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REVIEW TOPIC: PANCREATIC CANCER

M. Trede · H. D. Saeger · G. Schwall · B. Rumstadt

Resection of pancreatic cancer – surgical achievements

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Abstract *Introduction:* Looking back at the initially dismal record for pancreatic cancer surgery – Whipple himself felt that a 30–35% mortality was justifiable (!) – significant progress has been made. *Progress:* The operative mortality has fallen below 5% and the serious complications of pancretic resections such as leaks and haemorrhage have been reduced to some 10% and we are better equipped to deal with these if they occur. The 5-year-survival of patients in whom pancreatic cancer was amenable to an R0-resection has risen to 30%. These are the surgical achievements using the standard Kausch-Whipple technique *alone*. There has been no improvement in these results, either by increasing radicality (regional pancreatectomy) or by reducing it (pylorus-preserving pancreatoduodenectomy). The same can be said of all other modalities of oncological treatment that have been tried so far: adjuvant radiochemotherapy, regional chemotherapy, hormonal or genetic manipulations. *Perspective:* This does not mean that we should reduce efforts at improving early detection of the disease and unravelling its complex molecular biology. On the contrary, the results of surgery alone in spite of all improvements seem to have reached a plateau that gives little cause for complacency.

Key words Pancreatic cancer · Kausch-Whipple resection · Complications of pancreatic resection · Long-term survival

Introduction

The first successful en bloc resection of part of the pancreatic head, distal common bile duct and duodenum was performed by Walter Kausch in Berlin in the summer of 1909 [15]. Kausch, a pupil of von Mikulicz, based this pioneer operation on careful animal experiments. His patient was a 49-year-old messenger suffering from obstructive jaundice due to a papillary carcinoma. He survived the two-stage operation and returned to his work, only to succumb to septic cholangitis 9 months later. At autopsy this was found to be due to a stricture of the bilioenteric anastomosis. The pathologist found neither a local recurrence nor distant metastases.

Twenty-six years later (on 25 January and 7 February 1935) Allan O. Whipple of New York resected a similar tumor, also in a 49-year-old man. This patient – Whipple's third attempt at pancreatic resection – survived the two-stage procedure and was still alive when Whipple presented his classic paper to the American Surgical Association Meeting in Boston in June that year [31]. At the end of his remarkable career, Whipple could look back on a personal series of 37 pancreatoduodenectomies, an operation that has carried his name ever since. He is on record as saying that "the considerable risk (i. e., operative mortality) of 30–35% is justified if they (the patients) can be made comfortable for even a year or two" [30].

In spite of some improvements, pancreatoduodenectomy for cancer retained its reputation as a high-risk, high morbidity and low-yield procedure. For these reasons, it remained a very controversial operation. Many internists [11] and some surgeons [4] maintained that surgery should aim at palliation only, since cure was so elusive. Table 1 summarizes the results of a recent survey conducted by the American College of Surgeons of the treatment of pancreatic cancer in the United States [14]. Although the resection rate had risen to 15% and operative mortality had fallen below 6%, long-term survival remained disappoint-

Table 1 American College of Surgeons study of pancreatic cancer in the United States (1983–1985; 1990). From Janes et al. (1996)

n		16942
Resectability	1983–1985	11.9%
	1990	15.0%
Operative mortality	1983–1985	8.9%
	1990	5.8%
5-year survival	1983–1985	4.0%

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Table 2 Operative mortality of Kausch-Whipple duodenopancreatectomy for cancer [a]

Author	Date	Institution	*n*	Operative	
				n	%
Jones	1985	Toronto	87	4	4.6
Siedeck	1985	Cologne	112	2	1.8
Braasch	1986	Lahey Clinic	87	2	2.3
Tsuchiya	1986	Nagasaki	94	4	4.2
Ceuterick	1989	Free University, Brussels	79	4	5.0
Lygidakis	1989	Amsterdam	78	3	3.8
Pellegrini	1989	UC San Francisco	51	1	2.0
Gall	1991	Erlangen	96	5	5.0
Klinkenbijl	1992	Rotterdam	91	3	3.3
Roder	1992	Munich	110	2	1.8
Sarr	1993	Mayo Clinic	104	4	4.0
Baumel	1994	Coll. French Series	555	45	8.0
Beger	1994	Ulm	124	5	4.0
Fong	1995	Sloan Kettering	138	8	6.0
Klempnauer	1995	Medizinische Hochschule, Hannover	114	4	3.5
Patel	1995	UCLA	67	1	1.5
Wade	1995	159 US Vet. Hosp.	369	31	8.4
Yeo	1995	Johns Hopkins	201	10	5.0
Trede	1997	Mannheim	410	10	2.4
Total			2967	148	5.0

