MICKAEL PARVIAINEN

Pancreaticojejunostomy after Pancreatic Head Resections

Connection with postoperative complications and quality of life

ACADEMIC DISSERTATION
To be presented, with the permission of
the Faculty of Medicine of the University of Tampere,
for public discussion in the Small Auditorium of Building M,
Pirkanmaa Hospital District, Teiskontie 35,
Tampere, on November 19th, 2010, at 12 o'clock.

UNIVERSITY OF TAMPERE

UNIVERSITY
OF TAMPERE

ACADEMIC DISSERTATION
University of Tampere, Medical School
Tampere University Hospital, Department of Gastroenterology and Alimentary Tract Surgery
Finland

Supervised by
Docent Juhani Sand
University of Tampere
Finland
Docent Isto Nordback
University of Tampere
Finland

Reviewed by
Docent Juha Grönroos
University of Turku
Finland
Professor Jyrki Mäkelä
University of Oulu
Finland

Distribution
Bookshop TAJU
P.O. Box 617
33014 University of Tampere
Finland

Tel. +358 40 190 9800
Fax +358 3 3551 7685
taju@uta.fi
www.uta.fi/taju
http://granum.uta.fi

Cover design by
Mikko Reinikka

Acta Universitatis Tamperensis 1564
ISBN 978-951-44-8264-9 (print)
ISSN-L 1455-1616
ISSN 1455-1616

Acta Electronica Universitatis Tamperensis 1013
ISBN 978-951-44-8265-6 (pdf)
ISSN 1456-954X
http://acta.uta.fi

Tampereen Yliopistopaino Oy – Juvenes Print
Tampere 2010

This dissertation is lovingly dedicated to my parents and my family

CONTENTS

LIST OF ORIGINAL COMMUNICATIONS 8

ABBREVIATIONS 9

ABSTRACT 10

TIIVISTELMÄ 12

INTRODUCTION 14

REVIEW OF THE LITERATURE 15

1 History of pancreaticoduodenal resection 15

2 Role of various resections of the pancreatic head 17

2.1. Pancreaticoduodenal resection with antrectomy 17
2.2. Pylorus-preserving pancreaticoduodenal resection 19
2.3. Duodenum-preserving resections of the pancreatic head 20
2.4. Extent of resection 21
2.5. Total pancreatectomy 22

3 Postoperative complications 23

3.1. Clinically significant surgical complications 23

4 Anastomotic leakages following pancreatic head resections 26

4.1. Consequences of leakage of pancreaticojejunal anastomosis 26
4.2. Use of stents and drains in protecting the anastomosis 28
4.3. Other ways to protect the anastomosis 30

5 Impacts of hospital and surgeon on short-term and long-term complications following pancreatic head resections 31

5.1. Impact of surgeon on postoperative morbidity and mortality 31
5.2. Impact of hospital on postoperative morbidity and mortality 32

6 Anastomotic strictures and long-term postoperative pancreatic exocrine insufficiency after pancreatic head resections 34

6.1. Enzymatic methods of measuring pancreatic

exocrine function 34
6.2. Imaging of the pancreas 36
6.3. Postoperative pancreatic exocrine insufficiency 38

7 Health-related quality of life in patients having undergone pancreatic head resection 39

7.1. Different instruments for measuring HRQoL 39
7.2. Pancreatic resection and HRQoL 40

AIMS OF THE STUDY 43

PATIENTS AND METHODS 44

1 Study I – Pancreaticoenteric and bilioenteric leakages 44

2 Study II – Results of resections of the head of the pancreas with pancreaticojejunal anastomosis in Finland 45

3 Study III – Postoperative exocrine insufficiency after pancreatic head resection 45

4 Study IV – Early and late postoperative quality of life following pancreatic head resections with pancreaticojejunal anastomosis 48

5 Study V – A new biodegradable stent for the pancreaticojejunal anastomosis 49

6 Statistics 51

7 Ethical considerations 51

RESULTS 52

1 Study I – Pancreaticoenteric and bilioenteric leakages 52

2 Study II – Results of pancreatic head resections in Finland 53

3 Study III – Postoperative exocrine insufficiency after pancreatic head resection 57

4 Study IV – Early and late postoperative quality of life following pancreatic head resections 60

5 Study V – A new biodegradable stent for the pancreaticojejunal anastomosis 65

DISCUSSION 67

1 Finnish experience of pancreaticoduodenectomies with special reference to early complications (Studies I and II) 67

2 Pancreaticojejunostomy and long-term consequences of pancreaticoduodenectomies (Studies III-IV) 70

3 How to develop pancreaticojejunal anastomosis (Study V) 72

SUMMARY AND CONCLUSIONS 75

ACKNOWLEDGEMENTS 76

REFERENCES 78

ORIGINAL COMMUNICATIONS 101

LIST OF ORIGINAL COMMUNICATIONS

This thesis is based on the following original papers, referred to in the text by their Roman numerals (I-V).

I Parviainen MC, Sand JA and Nordback IH (1996): Coincidence of Pancreatic and Biliary Leakages after Pancreaticoduodenal Resections. Hepato-Gastroenterol 43: 1243 – 1249

II Nordback I, Parviainen M, Räty S, Kuivanen H and Sand J (2002): Resection of the Head of the Pancreas in Finland: Effects of Hospital and Surgeon on Short-term and Long-term Results. Scand J Gastroenterol 37: 1454 – 1460

III Nordback I, Parviainen M, Piironen A, Räty S and Sand J (2007): Obstructed Pancreaticojejunostomy Partly Explains Exocrine Insufficiency after Pancreatic Head Resection. Scand J Gastroenterol 42: 263 – 270

IV Parviainen M, Räty S, Nordback I, Sintonen H, Vehkalahti P and Sand J (2008): Late Postoperative Quality of Life Following Pancreatic Head Resections. Hepato-Gastroenterol 55: 711 – 716

V Parviainen M, Sand J, Harmoinen A, Kainulainen H, Välimaa T, Törmälä P and Nordback I (2000): A New Biodegradable Stent for the Pancreaticojejunal Anastomosis After Pancreaticoduodenal Resection: In Vitro Examination and Pilot Experiences in Humans. Pancreas 21: 14 – 21

