

Palliative treatment in “peri”-pancreatic carcinoma : stenting or surgical therapy ?

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Abstract

Mostly, patients with peri-pancreatic cancer (including pancreatic, ampullary and distal bile duct tumors) are diagnosed in a stage in which curative resection is not possible. The median survival rate of patients with non resectable peri-pancreatic cancer varies between 6 and 12 months. During this period palliative treatment is necessary, which should focus on major symptoms as obstructive jaundice, duodenal obstruction and pain. Controversy exists about how to provide optimal palliative treatment.

Both surgical and non surgical palliative procedures relieve obstructive jaundice. From early retrospective and prospective randomized studies it is known that in the early phase after treatment, more complications are found after surgical palliation, whereas in the late phase more complications are seen after endoscopic palliation. Because more recent studies clearly showed improved results after surgical palliation, current recommendations probably should be that patients with a suspected poor short-term survival (< 6 months) should be offered non surgical palliative therapy and those with a longer life expectancy may best be treated with bypass surgery.

Unfortunately, valid criteria for estimating the remaining survival time are not available, except for the presence of metastases. The use of a prognostic score chart might assist in estimating the prognosis. Literature does not give sufficient information to make a well deliberated (evidence based) selection between the different types of surgical bypasses, but a choledochojejunostomy is generally preferred.

After stenting, a correlation is found between survival and the development of duodenal obstruction, and between 9% and 21% of the patients who underwent a surgical biliary bypass without a prophylactic gastric bypass, will develop gastric outlet obstruction. Therefore, in patients with a relatively good prognosis it is recommended to perform routinely a double – biliary and gastric – bypass.

Pain is a frequent symptom and is related with poor survival. Pain management aside from pain medication can be performed by means of a celiac plexus blockade or a thorascopic splanchnicectomy, and also radiotherapy seems to have a positive result on pain. (*Acta gastroenterol. belg.*, 2002, 65, 171-175).

Key words : pancreatic neoplasm, palliation, obstructive jaundice, duodenal obstruction, pain, survival, stenting, surgery.

Introduction

Peri-pancreatic carcinoma (including pancreatic, ampullary and distal bile duct tumors) is the fifth leading cause of death from malignancy and its incidence is about 10 per 100.000. Surgery is the only possible curative treatment modality. However, at the time of diagnosis, surgical resection is feasible in only 10-15% and does not guarantee satisfying long-term results, as the overall 5-year survival is less than 5% (1,2). Therefore, appropriate palliation of the major symptoms of peri-

pancreatic tumors, which are obstructive jaundice, duodenal obstruction and pain, is of major importance.

Although both surgical and non-surgical strategies can be used for palliative treatment, no consensus has been reached on which strategy should preferably be used, nor the criteria for selection of the patients for either treatment are known. When a patient is selected for surgical treatment, still discussion remains on the type of bypass, and whether beside the biliary bypass a prophylactic gastroenterostomy should be performed. For patients with persistent pain, no consensus has been reached on the best way to relief it.

The aim of this article is to summarize methods of surgical and non-surgical palliative treatment of peri-pancreatic cancer.

Obstructive jaundice

Obstructive jaundice is the most important symptom in patients with peri-pancreatic cancer : about 70% of the patients suffer from jaundice at the time of presentation. If untreated, it will result in liver failure with all concomitant symptoms in short time (1-3). Biliary drainage is essential in relieving pruritus, nausea and anorexia, which are the major symptoms that patients suffer from. Obstructive jaundice can be treated surgically or non-surgically. Surgical options include internal bypass by means of cholecystoduodenostomy, choledochoduodenostomy, choledochojejunostomy, or hepaticojejunostomy. Non-surgical options include the percutaneously or endoscopically inserted endoprosthesis. The short-term success rates of a bypass- and an endoscopic procedure in term of relief of the biliary obstruction vary between 75-100% and 82-100%, respectively (4). The application of either surgery or endoprosthesis in the palliation of obstructive jaundice in patients with pancreatic cancer has been discussed extensively in the past.