[a] Detailed bibliographical information on the studies listed in the tables is available from M. Trede

ing: 5-year survival of patients whose pancreatic cancer had been resected was 4% for all stages combined. These figures set the stage for this review of the surgical achievements – early and recent – in the resection of pancreatic cancer.

Early results

Within the past decade, one of the key bench marks for assessing surgical achievement, namely, operative mortality, has come down to below 5% in centers of pancreatic surgery all over the world (Table 2). The reasons for this are by no means clear. Improved instruments and suture material, reduction of blood loss and replacement, and improved perioperative care all have at best only a marginal influence on results. The same remarkable improvement is also mirrored in other fields of human achievement: in open heart surgery, for instance, and also in Himalayan mountaineering (!) [25]. Perhaps the explanation is that more of these operations are being performed by surgeons with a specific interest in the field, resulting in standardization of technique. This has indeed led to an increasing number of reports on long consecutive series of Whipple procedures without any mortality at all (Table 3). And the fact that two of these series date back 20–30 years supports this explanation.

Our experience with more than 600 pancreatoduodenectomies (partial or total) performed at the Mannheim Surgical Clinic over the past quarter of a century are summarized in Table 4. Resections for severe and complicated chronic pancreatitis are included, since these can be as technically demanding (or more so) than resections for cancer. It may be pointed out that the operative and hospital mortality in this series has not changed significantly in the course of these 25 years. It was 2.7% in the 1970s and 2.5% in the 1980s.

Perioperative mortality is not the only bench mark when assessing early results. Postoperative complications are another. The two complications that are feared most are pancreatic leaks and haemorrhage. Complications at or around the pancreatic anastomosis range from a harmless fistula (that might well remain undiscovered) to an overt leak leading to sepsis, haemorrhage, and death. Experience with

Table 3 Consecutive pancreatoduodenectomies without operative mortality

Author	Year	Institution	No. of resections
Howard	1968	Philadelphia	41
Warren	1973	Lahey Clinic	56
Trede	1991	Mannheim	144
Warshaw	1995	Massachusetts General Hospital	160
Yeo, Cameron	1997	Johns Hopkins	190

Table 4 Early results of pancreatoduodenectomy (Surgical University Clinic Mannheim, 1 October 1972–24 October 1997)

Procedure	*n*	Diagnosis		OP and hospital mortality
		Neoplasm	Pancreatitis	
Whipple operation	557	410 (10 deaths)	147 (1 death)	11
Total pancreatectomy	63	46 (3 deaths)	17 (1 death)	4
Total	620	456 (13 deaths)	164 (2 deaths)	15 (2.4%)

Table 5 Pancreatojejunal leaks following Whipple operation (*nd* no data given)

Author	Date	Institution	Operations	Complications		Relaparotomy		Mortality	
				(*n*)	(%)	(*n*)	(%)	(*n*)	(%)
Braasch	1977	Lahey Clinic	279	20	7	nd		4	20
Nakase	1977	Coll. Jap. Series	824	114	14	nd		nd	
Papachr.	1981	Sloan Kettering	70	37	53	10	27	13	35
Grace	1986	UCLA	74	13	18	5	38	1	7
Pichlmayr	1986	Hannover	49	5	10	nd		4	80
Cameron	1989	Johns Hopkins	68	12	18	1	1.5	0	0
Bakkevold	1993	Bergen University	81	2	3	nd		1	50
Cullen	1994	Mayo Clinic	375	66	18	10	15	5	8
Trede	1997	Mannheim	557	52	9.4	25	48	7	13
Total			2377	321	13.5			35	11

Table 6 Complications occurring at or around 557 pancreatojejunostomies (Surgical University Clinic Mannheim, 1 October 1972 – 24 October 1997)