ABBREVIATIONS

NBT-PABA	n-benzoyl-l-tyrosil-p-aminobenzoic acid test
CT	computed tomography
D-MRCP	dynamic magnetic resonance cholangiopancreatography
DGE	delayed gastric emptying
DPPHR	duodenum preserving pancreatic head resection
EORTC QLQ-C30	Quality of Life Questionnaire C30 of the European Organization for Research and Treatment of Cancer
ERCP	endoscopic retrograde cholangiopancreatography
GIQLI	Gastrointestinal Quality of Life Index
HRQoL	health-related quality of life
LR-LPJ	local resection of the head of the pancreas combined with longitudinal pancreaticojejunostomy
MRI	magnetic resonance imaging
PD	pancreaticoduodenectomy
PET	positron emission tomography
PGA	polyglycolide
PLA	poly-L,D-lactide
PLT	pancreolauryl test
POPF	postoperative pancreatic fistula
PPPD	pylorus-preserving pancreaticoduodenectomy
RCT	randomised controlled trial
T_1	longitudinal relaxation time
T_2	transverse relaxation time
TE	time to echo (echo time)
TR	time to repetition
VAS	visual analogue scale

ABSTRACT

This study addresses early and long-term complications that may be linked to technical problems of pancreaticojejunostomy. Given the importance of the leakage of the pancreaticojejunostomy in increasing postoperative mortality and morbidity, a study was performed in which it was found that biliary leakage usually occurs together with pancreatic leakage. This gave rise to a hypothesis of a possible common aetiologic factor, which may be postoperative pancreatitis.

To investigate the effect of surgeon and hospital volume on postoperative morbidity and mortality, a nation-wide study was performed including 33 Finnish hospitals, where resections of the head of the pancreas (average 2.1 resections per year per hospital) were performed during a five-year period (1990-1994). There were 98 surgeons performing these resections (average 0.7 resections per year per surgeon). Most of the complications that resulted in death were a result of technical problems. Both surgeon and hospital volume affected postoperative morbidity and mortality. To reduce postoperative morbidity, mortality and hospital stay pancreatic head surgery needs to be centralized in fewer hospitals with adequate perioperative care and performed by surgeons professing special interest in pancreatic surgery. Long-term results, however, were related to the nature of the disease.

Given that most patients undergoing resection of the pancreatic head show severe signs of pancreatic insufficiency, a dynamic secretin-stimulated magnetic resonance cholangiopancreatography (D-MRCP) examination was performed to examine whether these symptoms were a result of anastomotic stricture or due to malfunction of the pancreatic gland. This study was performed on 26 patients who 3-76 (median 52) months earlier had undergone pancreaticoduodenectomy with end-to-end invaginated anastomosis, which was the method of choice in the 1990s. All those patients had severe exocrine insufficiency as measured by faecal elastase-1. D-MRCP failed in three patients, but revealed severe glandular malfunction in seven patients (30 %), total obstruction of the pancreaticojejunostomy in five patients (22 %), partial obstruction in six patients (26 %) and an open anastomosis in five patients (22 %), these five patients having the highest faecal elastase-1 values. Better long-term functional results may require better surgical technique.

To study postoperative quality of life in patients who had undergone pancreaticoduodenal resection, 15D, a generic instrument was used which enabled comparison of the results to healthy population.

In the early stage (24 months postoperatively), postoperative health-related quality of life was significantly poorer than in general population, but there was no difference in the late stage (110 months postoperatively).

As a possible solution to protect the pancreaticojejunal anastomosis, biodegradable, barium sulphate containing stents were manufactured to be inserted in the pancreatic duct during the operation. The degradability of these stents was followed-up *in vitro* in different pH and enzyme milieus and the stents were tested *in vivo* in two pilot patients. Degradation of the stents occurred after 24-52 weeks of incubation. Alkaline milieu together with the presence of pancreatic enzyme degraded the stents twice as fast as when either alkaline milieu or enzymes alone were present. In the milieu resembling pancreatic juice barium sulphate had no effect on the degradation time. Neither of the pilot patients experienced any postoperative complications.

TIIVISTELMÄ

Tämä tutkimus tuo esiin varhais- ja myöhäisvaiheen ongelmia, jotka voivat aiheutua huonosti toimivasta haima-ohutsuoliliitoksesta. Nojautumalla tietoon kyseisen liitoksen vuodon merkittävyydestä leikkauksen jälkeistä sairastavuutta ja kuolleisuutta lisäävänä tekijänä tehtiin tutkimus, jonka mukaan sappi-ohutsuoliliitoksen ja haima-ohutsuoliliitoksen vuotoa esiintyy usein samanaikaisesti. Näiden vuotojen syynä voi olla leikkauksenjälkeinen haimatulehdus.

Kirurgi- ja sairaalakohtaisen vuosittaisen haimaleikkausmäärän vaikutus leikkausten jälkeiseen sairastavuuteen ja kuolleisuuteen tutkittiin valtakunnallisella tutkimuksella, johon sisällytettiin ne sairaalat, joissa haiman pään poistoleikkauksia tehtiin vuosina 1990-1994. Sairaaloita oli 33 (keskimääräinen vuosittainen leikkausmäärä oli 2.1) ja näitä leikkauksia teki 98 kirurgia (keskimääräinen vuosittainen leikkausmäärä oli 0.7). Useimmat kuolemaan johtaneet ongelmat aiheutuivat teknisistä ongelmista. Sekä kirurgi- että sairaalakohtaisilla vuosittaisilla leikkausmäärillä oli vaikutusta leikkauksenjälkeiseen sairastavuuteen ja kuolleisuuteen. Leikkaustenjälkeisen sairastavuuden ja kuolleisuuden vähentämiseksi sekä sairaalahoidon lyhentämiseksi haiman pään leikkaukset tulisi keskittää muutamiin sairaaloihin, joissa on riittävät valmiudet hoitaa leikkausten yhteydessä ilmenneitä ongelmia sekä muutamille kirurgeille, jotka ovat erityisen kiinnostuneita haimaleikkauksista. Potilaiden pitkäaikaiseloonjääminen tosin oli yhteydessä taudin luonteeseen.

Huomioiden niiden haimaleikattujen potilaiden runsas määrä, joilla on pitkäaikaisongelmana haiman vajaatoiminta, sekretiini-stimuloitu, dynaaminen MRCP-tutkimus (D-MRCP) tehtiin sen asian selvittämiseksi, aiheutuuko vajaatoiminta haima-ohutsuoliliitoksen ahtautumisesta vai jäljellä olevan haimakudoksen puutteellisesta toiminnasta. Tutkimus tehtiin 26 potilaalle, joille oli tehty 3-76 kk (mediaani 52) aiemmin haiman pään poistoleikkaus käyttäen pää päätä vasten -liitosta haiman ja ohutsuolen välillä, mikä oli normaali käytäntö 1990-luvulla. Kaikilla näillä potilailla oli hankala haimaleikkauksen jälkeinen vajaatoiminta ulosteen elastaasi-1 -tutkimuksen pohjalta arvioituna. D-MRCP epäonnistui 3 potilaalla mutta osoitti vaikeaa haimakudoksen toiminnanvajausta seitsemällä potilaalla (30 %), haima-ohutsuoliliitoksen olevan täysin tukossa viidellä potilaalla (22 %), osittain tukossa kuudella potilaalla (26 %) ja avoin viidellä potilaalla (22 %). Viidellä viimemainitulla potilaalla oli kaikkein korkeimmat ulosteen elastaasi-1 -arvot. Pitkäaikaisten toiminnallisten tulosten parantaminen vaatinee leikkaustekniikan kehittämistä.