Initially, a surgical bypass was associated with high mortality (15%-30%) and substantial morbidity (20%-60%), a longer hospital stay, but little recurrent

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Table I. — Results of the initial and late morbidity after the palliation of obstructive jaundice with endoscopic endoprosthesis (stent) or surgical biliary bypass in patients with pancreatic carcinoma. Patients were stratified for short (< 6 months) and long (> 6 months) survival times (5)

MORBIDITY		Survival < 6 months n = 64	Survival > 6 months n = 43
Stent (n = 63)	Early *	7.5%	0
	Late	23%	61%
Bypass (n = 44)	Early	29%	5%
	Late	0	0

* early ~ < 1 week ; late ~ > 1 week.

obstructive jaundice (5,6). Biliary drainage by endoscopic stenting has a lower complication rate in the early phase, but cholangitis and recurrent obstructive jaundice are seen in up to 20% to 50% of the patients who survive longer than 6 months (5). In a retrospective study by Vd Bosch *et al.* (5), patients who underwent either a surgical biliary bypass (n = 44) or a stenting procedure (n = 63), were stratified for short (< 6 months) and long (> 6 months) survival times. In short-term survivors, higher early morbidity rates and longer hospital stays were seen in patients who had undergone a surgical bypass. In long-term survivors, there was no difference in the hospital stay between the two groups, but the late morbidity rate was significantly higher in the endoprosthesis group (Table I) (5). The authors concluded that endoscopic endoprosthesis is the optimal palliation for patients surviving less than 6 months, and surgical biliary bypass for those surviving more than 6 months.

However, the above-mentioned study is retrospective, and best evidence should be obtained from randomized controlled trials. Four prospective randomized trials addressing surgical and non-surgical palliative procedures have been published (4,7-9). Again these randomized trials demonstrate that there is no difference in relief of obstruction (Table II). A surgical bypass was associated with high mortality (15%-30%) and morbidity rates (20%-60%), but showed little recurrent obstructive jaundice during follow-up (4,7-9). So, the conclusion from these retrospective and prospective randomized studies is that in the early phase after treatment

more complications in terms of morbidity and mortality are seen after surgical palliation, whereas in the late phase more complications are seen after endoscopic palliation, especially recurrent jaundice, cholangitis and sepsis. In more recent studies however, mortality after bypass surgery is much lower, which might be partly due to patient selection (10-12). In a consecutive series of 124 patients who underwent bypass surgery in our center, a hospital mortality of 2.5% (30 days mortality 0.8%) was found. The surgery related complication rate was 17.5% and hospital stay 17 days, which is reduced more recently to 10 days (13). In selected patients bypass surgery is safe nowadays, which has also been shown in other studies (11,12).

Consequently, we advocate that surgical palliation should be preferably performed in patients with a relatively longer survival time (more than 6 months), while endoscopic palliation should be the optimal treatment for patients with a relatively short survival time (less than 6 months).

Unfortunately, it is still difficult to predict the remaining survival time of these patients. The identification of prognostic risk factors in order to predict the survival time has been studied previously (5,14-17). Presence of metastases appeared to be the only important risk factor, but the effect of other identified factors such as age, sex and weight loss were inconsistent. From the Triple-P Study performed of data from studies in 5 different institutions, we developed a prognostic score chart to predict survival probabilities for 3, 6 and 9 months after diagnosis. Data from all patients were pooled, and the factors age, sex, metastases and a center specific effect were incorporated in the chart (Table III). For example : a 65 year old female with a pancreatic head carcinoma without demonstrable metastases, admitted in a hospital with a reference 6 months mortality of 10%, will have a prognostic score of 55, and consequently a 6 months survival probability of 79%. Using this score chart we could select 339 patients (33%) with a predictive 6-month survival probability of 59% or more for bypass, and 447 patients (44%) with a predictive 6-month survival probability of 24% or less for endoscopic stenting (16). In patients with scores between 90 and 110, the choice of treatment should be based on other criteria. However, this score chart still needs to be tested

