Review

Standard surgical treatment in pancreatic cancer

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Summary

Pancreatic cancer is the third leading neoplasm of the gastrointestinal system and has a dismal prognosis. The majority of patients are no more suitable for resection at time of diagnosis due to early development of distant metastases or major infiltrations of adjacent structures. However, due to the resistance of pancreatic cancers against chemoradiation, curative resection represents the only therapy with a potential for cure. For the surgical treatment of pancreatic head cancer, the classical Whipple operation is still the standard procedure but during the last two decades, pylorus-preserving duodenopancreatectomy has been evolved as a more conservative procedure in order to omit the consequences of partial gastrectomy. For cancer of the pancreatic body and tail, distal pancreatectomy or total pancreatectomy represent the current standard treatment. More radical methods like regional pancreatectomy and resection with extended lymph node dissection have failed so far to demonstrate any improvements in long-term survival compared to the standard types of resection. To further improve the treatment of pancreatic cancer, prospectively randomised trials are needed to compare these extended surgical procedures with the standard types of resection.

Key words: classical Whipple operation, extended lymph node dissection, left resection, mortality, morbidity, long-term outcome, pancreatic cancer, pylorus-preserving duodenopancreatectomy, regional pancreatectomy, total pancreatectomy

Introduction

Pancreatic cancer constitutes currently the third leading neoplasm of the gastrointestinal system and is characterised by an aggressive growth and an extremely poor prognosis., therefore making pancreatic cancer the fourth leading cause of cancer-related death in the Western world [1]. Since current conservative oncological therapies have failed to show any long-term success, curative resection remains the only therapy with a potential for cure [1]. During the last two decades, the risks of pancreatic resections have decreased considerably and a mortality rate of under 5% after pancreatoduodenectomy is nowadays considered a standard achievement in experienced centres [2, 3]. During the same time period, a steady increase in the rate of resection can be observed so that some centres report now a resectability of over 50% [2]. Despite these significant advances in pancreatic surgery, improvements in long-term survival are less obvious since most patients suffer from the early occurrence of local recurrence or distant metastases even after curative resection. An recent survey under surgeons in the United States demonstrated an overall long-term survival rate of under 10% with a median survival period of 18 month after resection for pancreatic cancer and other studies from experienced centres have reported similar results [4-6].

The reasons for this biological aggressiveness are not known. However recent molecular-biological studies have shown that pancreatic cancers harbour a variety of genetic alterations and overexpress numerous growth factors and their receptors [7]. Although the biological significance of these multiple growth factor overexpression is currently not fully understood, experimental studies have shown that inhibition of the signaling pathway downstream of the receptor may inhibit pancreatic cancer growth [8, 9]. It may be hoped that a better understanding of the biological relevance of the molecular alterations of pancreatic cancer will lead to further improvements of current therapies and to the development of new treatment modalities in the near future such as gene therapy approaches for example [10].

Standard surgical procedures for the treatment of pancreatic cancer

Standard Whipple resection

It was the pioneering work of Allen O. Whipple to standardise the procedure of partial pancreatoduodenectomy which in honour of this great surgeon bears now his name [2]. Since 60-70% of all pancreatic cancers are located in the head region, the Whipple procedure is still considered the standard surgical procedure by most surgeons. The operation consists of resection of the pancreatic head together with the duodenum, the distal half or two thirds of the stomach together with the right half of the great omentum, the gallbladder with the common bile duct and the peripancreatic lymph nodes [11]. Reconstruction is performed by a pancreato-jejunostomy as favoured by most surgeons or by a pancreato-gastrostomy [2]. Although, the mortality has decreased to a rate of under 5% in experienced centres [2, 3], postoperative morbidity still remains considerably with the occurrence of pancreatic fistula and severe bleeding being the most serious ones [12]. However, the administration of synthetic somatostatin-analogues as a perioperative antisecretory regimen has lead to a significantly reduction of pancreatic fistulas in two randomised studies [13, 14]. In contrast to these improvements in perioperative morbidity and mortality, increases in long-term survival are less obvious. Although, some authors showed a 5-year survival rate of 15-28% [2, 15, 16], most institutions continue to report a survival rate of no more than 10% with an average survival time of 12-18 months [4, 17, 18]. Significantly better is the prognosis for patients resected with an early

Table 1.Mortalilty and 5-year survival after classical Whipple operation

Author	year	N	mortality	survival
Condie et al	1989	13	31%	7.7%
Funovics et al	1989	100	13%	5%
Lygidakis et al	1989	111	2%	
Trede et al	1990	133	2%	24%
Cameron et al	1991	52	9%	19%
Roder et al	1992	31	2%	3%
Beger et al	1994	101	4%	9%
Baumel et al	1994	555	8%	15%
Sperti et al	1996	113	5%	12%
Chou et al	1996	93	8%	
Van Berge Henderson et al	1997	100	6%	
Bern	1998	52	3.8%	

cancer stage (stage I according to the UICC classification), although few patients will present with these stage at time of diagnosis [16, 19, 20]. (Studies summarized in Table 1).