Haiman pään poistoleikkauksen jälkeisen elämänlaadun tutkimiseksi käytettiin 15D-tutkimusmittaria, joka on ns. yleinen elämänlaadun mittari ja sallii vertailun terveeseen väestöön. Varhaisvaiheessa (24 kk leikkauksen jälkeen) elämänlaatu oli heikompi kuin verrokeilla, mutta eroja ei ollut myöhäisvaiheessa (110 kk leikkauksen jälkeen).

Mahdollisena keinona suojella haima-ohutsuoliliitosta kehitettiin biohajoavia, bariumsulfaattia sisältäviä stenttejä, jotka voidaan ujuttaa haimatiehyeeseen leikkauksen aikana. Näiden stenttien hajoamista happamuuden ja entsyymien vaikutuksesta tutkittiin laboratorio-oloissa. Stenttien sulaminen tapahtui 24-52 viikkoa hauteeseen laiton jälkeen. Emäksinen ympäristö yhdessä haimaentsyymien kanssa kaksinkertaisti stenttien hajoamisen verrattuna pelkkään emäksiseen ympäristöön tai haimaentsyymien läsnäoloon. Bariumsulfaatilla ei ollut vaikutusta stenttien hajoamisaikaan haimanestettä muistuttavassa ympäristössä. Näitä stenttejä pilotoitiin myös kahdella potilaalla. Kummallekaan potilaalle ei kehittynyt leikkaukseen liittyviä komplikaatioita.

INTRODUCTION

In 1908 Sauvé reported a series of 11 patients undergoing pancreatic surgery (van Heerden et al. 1981). One of these operations was performed for a tumour located in the head of the pancreas and duodenum, and entailing the resection *en masse* of the tumour. Four years later, Kausch performed a successful two-stage pancreaticoduodenectomy (PD). During the next two decades, however, pancreatic resections were rare. In 1935, Whipple published a paper on a two-stage PD. For some decades, many surgeons considered PD a procedure that should be performed only in exceptional circumstances, due to the high risk of serious postoperative complications and high mortality. Originally, PD entailed resection of the distal part of the stomach. Brunschwig performed a one-stage resection of the pancreatic head in 1937 and Whipple in 1940 (Yeo et al. 1998). In 1978, Traverso and Longmire published a variation of pancreaticoduodenectomy, which is generally called pylorus-preserving pancreaticoduodenectomy (PPPD). Nowadays, both PD with gastric resection and PPPD are commonly used in benign and malignant periampullary diseases. The most important diseases for which pancreatic head resection is deemed necessary are periampullary malignancies and chronic pancreatitis resistant to conservative and endoscopic treatment, although there are also other operations in this indication. In recent years, postoperative mortality has fallen to less than 2 % in centres where the annual volume of these operations is high. Postoperative morbidity is still, however, significant, and the most important complication is leakage of the pancreaticojejunal anastomosis, as it may need reoperation and may be life-threatening. This complication also lengthens hospital stay and leads to higher costs. As postoperative expected survival time in benign and pre-malignant diseases is long, long-term quality of life is also important in patients with pancreaticoduodenal resections. A well-functioning anastomosis may diminish pancreatic insufficiency, thereby possibly improving long-term quality of life.

This study focuses on the association of pancreaticojejunostomy with the early complications and late clinical results after pancreatic head resection. A study was also performed to develop a new type of biodegradable stent designed to be used in pancreaticojejunostomy.

REVIEW OF THE LITERATURE

1 History of pancreaticoduodenal resection

Over one hundred years have passed since the first successful local transduodenal resection of a periampullary cancer by Halsted (Yeo et al. 1998). The first resection *en masse* of the pancreas and duodenum for periampullary cancer was reported in 1898 by Codivilla of Bologna (van Heerden et al. 1981). In this procedure the pancreatic duct was ligated and the pancreatic stump was left behind. In 1908, Sauvé demonstrated that the head of the pancreas and the second portion of the duodenum were anatomically inseparable and proposed a technique for pancreaticoduodenal resection *en masse*. Kausch performed the first successful such resection by using a two-stage approach (Yeo et al. 1998). Hirschel reported the first successful one-stage pancreaticoduodenectomy in 1914 at a time when most ampullary tumours were managed by transduodenal excision. It was not until 1935 that Whipple published his paper on a two-stage pancreaticoduodenal resection, which was performed on three patients with adenocarcinoma of the ampulla of Vater (Whipple et al. 1935). The first operation included a posterior gastroenterostomy, ligation and section of the common bile duct after determining the patency of the cystic duct and a cholecystogastrostomy. Three to four weeks after the first stage the second operation was performed, entailing the ligation of the pancreaticoduodenal and gastroduodenal arteries, resection of the descending portion of the duodenum and a V-shaped excision of the head of the pancreas wide of the growth together with the common duct. Last, the cut end of the duct of Wirsung (and also of Santorini, if present), were ligated and the cut surfaces were sutured with interrupted fine silk. Hospital mortality was 33 %; the patients died of cholangitis and liver abscesses (Whipple et al. 1935). In 1937 Brunschwig extended the indications for pancreaticoduodenal resection to include pancreatic cancer and performed the first radical one-stage resection of the head of the pancreas (Yeo et al. 1998). In 1940, Whipple performed his first one-stage pancreaticoduodenectomy, and in 1942 he included a pancreaticojejunal anastomosis. He believed that in order to prevent pancreatic fistula, it was important to join the pancreatic duct to the jejunal mucosa (van Heerden et al. 1981).