Complication	*n*	Deaths (*n*)
Anastomotic leak	25	6
Acute pancreatitis	18	1
Pancreatic fistula	9	–
Total	52	7

these complications from several centers is summarized in Table 5. It seems that they must still be reckoned with in about 13% of cases and that they will be fatal in 17% of those afflicted. In Mannheim there were 52 such complications in 557 consecutive Whipple operations. Apart from 9 bland fistulae and 18 cases of postoperative acute pancreatitis, there were 25 serious anastomotic leaks. Therefore this catastrophe occurred in less than 5% of cases, but, when it did occur, it was fatal in 6 out of 25 cases, i. e., in 24% (Table 6). The key to successful treatment of anastomotic leakage is early diagnosis. The clinical signs elicited by close observation of the patient in the surgical ICU are often more decisive than time-consuming laboratory or imaging procedures.

However, access for direct imaging of the pancreatic anastomosis is provided by the Völker tube routinely placed in the draining jejunal loop (Fig. 1). This is intended to protect the pancreatic and biliary anastomoses by decompressing this jejunal loop. It also serves as a port for radiological control. Contrast injection into this tube (with the patient lying on the left side) will opacify both the biliary and pancreatic anastomoses and may detect a leak (Fig. 2). Treatment of pancreatic leaks is best individualized as shown in Table 7.

Of 52 patients, 27 were treated entirely conservatively, that is, by total parenteral nutrition and 1 week's trial with somatostatin analogue (octreotide). Operative lavage and the placement of additional drains is an unsatisfactory second-best solution reserved for debilitated patients who would not tolerate anything more radical. For the remaining 16 a completion pancreatectomy seemed unavoidable and this did save the lives of 12 of these patients. Everything depends on removing the remaining pancreas early enough, before sepsis is generalized.

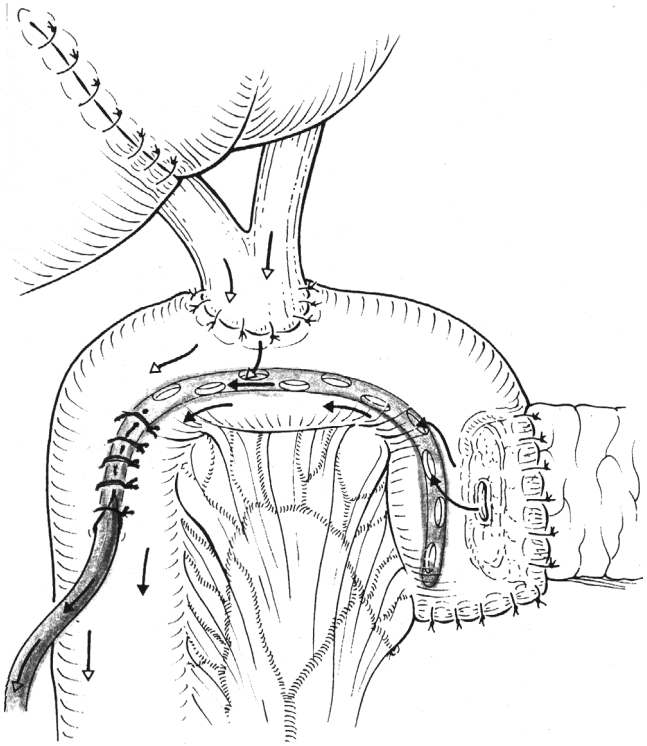

Fig. 1 Technique of draining the end-to-side pancreatojejunostomy and hepaticojejunostomy by means of a Völker drain placed in the draining jejunal loop

Thus, although four patients succumbed to uncontrollable erosion haemorrhage, completion pancreatectomy was worthwhile in that four other patients went on to survive for 6 years and longer (Fig. 3).

