when resection is required due to preoperative tumor bleeding.

However, there might also be a limited role for a planned palliative resection. Unfortunately there are no prospective studies in which a resection was performed or planned as a palliative procedure leading to an R2 resection, but results of the so-called R1 resection are available.

Retrospectively, two studies investigated the role of a pancreaticoduodenectomy for palliation by comparing the outcome of irradical resections to the outcome of patients who underwent a single or double bypass for a locally invasive tumour without metastases [46,47]. Again, most patients underwent laparotomy with the intention of undergoing a curative resection. Results show that a pancreaticoduodenectomy can be performed with similar mortality, morbidity rates, and hospital stay, compared to a palliative bypass (Table III). Remarkably, the survival after a palliative resection is significantly longer than after bypass. This difference is probably due to patient selection and the limited compatibility of the two groups. In another retrospective study survival was 15.8 versus 9.5 months, respectively ($p < 0.01$) [48]. It can be con-

Table III. Studies that compared palliative resection and bypass surgery.

Study	Reinders et al. 1995 [46]		Lillemoe et al. 1996 [47]		Kuhlmann et al. 2005 [48]	
	Resection n=36	Bypass n=24	Resection n=64	Bypass n=62	Resection n=80	Bypass n=90
Median tumour size (cm)	4.30	4.25	3.6	NS	2.9	3.5
Morbidity (%)	44	33	42	32	41	31
Hospital mortality (%)	3	0	1.6	1.6	0	2
2-year survival (%)	24	2	16	8	24	2
Hospital stay (days)	25	18	18	15	16	10
Chemoradiation (%)	17	17	78	48	14	44

NS, not stated in the article.

cluded that controversy remains as to the role of a pancreatic resection for palliation. The available data confirm that, in the case of questionable radical resectability, a resection can offer relatively good palliation, so a more aggressive approach could be advocated in patients with a doubtful resectable tumor.

Laparoscopic palliation

Diagnostic laparoscopy has been used frequently in the diagnostic work-up for patients with suspected pancreatic tumors. Due to improved CT scan techniques the benefit of diagnosing metastases has been reduced to around 10% [12,55]. The use of diagnostic laparoscopy has also introduced the minimally invasive approach for subsequent palliation if metastases or local ingrowth of tumors are found.

The procedures include palliation of obstructive jaundice by cholecystojejunostomy or choledochojejunostomy and GOO by a gastroenterostomy.

Although a cholecystojejunostomy as a biliary bypass is considered to be less suitable because of the higher incidence of recurrent jaundice, this strategy is easier and safer than a hepaticojejunostomy. To prevent short-term obstruction of the cholecystojejunostomy, the tumor status in relation to the cystic junction anatomy should always be assessed by performing cholangiography, otherwise a laparoscopic common bile duct exploration and hepaticojejunostomy is indicated. The available data show that the laparoscopic double bypass can be performed

safely, with acceptable morbidity and low mortality (Table IV). However, the long-term follow-up concerning recurrent jaundice and GOO is only highlighted briefly in these studies [56–58]. As mentioned earlier, the new endoscopic techniques including duodenal stenting for gastric outlet obstruction [59–61] should be compared with new minimally invasive laparoscopic approaches.

Conclusions

The most common symptoms that require palliation in patients with pancreatic cancer are obstructive jaundice, GOO, and pain.

To palliate obstructive jaundice, a biliary bypass should be performed on relatively fit patients. Compared with endoscopic biliary stenting, a biliary bypass provides optimal long-term prevention of biliary obstruction, but is associated with higher initial morbidity. Stents are preferred in patients with a relatively short survival (3–6 months).

In addition to the biliary bypass, gastric bypass should be performed routinely to prevent GOO due to tumor ingrowth or compression of the duodenum. Novel techniques for palliation of GOO are being developed, such as endoscopic duodenal stenting. However, these techniques still have to be validated.

More than 90% of patients will have to deal with severe pain during the course of the disease. The initial treatment can be analgesic, but when the disease progresses this will not be sufficient in several cases. A neurolytic celiac plexus block can be per-

Table IV. Three cohort studies evaluating combined laparoscopic biliary and gastric bypass.

Study	Rhodes et al. 1995 [56]	Rothlin et al. 1999 [57]	Kuriansky et al. 2000 [58]
	n=16	n=14	n=12
Successful laparoscopic treatment (%)	94	100	100
Mean operating time (min)	75	129	89
Morbidity (%)	12.5	7	33
Mortality (%)	0	0	8
Mean hospital stay (days)	4	9.4	6.4
Recurrent jaundice and/or cholangitis (%)	0	NS	NS
Gastric outlet obstruction (%)	NS	NS	17
Survival (days)	201	NS	85

NS, not stated in the article.

formed percutaneously or during laparotomy. When the tumor is found to be unresectable during exploration, a plexus block is a relatively straightforward procedure. Radiotherapy can also be applied to treat pain, but data are limited.

So far there is a very limited role for R2 palliative resection.

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