In 1968, Howard published a series of 41 consecutive one-step Whipple resections performed by one surgeon during a 13-year period. Operative mortality was nil. Ten per cent of the patients had pancreatic fistula postoperatively. In this paper Howard pointed out the importance of the presence

of a clinical team with a continuous interest in the pancreas and its surgical problems (Howard 1968). During the 1970s, radical pancreaticoduodenectomy fell into disrepute as a result of excessive postoperative morbidity and mortality due to inherent technical difficulties, the dismal long-term survival of adenocarcinoma of the pancreas, and enthusiasm for total pancreatectomy (van Heerden et al. 1981). In van Heerden's study on 146 patients operated on in Mayo Clinic in the 1970s, hospital mortality was 4 % and the incidence of pancreatic fistulas 11 %. He concluded that Whipple's resection is indicated in carefully selected patients but individual judgment and meticulous techniques are mandatory (van Heerden et al. 1981). According to Tarazi et al. (1986), in the 1970s comparisons were made of operative mortality and postoperative morbidity after radical resection and simple bypass of the obstructed bile duct. There was very little difference in the survival after both radical resections and bypass procedures that some authors did not consider postoperative mortality and morbidity worthwhile after radical resections (Tarazi et al. 1986). High morbidity and mortality rates following pancreatic resection in the 1970s and early 1980s led many surgeons to suggest that surgical resection of pancreatic cancers should be abandoned. On the other hand, the postoperative mortality rate after total pancreatectomy has been even higher than after Whipple's procedure in several series, although the pancreaticojejunal anastomosis is avoided (Tarazi et al. 1986). Ever since, pancreatic resections have been performed with increased frequency in many specialized centres reporting acceptable morbidity and mortality rates of less than 5 % (Sohn et al. 2000b).

According to an evidence-based methodology using review, which was limited to articles published between 1990 and 2001, the mortality rate from pancreaticoduodenectomy has declined to less than 5 % for chronic pancreatitis and to 3-8 % for pancreatic cancer. Morbidity rates, however, have remained high, ranging between 20 % and 70 %. Of these, delayed gastric emptying accounted for almost half of the complications. Incidence of pancreaticojejunal leakage varied from 0 % to 30 % (Schäfer et al. 2002). Postoperative complications in the surgery of the pancreatic head lead to decreased survival (Reddy DM et al. 2009). Experienced centres should perform pancreaticoduodenectomies with a mortality less than 5 % and major complication rates less than 40 % (Orr 2010). According to Schäfer et al. (2002) both actuarial and actual 5-year survival rates for ductal pancreatic adenocarcinoma were poor and ranged from 7 % to 12 % and 6 % to 10 % respectively. The median reported survival of pancreatic adenocarcinoma in the literature showed only a slight variation and ranged from 12 to 18 months. Of periampullary malignancies, pancreatic adenocarcinoma is known to have the lowest actuarial and actual survival rates. According to a

single-institution analysis of 5-year survivors, the survival rate in adenocarcinoma of the duodenum was 59 %, ampulla 39 %, bile duct 27 % and pancreas 15 % (Yeo et al. 1998).

PD is nowadays indicated for curative resection of malignancies of the periampullary region, i.e. pancreatic head, ampulla of Vater, duodenum and distal bile duct (Collier and Pollard 1992). It may also be used in chronic pancreatitis to relieve pain, to relieve obstructive symptoms related to chronic pancreatitis and when cancer cannot be excluded (Martin and Rossi 1998). It may occasionally also be indicated in cases of trauma (Collier and Pollard 1992).

2 Role of various resections of the pancreatic head

2.1. Pancreaticoduodenal resection with antrectomy

Resection of the head of the pancreas, which is commonly called pancreaticoduodenectomy, has been performed for many decades as a two-stage operation. Nowadays, PD is performed as a one-stage operation, mainly for periampullary suspected malignant or pre-malignant tumours and chronic pancreatitis. It is performed either through a midline upper abdomen or transverse subcostal incision (Di Carlo et al. 1998). Prospects for performing curative resection can be determined preoperatively by laparoscopy (Orr 2010). Peroperatively after mobilizing the duodenum and visualizing the pancreatic head, the lymphatic nodes can be palpated. Invasion of the tumour to the portal or mesenteric vein or extension behind the mesenteric artery or vein is considered an ominous sign (Cooperman 1990). The transection of the stomach is performed at the distal or midportion. The right gastric artery and the gastroduodenal artery are divided and ligated. The common hepatic duct is divided above the entrance of the cystic duct and a cholecystectomy is performed. The ligament of Treitz is exposed following reflection of the transverse colon superiorly. The ligament is divided, the third and fourth portions of the duodenum are dissected from the posterior abdominal wall and the jejunum is interrupted distal to the ligament. The vessels are divided close to the bowel wall to avoid damage of the superior mesentery artery and vein. The pancreatic neck anterior to the superior mesenteric vein is usually the site of pancreatic division. The resection line is extended to the left if the frozen-section examination shows that the tumour reaches the transection line. Branches of the superior mesenteric vein to the pancreatic head and the uncinate process are carefully ligated. The extension of the dissection may be limited to the peripancreatic nodes, which are removed together with a specimen of the PD, or possibly extended

to the retroperitoneal tissue behind the pancreatic head removing distal lymph nodes, such as the periaortic nodes, from the celiac trunk to the renal arteries, the pericaval nodes, and the nodes around the superior mesenteric artery (Di Carlo et al. 1998).

A variety of reconstructive methods have been proposed. In most institutions, pancreaticojejunal anastomosis is the current mode of management, but other methods have also been reported, as pancreaticogastrostomy and occlusion of the pancreatic duct, thus avoiding pancreatic anastomosis. According to a meta-analysis, both anastomoses provide equally good results (Wente et al. 2007). Pancreaticojejunostomy can be performed end-to-end either by partly invaginating the remaining pancreas into the jejunum or by performing a mucosa-to-mucosa anastomosis of the pancreatic duct to the jejunum. If the pancreatic duct is small, a stent can be placed across the anastomosis to ensure patency of the ductal system.

End-to-end anastomoses can also be performed with modifications. A seromuscular flap can be developed on 1 cm of small bowel to cover part of the remaining pancreas (Maki et al. 1990). The anastomosis may also be of the dunking type (Reissman et al. 1995).

End-to-side anastomosis between pancreas and jejunum is preferred by many surgeons instead of end-to-end anastomosis. It can be performed using single-layer (Adam et al. 2002) or two-layer techniques. The duct can be sutured by individual stitches or e.g. by a parachute-type technique (Ohwada et al. 2001). The outer part of the anastomosis can be performed by directly suturing the pancreatic remnant with the seromuscular part of the jejunum (Kingsnorth 1989) or by invaginating the pancreatic remnant 1 cm into the jejunum (Z'graggen et al. 2002).

As anastomotic reconstruction, pancreaticogastrostomy has been preferred to pancreaticojejunostomy by some authors, because it may be simpler to perform and may be associated with lower incidence of anastomotic leakages (Arnaud et al. 1993, Kim et al. 1997). There were, however, no statistical differences in a one-centre retrospective study (Andivot et al. 1996). Nor did randomised, controlled trials (RCTs) show any statistical difference between these anastomotic techniques regarding postoperative complications (Yeo et al.1995, Duffas et al. 2005).

Hepaticojejunostomy is usually performed end to side using interrupted one-layer sutures. The gastrojejunal anastomosis is usually performed last, and is usually placed about 40 cm distal to the biliary anastomosis in order to promote neutralization of the gastric-acid secretion (Di Carlo et al.