Of course prevention of this catastrophe is better than cure and there is no lack of suggested technical variations to protect that pancreatojejunal anastomosis (Table 8). The very length of this list seems to support our view that the actual technique used is of less importance than the meticulousness with which it is performed. Nor are we convinced that this problem can be solved by medication, in spite of

Table 7 Treatment of 52 postoperative complications (Surgical University Clinic Mannheim, 1 October 1972–24 October 1997)

Complications	*n*	Treatment			Deaths
		Conservative	Drainage	Total pancreatectomy	
Anastomotic leak	25	6	9 (2 deaths)	10 (4 deaths)	6
Acute pancreatitis	18	12 (1 death)	–	6	1
Pancreatic fistula	9	9	–	–	–
Total	52	27 (1 death)	9 (2 deaths)	16 (4 deaths)	7

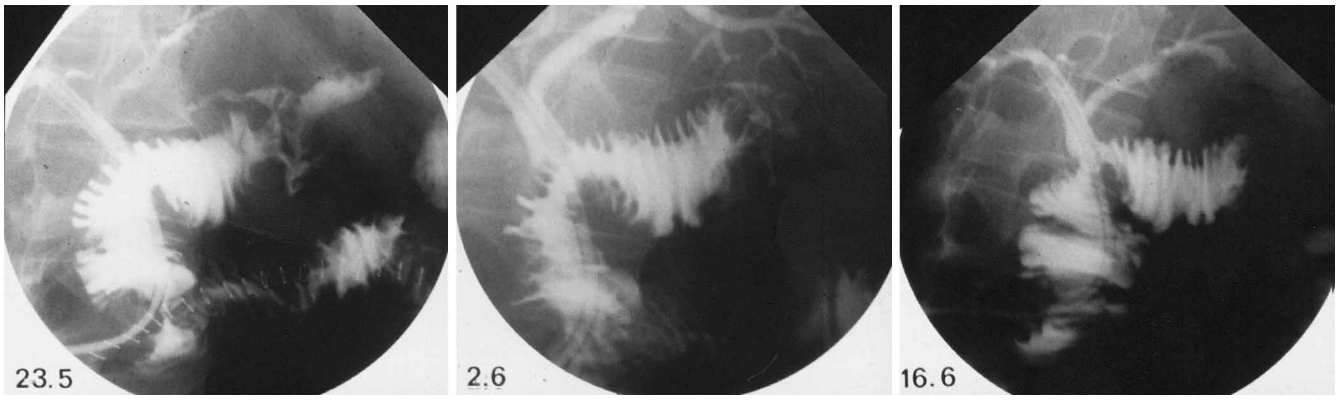

Fig. 2 *23.5* Clinically "silent" leak of the pancreatojejunostomy demonstrated by instilling contrast medium into the Völker drain; *2.6* The radiographic control shows that the fistula has almost closed; *16.6* Final radiographic control no longer shows any lead (note that in this case the anastomosis was an end-to-end telescope pancreatojejunostomy and the Völker drain was placed into the bile-duct through the hepaticojejunostomy)

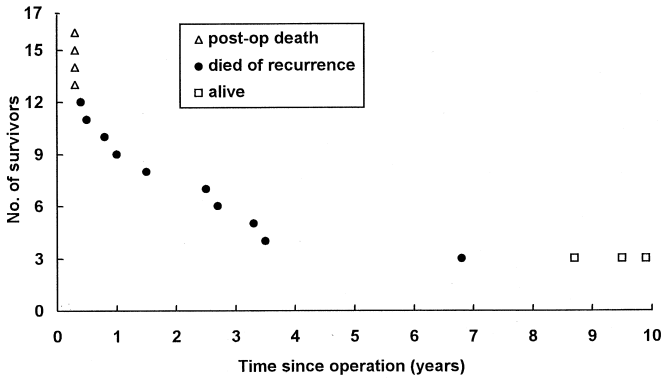

Fig. 3 Actual survival after completion pancreatectomy (Surgical University Clinic, Mannheim, 1.10.1972–31.12.1994); from Farley et al., Brit J Surg (1996) 83:176

some reports showing a slight reduction of leaks using prophylactic octreotide [2].

Bleeding is a close second to anastomotic dehiscence in the list of dangerous complications. Experience with postoperative haemorrhage from several large centers shows that it occurs in some 10% of cases and that it will be fatal in one third of these (Table 9). It is important to distinguish between gastrointestinal (that is, intraluminal) bleeding and haemorrhage from the retroperitoneal operative field. In our experience with 23 cases, gastrointestinal haemorrhage can be diagnosed and treated effectively in two thirds of patients by immediate endoscopy. In all but one of the remaining nine patients, early relaparotomy with additional sutures stopped the bleeding (Table 10). Significant haemorrhage from the operative site of course invariably requires reoperation. A dangerous combination of these two types of haemorrhage manifests itself quite typically by a "sentinel bleed". If, after an uneventful course, the patient's temperature increases and he experiences minor abdominal pain and he then passes some blood in his stools, chances are that a pancreatic leak with infection has led to erosion of a retropancreatic vessel with bleeding back into the jejunal loop [22a]. Immediate endoscopy may rarely locate the bleed directly. Often, though, it will at least exclude other more proximal sources of bleeding and so direct the surgeon towards relaparotomy with suture ligature of the bleeding vessel and drainage of the abscess. The pancreatic remnant is then best removed (completion pancreatectomy).