Table II. — Four prospective randomised trials addressing surgical and non-surgical palliative procedures in obstructive jaundice (4,7-9)

	Bornman 1986		Shephard 1988		Andersen 1989		Smith 1994	
	stent n = 25	bypass n = 25	stent n = 23	bypass n = 25	stent n = 25	bypass n = 25	stent n = 101	bypass n = 100
Success (%)	84	76	80	92	96	88	94	93
Morbidity (%)	28	32	30	56	36	20	30	58
Mortality (%)	8	20	9	20	20	24	8	15
Hospital stay (days)	18	24	5	13	26	27	19	26
Recurrent jaundice (%)	38	16	30	0	0	0	36	2
Duodenal obstruction (%)	14	0	9	4	0	0	17	7
Survival (weeks)	19	15	22	18	12	14	21	26

Table III. — Chart for calculation of prognostic scores (PS) for the first 6 months after diagnosis and the observed survival rates for different time periods after diagnosis (16)

Variable	6 months PS			
Sex	Male	⇒	age	O
	Female	⇒	50	O
Metastases	yes	⇒	40	O
Center effect	reference mortality		$O \times 50 =$	O
Total PS				O
				N (%)
				6 months
				< 70
				96 (9%)
				0.79 (0.04)
				70-90
				243 (24%)
				0.59 (0.03)
				90-110
				234 (23%)
				0.49 (0.03)
				110-130
				269 (26%)
				0.24 (0.03)
				> 130
				178 (18%)
				0.15 (0.02)

prospectively to confirm which factors are of really significantly predictive value.

When surgical palliation is preferred, the questions remain which biliary bypass procedure should be performed, and whether a prophylactic gastric bypass is indicated to prevent gastric outlet obstruction. Several different surgical biliodigestive bypasses can be performed. The most simple surgical biliary drainage procedure is a cholecystoenterostomy, which also can be performed laparoscopically (18). The disadvantages of a cholecystoenterostomy are a relatively high occurrence of recurrent jaundice around 20%, high failure rate and postoperative complications. Whereas after choledochojejunostomy recurrent jaundice is seen in only 8%, accompanied by a lower failure and complication rate (6,18). If despite these disadvantages a cholecystoenterostomy is considered, in particular in the laparoscopic area, cholangiography should be performed to monitor the patency of the cystic duct (19). Most surgeons do not recommend a choledochoduodenostomy, because this procedure also leads more frequently to recurrent jaundice during follow-up caused by local tumor ingrowth. However, Di Fronzo *et al.* recently reported 71 patients with a choledochoduodenostomy who did not develop recurrent jaundice during a mean survival of 13 months. Gastric outlet obstruction was only found in 11%, for which in all cases a gastroenterostomy was performed (20). There is not sufficient evidence in literature in favor of one type of bypass surgery. Indications for a prophylactic gastric bypass will be discussed in next paragraph.

Duodenal Obstruction

Although symptoms of nausea and vomiting occur in 30-50% of the patients with peri-pancreatic cancer, this is not always caused by mechanical obstruction. Approximately 10-20% of patients with advanced pancreatic cancer develop duodenal obstruction at some point before death (21-23).

After non-surgical palliation by stenting, duodenal obstruction occurs in the early and late postoperative phase. In a large retrospective series in which 691 consecutive patients receiving a stent in our institution for a

peri-pancreatic tumor were followed, 75 (11%) developed duodenal obstruction : 9% of the patients with pancreatic cancer and 23% of the patients with ampullary tumors. Median time between stenting and the moment when the diagnosis of duodenal obstruction was made, was 8.5 months. Clearly, a correlation was found between survival and the development of duodenal obstruction : the longer the survival, the higher the rate of duodenal obstruction (Table IV). A subsequent open gastroenterostomy was performed in 68 (90%) patients and 24 (30%) patients also underwent a biliary bypass with a high mortality (20%) and short survival (4 months) (24).