1998). The entero-enteroanastomosis in the jejunal loop prevents reflux of the bile and pancreatic fluid to the stomach.

2.2. Pylorus-preserving pancreaticoduodenal resection

Pylorus-preserving pancreaticoduodenectomy (PPPD) was first performed in 1944 by Watson. He assumed that preserving the antrum, pylorus and one inch of the duodenum would allow better digestion and would prevent jejunal ulceration. This report remained an exceptional individual opinion until 1978, when Traverso and Longmire reported their experience of PPPD in two patients (Traverso and Longmire 1978). In this procedure, the gastroduodenal artery is divided, whereas the right gastric artery is usually preserved (Cameron 1990, Di Carlo et al. 1998). Preservation of 5 cm of the duodenum is sometimes possible, but in case of malignancy preservation of only 2 cm seems to be appropriate. PPPD is contraindicated if the tumour involves the duodenopancreatic angle (Röher et al. 2000) and if the patient has previously undergone vagotomy (Di Carlo et al. 1998). Both PD and PPPD alter normal upper gastrointestinal protective mechanisms, but there are only retrospective studies of marginal ulceration. Some series suggest that a higher rate of marginal ulceration is associated with PPPD (Martin and Zuberi 2010).

In terms of radicality, some groups have argued against PPPD for cancer of the pancreatic head. Patel et al. (1995) did not find evidence of any advantage of PPPD in malignant periampullary tumours. However, studies on survival have shown similar rates after PPPD or even better than after classical PD (Ogata and Hishinuma 2002). According to a small RCT of 36 patients, there was no significant difference between PPPD and PD in terms of operating time, blood loss, operative mortality and long-term survival (Lin et al. 2005). Delayed gastric emptying (DGE) was more frequently encountered in PPPD than in PD. This could not be shown in a meta-analysis performed by Martin and Zuberi (2010). Another systemic review and meta-analysis have been reported based on six trials that included 574 patients undergoing PPPD or PD. These showed that PPPD was 72 minutes faster, with 284 ml less blood loss and 0.66 fewer units of blood transfused. In terms of survival, there were no significant differences in the results. They favoured PPPD, though trends were weak (Karanicolas et al. 2007). Another review of seven randomised, controlled studies did not show significant differences between PPPD and PD in hospital mortality, overall survival or morbidity. Operating time and intra-operative blood loss were significantly reduced in the PPPD group compared to PD in pancreatic and periampullary carcinoma (Diener et al. 2007).

The pancreaticojejunal anastomosis after PPPD is performed as in classic Whipple's resection. Entero-enteroanastomosis is not used with PPPD.

It is generally accepted that the incidence of postoperative complications is similar after PD and PPPD. According to a single-centre study comparing PD (n = 41) and PPPD patients (n = 44), no significant differences were found in mortality, overall complications, major or minor complications, operative time, blood loss, gastric suction (days), oral solid diet (days) or hospital stay (days) (Di Carlo et al. 1998). Similar results were reported by Mosca et al. (1997) in a single-centre study of 513 patients. A multi-centre RCT of 170 patients did not show any significant differences between postoperative complications when classic Whipple and PPPD were compared (Tran et al. 2002). A smaller RCT of 27 patients showed more DGE in PPPD patients than those undergoing PD, the results of other complication parameters measured being statistically similar in both groups (PD vs. PPPD) (Srinarmwong et al. 2008).

2.3. Duodenum-preserving resections of the pancreatic head

In the treatment of chronic pancreatitis operative interventions are indicated when severe pain and local complications are resistant to conservative and endoscopic treatment or potential malignancy is present. An ideal procedure should be easy to perform, have a low morbidity and mortality rate, provide long-lasting pain relief, and not exacerbate exocrine or endocrine insufficiency. No operation fulfils this ideal (Frey and Mayer 2003). It is not always clear what the cause of pain is in chronic pancreatitis, but ductal pressure and peripancreatic inflammation are often involved (Touzios et al. 2005). Recently there have also been studies of the role of pancreatic neuropathy, either in the pancreatic or peripancreatic nerves, as a cause of pancreatic pain (Ceyhan et al. 2008, Ceyhan et al. 2009). Two operations have been developed to reduce ductal hypertension by excising the inflammatory mass of the head of the pancreas. These operations can only be performed, however, if malignancy can be excluded. They are local resection of the head of the pancreas combined with longitudinal pancreaticojejunostomy (LR-LPJ, Frey's operation) and duodenum-preserving resection of the head of the pancreas (DPPHR, Beger's operation). In Frey's operation diseased tissue in the head of the pancreas is resected, the main duct in the neck, body and tail is opened and thus the entire main pancreatic duct is either decompressed or resected. One Roux-en-Y limb is used to drain the body and tail of the pancreas (Frey and Mayer 2003). Beger's operation is indicated especially when the inflammatory process is located in the pancreatic head and in cases with portal hypertension due to inflammatory mass. After resecting the pancreatic head through the

uncinate process, a jejunal loop is excluded and interposed, needing two pancreatic anastomoses, one for the pancreatic tail and the other to cover the resected head (Beger et al. 1999). In cases with an intrapancreatic severe stenosis of the common bile duct due to inflammation, an additional internal biliary anastomosis between the common bile duct and jejunal loop has to be carried out.

According to an evidence-based review of pancreatic head resection for pancreatic cancer and chronic pancreatitis, the complication rates for standard and pylorus-preserving PDs range between 30 and 55 %, while duodenum-preserving procedures, particularly the Frey procedure, are associated with significantly lower morbidity rates, ranging between 9 and 22 % (Schäfer et al. 2002). According to a recent meta-analysis, where the effectiveness and safety of DPPHR versus PD in the treatment of chronic pancreatitis was compared, postoperative pain relief, overall mortality and morbidity showed no significant difference, but intraoperative blood transfusion, hospital stay, weight gain, exocrine insufficiency, occupational rehabilitation and quality of life were significantly improved in the DPPHR group (Diener et al. 2008).

In all of the operations except total pancreatectomy, postoperative mortality and morbidity are strongly associated with the problems of pancreatic anastomosis.

2.4. Extent of resection

The purpose of pancreatic resection when malignancy is suspected is to achieve an R0 resection, and PDs or PPPDs may be converted into total pancreatectomies if there is a sign of positive pancreatic neck margin. There is no evidence that conversion of R0 resection to R1 resection improves survival (Martin and Zuberi 2010). Raut et al. (2007) did not find in a multivariate analysis of 360 patients having undergone R0 or R1 resection that resection status affected survival independently.