As we review these early results it is only natural to ask whether we should be training all general surgeons to do this procedure and, secondly, if we do train them, whether they should be allowed to do the procedure if they choose [1]. The data for the state of Maryland seem clear enough (Table 11). The single high-volume academic enter achieved superior outcomes at lower cost than did the remaining 38 lower-volume hospital providers [10]. The likely explanation includes special expertise provided by large numbers, around-the-clock observation on the surgical ICU with earlier detection and treatment of complica-

Table 8 Suggested methods for the prevention of pancreatic leaks

Method	Authors
Pancreatogastrostomy	Mackie (1975), Kapur (1986), Delcore (1990), Waugh (1946), Telford (1981), Reding (1988), Icard (1988), Bradbeer (1990), Yeo (1995)
End-to-side pancreatojejunostomy with jejunoplication	Siedeck (1985)
Two or three separate jejunal loops	Schreiber (1977), Lygidakis (1985) Schopohl (1986)
Pancreatic duct drainage	Porter (1958), Longmire (1974), Manabe (1986), Hall (1990)
Pancreatic duct ligation	Goldsmith (1971), Fortner (1980), Shiu (1982), Aretxabala (1991)
Pancreatic duct occlusion	Gebhardt (1978), Di Carlo (1989)
Anastomotic coverage with fibrin	Waclawiczek (1989), Scheele (1990), Kram (1991)
Open drainage of pancreatic remnant	Funovics (1987)
Preoperative external radiation	Ishikawa (1991)

Table 9 Haemorrhagic complications following pancreatoduodenectomy (*nd* no data)

Author	Date	Institution	Operations	Complications		Mortality	
				(*n*)	(%)	(*n*)	(%)
Braasch	1977	Lahey Clinic	279	31	11	18	58
Nakase	1977	Coll. Jap. Series	869	93	11	nd	
Grace	1986	UCLA	96	12	12.5	4	33
Pichlmayr	1986	Hannover	62	6	9.6	nd	
Cameron	1989	Johns Hopkins	88	15	17	nd	
Miedema	1992	Mayo Clinic	279	22	8	5	23
Trede	1997	Mannheim	620	46	7.4	4	8.7

Table 10 Haemorrhagic complications of the 620 pancreatoduodenectomies (Surgical University Clinic Mannheim, 1 October 1972–24 October 1997)

Site of hemorrhage	*n*	Relaparotomy	Deaths
Gastrointestinal	23	9	1
Operative field	23	23	3
Total	46	32	4

Table 11 The effects of regionalization on cost and outcome for pancreatoduodenectomy; from Gordon et al. (1995)

	Hospital surgical volume	
	High (>20 cases)	Low (1–20 cases)
Operative mortality	2.2%	13.5%
Mean length of stay	23 days	27 days
Mean total charges	$ 26204	$ 31659

tions. In Mannheim, for example, the standardized approach of an experienced team has led to the simplification of perioperative care and monitoring (fewer tubes and catheters, fewer laboratory and radiological investigations, a shorter hospital stay) which contributes towards a lowering of costs in accordance with the principle that "less is more" [26].

Late results

After mortality and morbidity rates, long-term survival is the third bench mark in assessing surgical achievement. Given that more than 95% of patients with resectable pancreatic cancer will survive the operation, one would have hoped that more would survive for 5 years or even longer. So far this progress has been slow in materializing but it is beginning to show in many American and European centers and of course for the small tumors collected from over 400 Japanese units (Table 12). These 5-year-survival figures of 20–30% reported recently approach those for oesophageal or bronchial carcinoma and they do represent some progress in comparison to the 4% long-term survivors stipulated by Gudjonsson and others [11].