The pylorus-preserving pancreatic head resection

The pylorus-preserving pancreatic head resection represents a more conservative alternative to the classical Whipple procedure and was developed for the treatment of tumours of the papilla of Vater to omit the side effects of partial gastrectomy [21]. The procedure was popularised by Traverso and Longmire and many surgeons have now adopted the procedure for the treatment of chronic pancreatitis and pancreatic cancer as well [2]. Technically, the duodenum is divided 2-3 cm distal the pylorus region, the pylorus together with its neurovascular supply is preserved and reconstruction is performed by a end-to-side duodenojejunostomy [2]. The remaining steps of the operation are identical with the classical Whipple-procedure.

Doubts have been raised as to the radicality of the pylorus-preserving procedure for pancreatic cancer [2]. However, histopathological studies from 140 operative specimen from patients with pancreatic head cancer showed no tumour infiltration of the pylorus region or the lymph nodes along the major and minor curvatures of the stomach [22]. Analysing comparable tumour stages, long-term survival after the pylorus-preserving technique seems to show no significant deviation from the results after classical duodenopancreatectomy with the exception of one retrospective study on a small patient sample which reported an advantage for the classic Whipple procedure in patients with stage III disease [2, 23, 24]. Today, preservation of the pylorus is now widely accepted as a suitable alternative to the classic Whipple procedure for all stages of pancreatic cancer [25].

Another point of debate remains the effect of pylorus-preserving Whipple resection on gastrointestinal function since some authors reported a higher incidence of delayed gastric emptying after pylorus-preserving resection while others could not [2, 23, 26]. Commonly, delayed gastric emptying is a temporary occurrence and gastric function will normalise within a period of 2-4 weeks postoperatively in the majority of patients [27]. A plausible explanation for this temporary delay in gastric function may be the formation of an anastomotic oedema in the initial postoperative period which could be aggravated by a disturbance in neurovascular supply. In a recent study, the presence of intraabdominal complications was detected as a major risk factor for delayed

gastric emptying independently of the performed type of resection [26]. This observation goes along with our own experience in 112 consecutive pancreatic head resections for pancreatic cancer. However, controlled randomised trials comparing long term survival, gastrointestinal function and quality of life after classical Whipple and pylorus-preserving resection are needed in order to evaluate these two procedures in the future.

Another advantage of the more conservative pylorus-preserving technique concerns postoperative weight gain which seems to favour the preservation of the pylorus [24, 28]. However, data from randomised studies are still lacking to prove this hypothesis. (Studies summarized in Table 2)

Resection of cancer of the pancreatic body and tail

In about 30% of cases, pancreatic cancers are located in the body and tail of the pancreas. Due to their lack of symptoms, these tumors are typically diagnosed in advanced tumour stages and therefore only a minority of patients are suitable for resection. [29]. If only the pancreatic tail is involved, pancreatic left resection can be performed. Therefore the greater curvature of the stomach is mobilised as well as the left colon flexure. The splenic artery is lighted and the pancreas is dissected near the body region with a sufficient large resection margin to the tumour. The distal pancreas is then removed together with the peripancreatic lymph nodes and the spleen to ensure radical resection. Median survival period was given by 13 month in a recent study while others report a 3-year or 5-year survival rate of 19% and 16.6% for localised cancers respectively [29-31].

If the cancer infiltrates the pancreatic body or if there is multi-locular disease, total pancreatectomy may be indicated [32]. The technique is formally identical to a Whipple resection, however the pancreas is fully mobilised and resected together with the spleen and the lymph nodes around the pancreas as well as along the left gastric artery, the splenic artery and the celiac trunc. Reconstruction is simplified and consists of a hepato-jejunostomy and a gastrojejunostomy. If the pylorus region is not infiltrated by tumour masses, we prefer to perform a pylorus-preserving total pancreatectomy similar to the pylorus-preserving Whipple resection. Total pancreatectomy was first described by Ross and Porter in 1954 in order to decrease the substantial mortality and morbidity of pancreatic leakage after pancreatic head resection and to improve long-term survival [2]. However, most surgeons experienced no significant advantage in long-term survival when compared

Table 2. Mortality and 5-year survival after pylorus-preserving Whipple operation.