Large prospective studies have been conducted studying the effect of lymphadenectomy on survival. Pedrazzoli et al. (1998) suggested a survival advantage in patients treated with an extended lymphadenectomy. Subsequent prospective studies did not show survival difference at 1-, 3- and 5-year survival between the standard and extended lymphadenectomy groups (Yeo et al. 1999, Yeo et al. 2002). According to a meta-analysis comparing standard and extended lymphadenectomy in PD for pancreatic cancer, extended lymphadenectomy did not benefit overall survival (Michalski et al. 2007). Instead, there was a trend towards increased morbidity (diarrhoea, DGE) after extended

lymphadenectomy. The addition of vascular resection to PD or PPPD for achieving an R0 resection can be accomplished safely and effectively with low perioperative mortality and morbidity, but long-term survival is poor (Martin and Zuberi 2010). Tumour infiltration is an important determinant of survival, not the vascular resection itself (Bachellier et al. 2001).

There are few studies evaluating outcomes, survival, complications or morbidity associated with adjacent organ involvement with pancreatic ductal adenocarcinoma (Martin and Zuberi 2010). Considering pancreatic resections reported for metastases to the pancreas, 80 % result from 4 primary cancer types: renal cell cancer, colorectal cancer, sarcoma and melanoma. The usefulness of pancreatic metastasectomy can be assessed by evaluating long-term survival in retrospective analyses (Martin and Zuberi 2010).

2.5. Total pancreatectomy

Total pancreatectomy for pancreatic cancer was first reported by Billroth in 1884 (Heidt et al. 2007), and re-introduced in 1954 by Ross and in 1958 by Porter, to avoid pancreatic anastomosis-related complications (Müller et al. 2007). The indications are chronic pancreatitis with intractable pain, familial pancreatic adenocarcinoma, neuroendocrine tumours and main duct type intraductal papillary mucinous neoplasms (Heidt et al. 2007). Despite the absence of pancreaticoduodenal anastomosis, total pancreatectomy has even higher early postoperative mortality than subtotal pancreatectomy, which precludes the consideration of total pancreatectomy as a routine treatment of sporadic pancreatic adenocarcinoma (Heidt et al. 2007). Serious postoperative complications following total pancreatectomy include intra-abdominal abscess and sepsis, intra-abdominal bleeding and gastrointestinal bleeding (Ihse and Andrén-Sandberg 1998). These patients have a five-year survival similar to that seen in patients who have undergone partial pancreatectomy (Heidt et al. 2007). Total pancreatectomy leads to diabetes by complete insulin deficiency and to steatorrhoea. Such diabetes is considered to be of the brittle type, characterized by a supranormal sensitivity to insulin, probably reflecting a lack of glucagon (Ihse and Andrén-Sandberg 1998). Another metabolic consequence of the apancreatic state is the development of steatohepatitis with progressive liver failure. This may be a result of progressive fat deposition in the liver following impaired hepatic stimulation by glucagon. Also, these patients are at increased risk of developing peptic ulcer disease secondary to lack of bicarbonate secretion (Heidt et al. 2007). Exocrine pancreatic insufficiency is obvious after total pancreatectomy regardless of the primary diagnosis. Patients tend to have steatorrhoea even after aggressive enzyme supplementation (Ghaneh and

Neoptolemos 1999). According to a single-centre retrospective study, there were no subjective or objective differences in the balance of post-pancreatectomy diabetes as a whole when compared to type 1 diabetes patients. Good balance was more often achieved in patients with malignancy than in those with chronic pancreatitis (Jethwa et al. 2006).

Currently, total pancreatectomy is appropriate in patients in whom complete removal of the pancreas is required for oncologic, technical, prophylactic or complication-related reasons (Müller et al. 2007, Martin and Zuberi 2010). In pancreatic cancer this means that it has a place in those cases where the tumour extends throughout the main duct, as evaluated intraoperatively by frozen-section examination or when the remaining part of the pancreatic body or tail is too frail for a safe anastomosis to be attempted. As it has unavoidable metabolic sequelae and does not decrease the recurrence rate of malignancies, total pancreatectomy is nowadays rarely used when compared to PD (Ihse and Andrén-Sandberg 1998).

3 Postoperative complications

3.1. Clinically significant surgical complications

Mortality after pancreatic resections has fallen to less than 5 % in specialized centres. However, the most severe complications, such as anastomotic leakage, haemorrhage, abscesses and delayed gastric emptying (DGE) may lead to reoperations, prolonged hospital stay, fatigue and nutritional disorders compromising quality of life (Cameron et al. 1993, Yeo et al. 1997, Bassi et al. 2001).

There is no common definition of pancreaticointestinal leakage. The reported incidence of pancreaticointestinal anastomotic leakage varies between 0 and 30 % (Cullen et al. 1994, Yeo et al. 1997, Büchler et al. 2000, Sohn et al. 2000, Balcom et al. 2001, Bassi et al. 2001, Li-Ling and Irving 2001, Bassi et al. 2004, Lin et al. 2004, de Castro et al. 2005). It may present as an elevated amylase activity in drains, but may also have manifestations of intra-abdominal abscess, sepsis, pancreatitis, or DGE. Leakage of pancreatic anastomosis is mainly associated with soft texture of the pancreatic remnant and coronary heart disease of the patient. The link between these risk factors and leakage seems to be postoperative pancreatitis (Räty et al. 2006).

Leakage of hepaticointestinal anastomosis is rarer than pancreatic leakage. It is most likely to be discovered by discharge of bile-stained fluid through the drains and is often caused by technical problems in performing this anastomosis. The incidence of this is about 2 % (Richter et al. 2003). Whether biliary leakage is more frequent in patients with pancreatic leakage is not known.

Haemorrhage can be divided into early postoperative bleeding and delayed haemorrhage after two or three weeks, which may be a result of a pseudoaneurysm, the reason for which may be anastomotic fistula. These pseudoaneurysms are treated angiographically with coils if the patient is clinically stable, otherwise they need immediate surgical treatment. Delayed haemorrhage has been reported in between 5 and 16 % but may occur in up to 60 % of cases of pancreatic leakage (van Berge Henegouwen et al. 1997, Rumstadt et al. 1998).

Septic complications and intra-abdominal abscesses are usually a result of anastomotic fistulas or leakages. Abscesses are seen in about 3 to 10 % after PD and are most often located in the right subhepatic region or under the left diaphragm. These can be drained under ultrasonographic or CT guidance, and additionally antibiotics are given intravenously. If there is no clinical improvement, surgical reintervention must be considered (Yeo 1995).