There are two approaches to measuring long-term survival. We applied both to those 251 patients who had resected adenocarcinoma of the head of the pancreas. First using the figures from our own follow-up, we plotted the survival curves according to Kaplan-Meier (Fig. 4). For the 98 patients in whom micro- (or even macro-)scopic residual tumor was left in the body, median survival is only 10 months and the curve ends at around 2 years. However, low mortality and morbidity, together with the improved quality of life of these patients, make pancreatic resection appear worthwhile, even in a palliative setting [12]. This supports our view that, if removal is technically possible,

Table 12 Long-term survival after Whipple operation for cancer

Author	Date	Institution	*n*	5-year survival (%)
Cooperman	1981	Columbia, NY	70	7.1
Lerut	1984	Insel Spital, Bern	25	6.0
Jones	1985	Toronto	28	7.0
Grace	1986	UCLA	37	3.0
Conolly	1987	Chicago University	89	3.4
Tsuchiya	1986	Coll. Jap. Series (<2 cm)	103	30.3
Sarr	1993	Mayo Clinic	104	10.0
Baumel	1994	Coll. French Series	555	15.0
Fong	1995	Sloan Kettering (>70)	138	21.0
Klempnauer	1995	M. H. Hannover	107	13.8
Yeo	1995	Johns Hopkins	201	21.0
Trede	1997	Mannheim	153	27.0

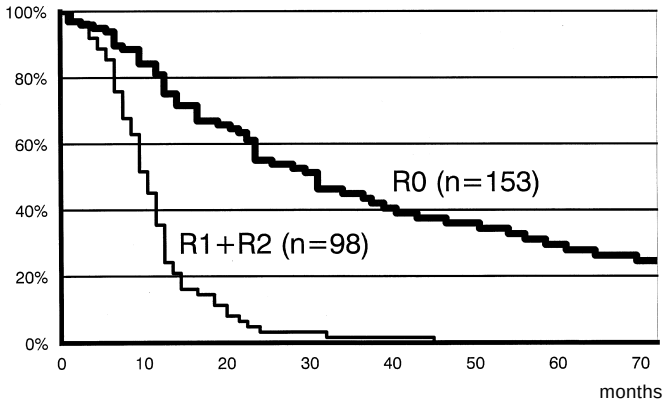

Fig. 4 Survival rate after pancreatectomy for adenocarcinoma of the pancreas (Kaplan-Meier survival curves ($n=251$): *R1* macroscopic tumor left behind, *R2* microscopic tumor left behind *R0* apparently complete resection of the tumor (Surgical University Clinic Mannheim, 1.10.1972–1.1.1997)

a pancreatic tumor should be resected, even if cure is unlikely. For the 153 patiens with apparent R0-resections, the curve crosses the magic 5-year-survival line at just under 30%. Actuarial survival curves tend to carry the stigma of statistical error. Therefore, if the numbers are large and the observation period long enough, it is preferable to arrive at the actual survival rate. Thus we looked at the fate of those 109 patients with adenocarcinoma of the head of the pancreas whose pancreatectomy (partial or total) was performed more than 5 years ago, that is, before January 1992. Of these, 29 crossed the 5-year-survival line. This is 27% actual (not actuarial) survival achieved by surgery alone. But survival is not cure. As Table 13 indicates, 20 of these 29 survivors died after reaching 5-year survival, and they died mostly of late recurrence, local or metastatic.

Of all the data analyzed that might have influenced survival (the type of resection, operating time, perioperative blood loss, tumor biology, including DNA-ploidy), only one was of significance in both uni- and multivariate analysis, and that was tumor stage. This is illustrated in Figure 5 in which survival is plotted against tumor stage (as defined by the most recent UICC classification). It is clear from this diagram that the vast majority of long-term survivors are those without lymph-node metastases.