Author	year	N	mortality	survival
Grace et al	1986	13	4%	25%
Braasch et al	1986	14	2%	
Klinkenbijl et al	1992	25	2%	
Roder et al	1992	22	2%	0%
Büchler et al	1993	19	5%	9%
Kozuschek et al	1993	24	8%	19%
Mosca et al	1994	76	7.5%	12%
Tsao et al	1994	22	2%	7%
Van Berge Henderson et al	1997	100	1%	
Yeo et al	1997	650	1.9%	
Bern	1998	59	3.4%	

with the results after a standard Whipple procedure [33]. Furthermore, early total resection of the pancreas was compromised by a substantial mortality of up to 37% and the consequences of both exocrine and endocrine depression of pancreatic function [33, 34]. Thus, some authors reported the occurrence of lethal hypoglycaemia due to unmanageable diabetes mellitus [33]. With the advances in pancreatic surgery and the development of antisecretory regimens, pancreatic anastomosis can now be performed safely and total pancreatectomy is no longer indicated today for localised tumours in the pancreatic head [33].

More radical surgical procedures

Despite marked advances in pancreatic surgery, the majority of patients suffer from distant metastases or local tumour recurrence a short period after resection. In an effort to improve long-term results after pancreatic resection, more radical procedures have been developed. At present, these techniques are not accepted as standard operations and are therefore performed only by few surgeons in the Western world as well as in Japan. To evaluate the indications and impact on survival of these procedures, additional studies in the near future are urgently needed.

Subtotal pancreatectomy
This procedure is based on the observation that the pancreatic tail and its lymph nodes are rarely affected by pancreatic cancer [35]. Utilising this fact, Gall et al. developed subtotal pancreatectomy in order to allow wider resection margins in combination with a more complete lymph node dissection and to omit the metabolic side effects of total pancreatectomy [36]. The operation is identical to a standard Whipple operation but only the very last 5 cm of the pancreatic tail are preserved and the pancreatic remnant is then oversutured so that reconstruction comprises a hepaticojejunostomy and a gastroenterostomy.

The procedure was adopted only by few surgeons. The reported mortality and morbidity equals that of a standard Whipple resection [36]. A major drawback of the procedure is the high occurrence of pancreatic fistula in up to 20% of cases [37]. Long-term results are sparse and the impact of this alternative procedure can therefore not clearly be estimated. However, total pancreatectomy as a more radical type of resection has failed to improve survival and pancreatic anastomoses can nowadays be performed safely. Therefore, subtotal pancreatectomy offers no advantage versus a standard Whipple resection for cancer of the pancreatic head.

Regional pancreatectomy
The principle of regional pancreatectomy was first introduced by Joseph Fortner in 1973 in order to improve resectability in advanced tumour stages [38]. The procedures consists of an *en bloc* removal of the total or subtotal pancreas with a 4cm soft tissue margin along with a distal gastrectomy, duodenectomy and cholecystectomy and the common bile duct [38]. The regional lymph nodes from the diaphragm to the inferior mesenteric artery including the lymph stations around the inferior mesenteric artery, the hepatic artery, the celiac trunc, the superior mesenteric artery

and the portal vein together with the intrapancreatic segment of the portal vein are carefully dissected [38].

Since the initial series reported a mortality of 25%, regional pancreatectomy was rarely employed by surgeons in Europe and North America [2]. In addition, first series did not show any advantage in long-term survival as compared to a standard duodenopancreatectomy [2]. However, a recent study reported a mortality rate equally to those reported after a classical Whipple procedure and a 5-year survival rate of 33% for tumours less than 2.5 cm in diameter [39]. To evaluate this procedures randomised studies comparing the results of regional pancreatectomy with those after standard Whipple resection in patients with identical tumour stages would be needed. At present, the procedure can not be recommended as a standard surgical procedure.

Pancreatectomy with extended lymph node resection
Despite the advances in pancreatic surgery during the last decades, all efforts to improve long-term survival after radical pancreatectomy have only slightly increased the 5-year survival rates [1]. The reasons for this persistent dismal prognosis are on one hand diagnosis in mostly advanced stages and on the other hand the biological aggressiveness of these cancers [1]. Thus, around 80% of patients have positive lymph nodes or distant metastases at time of diagnosis [2]. Although, presence of distant metastases is regarded as a general contraindication for surgery, lymph nodes can be removed thus enabling curative resection theoretically. Therefore surgeons in Japan have developed an extended lymph node dissection, based on the principles of regional pancreatectomy, which has now been adopted and standardised by the Japanese Pancreatic Society as a routine procedure for pancreatic cancer. The procedure includes regional lymphadenectomy of the lymph stations around the aorta and caval vene, the inferior and superior mesenteric vene as well as the portal vene. Furthermore, the lymphatic tissue around the hepatoduodenal ligament, the superior mesenteric artery, the splenic artery and the celiac trunc are totally dissected [40, 41].