After surgical palliation with only a biliary bypass, gastric outlet obstruction has been described in 9-21% of the patients (6). Therefore, a prophylactic gastroenterostomy is routinely performed in a number of centers during a biliary bypass procedure (12, 25). The only prospective, randomized trial evaluating the role of prophylactic gastroenterostomy demonstrated that it significantly decreased the incidence of late gastric outlet obstruction. Moreover, because morbidity and mortality did not increase by adding a gastroenterostomy to the procedure in this study, this should be the treatment of choice (25). One should realize however, that most patients in this trial underwent surgery in an attempt to perform a resection, and therefore there might be a bias by patient selection. In earlier studies, high morbidity and mortality up to 25% have been described following a gastrojejunostomy (6). Others prefer to perform selectively a gastroenterostomy depending on symptoms of nausea and vomiting, or evidence of duodenal obstruction by endoscopy barium studies or during surgery (4,5). Conclusive, in patients who have a relatively good prognosis, a double bypass – a biliary and prophylactic gastric bypass – should preferably be performed.

Pain

Pain is another major symptom in pancreatic cancer and is reported in 30-40% of patients at the time of diagnosis and increases to 90% shortly before death (2). Pharmacological treatment is the mainstay of pain treatment for patients with pancreatic cancer (26,27).

Table IV. — Duodenal obstruction after palliative endoscopic treatment of patients (n = 691) with obstructive jaundice due to a pancreatic head region tumor (23)

Type of tumor	Pancreatic head	Bile duct	Ampullary
Number of patients	581	29	81
Duodenal obstruction	9%	14%	23%
Onset (days)	206	293	419
Survival (months)	5	6.5	13.5

However, various side effects have been reported. Non-Steroid Anti-Inflammatory Drug (NSAID) therapy can cause gastrointestinal toxicity (25). Opioid treatment is generally associated with persistent constipation, and can less frequently cause nausea, vomiting, sedation or anxiety (26,27).

In a prospective randomized trial it has been shown that the celiac plexus blockade with 50% alcohol injection performed during surgery could markedly reduce pain in patients with pre-existing pain and it also reduced the need for postoperative pharmacological treatment without additional morbidity (28). In this study the median pain free survival after alcohol injection of the celiac plexus was 3.3 months compared to 0.8 months in the placebo group. Percutaneous celiac plexus blockade also reduces pain (29-31). Unfortunately, these effects of both types of celiac plexus blockade are not permanent and side effects have been reported as diarrhea and orthostatic hypotension (28-30). Alternatively, neural blockade can be performed surgically by thorascopic splanchnicectomy (32).

Radiotherapy has been applied for local tumor control in an attempt to improve the survival time while maintaining an acceptable quality of life (33). Several studies demonstrated that radiotherapy (external beam radiation, intra-operative, interstitial) resulted in reduction of pain and consumption of pain medication (33-35). The most frequent side effects of external beam radiotherapy are nausea and vomiting (35).

In a recent series of 98 patients that underwent palliative bypass surgery in the Academic Medical Center, 13 mostly for unresectable disease found during exploration, pain treatment with a pain medication, celiac plexus blockade, or radiotherapy was analyzed retrospectively. The consumption of pain medication increased during follow-up to 52%, 57%, and 46%, respectively, at three-quarter of the survival time but did not differ in the three groups. No significant differences for the median (non-opioid or opioid) pain medication free survival were found between the bypass and celiac plexus groups, although a lower consumption of pain medication could be expected after administration of the intraoperative celiac plexus blockade (13).

Conclusions

Adequate palliative treatment is essential in patients with peri-pancreatic cancer. Current recommendations

probably should be that patients with a poor short-term survival time (< 6 months) should be offered non surgical palliative therapy, and those with a longer life expectancy (> 6 months) may best be treated surgically. Most authors prefer a choledochojejunostomy, and we advise to perform a prophylactic gastroenterostomy in patients who have a relatively good prognosis.

Pain is a frequent symptom and is related with a poor survival. Pain management aside from pain medication by means of a celiac plexus blockade has been proven to be effective, however our own data do not support these findings. Radiotherapy seems to have a positive result on pain.

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