Differing definitions for DGE have been proposed, but patients undergoing pancreaticoduodenal resection are at high risk of developing it. The range is from 4 to 70 %. It does not increase mortality but results in prolonged hospitalisation, impaired quality of life and increased hospital costs. Its pathogenesis remains unclear, but the most important risk factor is the presence of other intra-abdominal complications, such as pancreatic fistula or anastomotic leakage (Räty et al. 2006). One explanation may also be gastric atony resulting from disruption of the gastroduodenal neural network. Small doses of erythromycin, which is an agonist of motilin, a hormone produced in the duodenum and proximal jejunum, have been reported to reduce DGE by 75 % (Niedergethmann et al. 2004).

A lack of a consensus on how to report and quantify morbidity after pancreatic surgery has recently led to a new classification of postoperative complications. This classification has five grades: grade I (no need for specific intervention), grade II (need for drug therapy), grade III (need for invasive therapy), grade IV (organ dysfunction with ICU stay) and grade V (death). This classification has been suggested to provide replicable assessment of pancreas surgery and comparison over time (DeOliveira et al. 2006).

Table 1 presents a list of studies in various periods where the results of pancreaticoduodenal resections are mentioned. There is a trend towards decreased hospital mortality in more recent studies.

Table 1. Some published studies on the results of pancreaticoduodenal resections

Authors	Period	Patients	Pancreatic fistula	Hospital mortality
Whipple et al. (1935)	1934-35	3	33 %	33 %
Howard (1968)	1955-68	41	10 %	0 %
van Heerden et al. (1981)	1970-79	146	11 %	4.1 %
Tarazi et al. (1986)	1950-84	105	23 %	7.8 %
Kairaluoma et al. (1990)	1968-87	89	4.4 %	*
Edge et al. (1993)	1989-90	168	not mentioned	6 %
Gordon et al. (1995)	1988-93	502	not mentioned	**
Lieberman et al. (1995)	1984-91	1972	not mentioned	***
Sperti et al. (1996)	1970-92	113	29 %	15 %
Martin et al. (1996)	1980-94	45	6.6 %	2.2 %
Barnes et al. (1996)	1987-95	108	18 %	1 %
Chew and Attiyeh (1997)	1981-96	29	3.4 %	3 %
Yeo et al. (1998)	1970-92	242	17 %	5.4 %
Sosa et al. (1998)	1990-95	496	not mentioned	****
Heslin et al. (1998)	1994-96	74	6.6 %	1.4 %
Yeo et al. (1999)	1996-97	114	8.8 %	4.4 %
Berney et al. (2000)	1984-93	68	8.1 %	1.5 %
Sohn et al. (2000b)	1984-99	526	5 %	2.3 %
Gouma et al. (2000)	1994-98	300	7.7 %	1 %
Porter et al. (2000)	1996-98	148	7.4 %	1.5 %
Balcom et al. (2001)	1990-2000	489	11 %	1 %
Wamser et al. (2002)	1994-2000	130	20 %	2.7 %
Urbach et al. (2003)	1994-99	686	not mentioned	10 %
Schmidt et al. (2004)	1980-2002	516	9 %	3.9 %
Lin et al. (2005)	1994-2002	36	5.6 %	8 %
Cameron et al. (2006)	1969-2003	1000	12 %	1 %
Ho et al. (2006)	*****	8253		*****
Brozzetti et al. (2006)	1990-2000	166	14 %	7.1 %
Shinchi et al. (2006)	1996-2002	207	14 %	0 %
Scurtu et al. (2006)	1995-2003	70	2.9 %	2.6 %
DeOliveira et al. (2006)	2003-05	633	9.0 %	1.8 %
Goh et al. (2008)	1986-2006	232	31 %	3 %
Schmidt et al. (2009)	1980-2002	510	9 %	4 %
Fuks et al. (2009)	2000-06	680	16.3 %	2 %

* This study was divided into two periods. In the first one (1968-73), hospital mortality was 33 % and in the second one (1983-87), it was 0 %.

** In Johns Hopkins' Hospital, mortality was 2.2 %, but in other hospitals in Maryland, it was 19 %.

*** According to the classification of the study, hospital mortality in high volume hospitals was 4.0 %, in low volume hospitals 22 %. When surgeons' experience was considered, hospital mortality was 4.7 % when

the operation was performed by an experienced surgeon and 16 % when performed by a non-experienced surgeon.

**** According to hospital volume, hospital mortality was 0.9 %, 6.9 % or 19 %.

***** The study was divided into three periods: 1988-91, 1992-96 and 1997-2000. Hospital mortality was 11 %, 10 % and 8.3 % respectively.

4 Anastomotic leakages following pancreatic head resections

4.1. Consequences of leakage of pancreaticojejunal anastomosis

Pancreatic leakage is the major factor most strongly implicated in death in most PD series (Shyr et al. 2003). It is considered a serious, life-threatening event that may prolong hospital stay and increase costs (Bassi et al. 2005). It has been assumed that the variety of different incidence rates of pancreatic fistula may be a result of the absence of a general definition. Also, in the literature different terms can be found referring to the same complication, e.g. fistula, leak, leakage, focal postoperative pancreatitis, anastomotic failure or anastomotic insufficiency (Bassi et al. 2005). This condition may be suspected on the basis of the amount of drain fluid on or after postoperative day 3, and an amylase activity greater than three times the upper normal serum value. Associated clinical findings may include abdominal pain and signs of infection (Bassi et al. 2005).

An international panel of pancreatic surgeons (Bassi et al. 2005) developed and proposed a definition of postoperative pancreatic fistulas (POPF):

Grade A: Transient fistula with no clinical impact

Grade B: Requires a change in management and leads to a delay in discharge or readmission

Grade C: A major change in clinical management occurs, and clinical stability may be borderline. The patient needs extended hospital stay, and reoperation may be needed. Serious postoperative complications and mortality may be associated (Bassi et al. 2005, Reid-Lombardo et al. 2007a).

The grade of severity may be determined after complete follow-up, including discharge from hospital or death.

This classification has, in any case, been criticized and a new one has been proposed on the basis of the University of Toronto classification of surgical complications and the University of Zurich classification of surgical complications (Strasberg et al. 2007). It favours the definition of fistulas proposed by the Johns Hopkins group (Yeo et al. 1995), according to which before day 10 the drainage of high amylase fluid is rarely of clinical significance provided it has ended or is less than 50 ml/day by day 10 (Strasberg et al. 2007). On the other hand, not placing a drain after pancreaticoenterostomy has been shown in an RCT to be equally effective as placing a drain in terms of clinical outcome and is thus an accepted practice (Conlon et al. 2001). Shyr et al. (2003) did not find biochemical amylase-rich drainage fluid level to be of clinical significance according to an RCT. They did, however, recommend that assessment of pancreatic leakage should be based on persistent pus-like drainage and confirmed by roentgenography with a contrast medium or dye such as methylene blue in the drainage fluid (Shyr et al. 2003).