Applying this technique, the resection rate has gradually increased from a mere of 20% up to 60% as reported by a recent study [42]. With the advances in surgery and perioperative intensive care unit management, the initially considerable mortality has now decreased to rates similar to those reported after a classical Whipple procedure [43, 44]. In contrast to the decreasing mortality, morbidity remains high and quality of life can severely be impaired after extended lymph node dissection mainly due to the occurrence of severe diarrhoea which may be caused by autonomous denervation of the bowels [45].

Histopathological studies from specimen after extended lymph node dissection have demonstrated positive lymph node metastases in 78% [46]. Similar, another study has shown that even small tumours of less than 2 cm in diameter which do not infiltrate the organ capsule showed positive paraaortal lymph nodes in 40% of cases [47]. The highest prevalence of lymph node metastases are found in the anterior and posterior pancreatoduodenal lymph nodes as well as in the paraaortal region [48]. Despite these interesting histopathological data which seem to confirm the importance of extended lymph node dissection, the impact of this strategy on long-term survival is less obvious. Studies

Table 3. Surgical treatment of pancreatic cancer in Bern (n=238)

Procedure	N	Percentage
Exploration	43	18
Bypass	54	23
Double bypass	32	
Hepatojejunostomy	12	
Gastroenterostomy	10	
Resection	141	59
Pylorus-preserving Whipple	59	
Classical Whipple	52	
Total pancreatectomy	16	
Left resection	14	

Table 4. Morbidity and mortality after pancreatic resection in Bern (n= 141)

	N	Percentage
Surgical morbidity	42	30
Delayed gastric emptying	31	22
Wound sepsis	5	3.5
Pancreatic fistula	3	2.1
Non-surgical morbidity	32	23
Pulmonary	15	11
Cardial	8	6
Mortality	5	3.5
Reoperations	6	4.3

from Japan reveal a 5-year survival rate for small and early pancreatic cancers of 28-56% [16, 41, 49]. However, only a minority of patients are operated with such early cancer stages and when results for overall survival are taken into account the results are comparable to those reported for standard Whipple resection in Europe and the United States [4, 16, 50-52]. Similar, several recent non-randomised studies and one prospective randomised study could not find a difference in survival between standard resection and pancreatectomy with extended lymph node dissection [51, 53-55]. However, there seems to be a trend, that the subgroup of patients with lymph node metastases have improved survival after radical lymphadenectomy [53]. Since at present, there is no obvious survival benefit after extended lymph node dissection in comparison after a standard pancreatoduodenectomy but morbidity remains considerable, more randomised studies are needed to assess the value of this radical procedure.

Treatment of pancreatic cancer in Bern

Between November 1993 and January 1999 238 patients (104 women, 134 men; median age 67 of years with a range of 36-87 years) with pancreatic cancer were treated in the Department of Visceral and Transplantation Surgery at the

University of Bern. At the time of diagnosis 9% of patients had stage I, 21% had stage II, 45% had stage III and 25% had stage IV disease according to the UICC classification. 59% of the patients (141 cases) were treated by tumour resection, 23% had a bypass procedure and 18% underwent surgical exploration alone. Following tumour resection, mortality was 3.5% (5 of 141 patients) and in-hospital surgical related morbidity was 30% with delayed gastric emptying being the most common complication (22%) followed by wound sepsis (3.5%). Pancreatic fistula occurred in 1.4% of cases and were treated by a conservative approach. Estimated 5-year survival by Kaplan-Meier in patients in which resection was performed was 18%.

(Data summarized in Tables 3 and 4)

Conclusion

During the past decades, a considerable decrease in perioperative mortality after pancreatic resection and a significant increase in the rate of resection has been achieved. Standard types of resection are the classical Whipple resection for cancers of the pancreatic head and distal or total pancreatectomy for cancers of the pancreatic tail and body respectively. The pylorus-preserving pancreatic head resection has now become an acceptable alternative to the classical Whipple resection, although there exist no prospectively randomised studies demonstrating the superiority of either method. However, data from case-control-studies seem to indicate that preservation of the pylorus goes along with improved quality of life and a faster regain of body weight when compared to the classical Whipple procedure. Advances in long-term survival are less obvious and a 5-year overall survival rate of about 10% is still considered a standard achievement. Efforts to improve survival by applying more radical types of resection such as regional pancreatectomy or radical lymph node dissection have failed to show any clear benefit so far and are compromised by a considerable morbidity. Although, surgery will remain most likely the primary option for cure, prospective randomised trials are needed to compare the value of these more radical procedures with the standard types of resection.

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