Other forms of surgical resection

Of course the surgical achievements in the treatment of pancreatic cancer are not solely confined to pancreatoduodenectomy, the Kausch-Whipple operation. Pylorus-preserving pancreatoduodenectomy (PPPD), reintroduced by

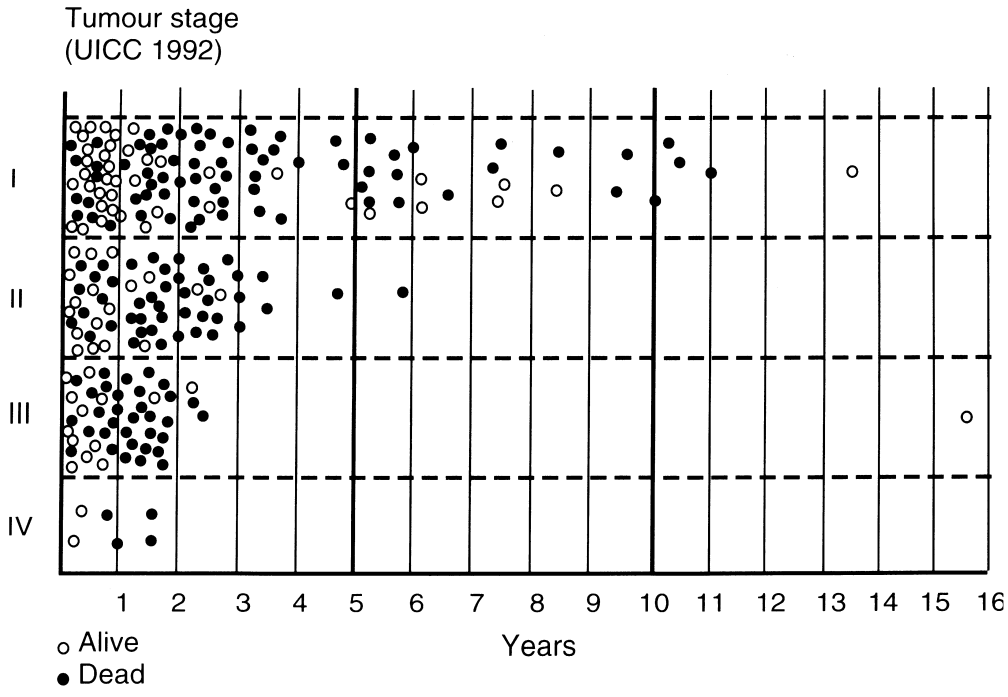

Fig. 5 Survival of 226 patients who had resections for pancreatic adenocarcinoma during the period 1.10.1972–1.1.1996 at the Surgical University Clinic Mannheim

Traverso and Longmire in 1978, has found its place not only for the resection of benign lesions [24]. It has two advantages, one practical and one theoretical. The practical advantage is a saving in operating time since antrectomy is avoided [16]. The second advantage – a "more physiological gastrojejunal food passage" – appears to be mainly theoretical and has not been substantiated convincingly so far, even by the protagonists of this variant [6, 17].

But it is the disadvantages of PPPD that have prevented its universal acceptance. Delay in gastric emptying [29] and jejunal ulceration [19] are significantly more troublesome in PPPD than after standard pancreatoduodenectomy. The third drawback, that of compromised radicality, has probably been overrated, considering that the long-term results of standard resection are poor in any case and so far could not be improved by extending radicality [3]. Nevertheless, surveys of pancreatic surgeons in both Germany and the United States have shown that the majority of patients (78–89%) with an operable cancer of the head of the pancreas are being treated with the standard Kausch-Whiple operation [18, 27].

At the other end of the scale, there are the more radical resections: total or regional pancreatectomy as suggested by Fortner [7, 8] as well as extended retroperitoneal lymphadenectomy, mainly propagated by Japanese surgeons [13, 21, 22]. So far, none of these has even come close to the results (however poor) of the standard Kausch-Whipple procedure [20, 23, 32].

Suffice it to say that total pancreatectomy has its place in the resection of tumors of the body of the pancreas or of those in the head, if these reach close to the plane of a potential Kausch-Whipple resection. Regional pancreatectomy – when it involves en bloc resection of the large retropancreatic veins – may well be performed out of necessity (not on principle!) if that is the only way to remove an otherwise inoperable tumor [9, 26].

Conclusion

Advances in the surgical resection of pancreatic cancer are encouraging. However, it appears that the results of surgical treatment alone have reached their limits, as regards postoperative morbidity and mortality and long-term survival. It remains to be seen what the other modalities of oncological therapy – radio-chemotherapy and hormonal or genetic manipulation – are able to contribute. All of these have shown some promising experimental results but none have so far succeeded convincingly when applied in clinical practice.

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