Certain predisposing factors are known that may result in anastomotic leakage following PD. A narrow pancreatic duct ($\leq$ 2 mm) makes anastomosis more difficult to perform (van Berge Henegouwen et al. 1997). According to a prospective RCT there is a strong association between pancreatic texture and anastomotic leakage (Yeo et al. 2000). This means that a fibrotic pancreatic remnant in patients with chronic pancreatitis facilitates pancreaticoenteric anastomosis, whereas a soft and friable pancreatic parenchyma makes anastomosis difficult to perform (Yang et al. 2005). The pancreaticojejunal anastomosis can be performed either end-to-end or end-to-side. The method depends on the surgeon's choice and on anatomic circumstances. Marcus et al. (1995) compared different anastomotic methods according to patients' risks, and concluded that end-to-side anastomosis appears safe in low-risk patients and end-to-end invagination in high-risk patients.

When preoperative exocrine pancreatic function was measured using preoperative N-benzoyl-L-tyrosyl-p-aminobenzoic acid (NBT-PABA) excretion test it was found that patients with low NBT-PABA results had fewer anastomotic leakages than those with normal results (Sato et al. 1998). According to an RCT of 39 patients having both malignant and benign diseases as indications for PD, postoperative acute pancreatitis was a major determinant of postoperative delayed gastric emptying and was suggested to be a risk factor of anastomotic leakage by possibly impairing healing of the anastomosis (Räty et al. 2006). Other risk factors include age, gender, malnutrition, presence of jaundice, duration of surgery, intraoperative blood loss, resection type and anastomotic

technique (Yang et al. 2005). Surgeon's experience has also been shown to correlate with pancreatic leakage rate (Yeo et al. 1995, Yang et al. 2005).

To minimize the risk of anastomotic leakage, different techniques have been proposed. Most authors recommend duct to mucosa pancreaticojejunal anastomosis (Kingsnorth 1989, Maki et al. 1990, Nagakawa et al. 1997, Ohwada et al. 2001, Hosotani et al. 2002), regardless of the reconstruction method used. Many retrospective studies consider PG superior to PJ but the results of level 1 data show that both anastomoses are equally effective, and they do not have significant differences in fistula rates (Martin and Zuberi 2010). Peng et al. (2007) in an RCT of 217 patients compared conventional and binding pancreaticojejunostomies, where the everted jejunum is fixed on the pancreatic stump with a binding ligature. They found significantly lower incidence of pancreatic anastomotic leakage in the binding group. In a dual-institutional prospective randomized trial, 197 patients were stratified by pancreatic texture and randomized to an end-to-side invagination or duct-to-mucosa anastomosis (Berger et al. 2009). There was a 24 % pancreatic fistula rate in the duct-to-mucosa cohort and a 12 % fistula rate in the invagination cohort ($p < 0.05$). The investigators suggested that the greatest risk factor for pancreatic fistula was soft gland texture. Adams (2009) found over 1700 publications on pancreatic anastomosis. He concludes that the choice of pancreatic anastomotic technique should be based on individual experience.

According to a retrospective case series of 437 patients of a major pancreatic surgery centre, 13 % of the patients operated on during a 7.5-year period developed a pancreatic fistula. Of these, 95 % had successful conservative treatment with prolonged tube drainage and only 5.5 % needed reoperation (Kazanjian et al. 2005). Similar results have also been reported by Abete et al. (2005), who point out the importance of completion pancreatectomy to maximize survival if re-exploration is necessary.

4.2. Use of stents and drains in protecting the anastomosis

Different kinds of stents have been tested for protecting the anastomosis against both leakage and stricture. These drain the anastomosis either internally or externally, in case of early protection. To protect the anastomosis, many use a small plastic tube intraluminally (Kingsnorth 1989, Kim et al. 1997, Hosotani et al. 2002, Jang et al. 2002). Protection of the anastomosis has also been reported when an externally directed drain has been used (Matsumoto et al. 1992). Marcus et al. (1995) compared three types of pancreticojejunostomies. They recommend end-to-side anastomosis by

performing the anastomosis in two layers and using a small plastic catheter as a protecting stent in low-risk patients. In high-risk patients with small, unobstructed pancreatic ducts or soft, friable pancreata, they recommend end-to-end invaginating anastomosis without an inner layer but using a protecting plastic catheter (Marcus et al. 1995). Nagakawa et al. (1997) discussed three different anastomoses where plastic tubes were used to protect the anastomosis. These were named impaction method, submucosal anastomosis and non-division procedure. They considered non-division procedure a method with a low risk of suture insufficiency. In that procedure the end of the pancreatic duct and the tube for the external fistula were approximated to the jejunal wall and the pancreas and serosal tunica muscularis of the small intestine were sutured together (Nagakawa et al. 1997). There are a few studies on the use of stents in protecting the anastomosis from leakage. According to a randomised prospective study of 238 patients, the use of a segment of paediatric plastic feeding tube as a stent did not protect the anastomosis from leakage when the pancreatic tissue was soft nor when it was hard. Anastomosis was either done duct to mucosa or by invaginating the pancreas into the jejunum (Winter et al. 2006). Plastic stents may also migrate in about 7 % of cases and lead to serious complications, which may even require surgical intervention (Diller et al. 2003). In rare cases a plastic stent may be occluded and lead to symptoms of pancreatic insufficiency, which resolve or improve after removal of the stent (Levy et al. 2004).

Some use exterior drainage to protect pancreaticojejunal anastomosis (Keck et el. 1991, Matsumoto et al. 1992). Z'graggen et al. (2002) described a technique performed on 331 patients with a fistula rate of 2 %. They performed an end-to-side anastomosis and invaginated the remaining pancreas 1 cm into the jejunum. They did not use any catheter in the pancreatic duct. A retrospective study of using venting tubes (externally draining devices traversing the bowel) for a period of 29 days postoperatively reported no significant advantage of using such drains when morbidity and mortality were considered. The authors found that there was a risk of extra complications when these drains were removed (Fallick et al. 1999). In the study by Reissman et al. (1995), the pancreatic duct was ligated and local control was achieved by drains. Early results favoured this technique, but the study groups were small. No significant differences in intra-abdominal complications were observed when temporary fibrin glue occlusion of the main pancreatic duct was used and compared with pancreatic anastomosis (Suc et al. 2003).

At present, there is no consensus about the role of stents in protecting the anastomosis. Theoretically, protection of the pancreaticojejunal anastomosis using stents may decrease complications thereby having a positive effect on the short-term and long-term results.

Use of intraperitoneal drains has been considered routine after pancreatic resections (Conlon et al. 2001). Their purpose is to remove accumulating blood, bile, pancreatic juice, and also serve as a warning of haemorrhage or anastomotic leakage. A randomized, prospective trial was performed on 139 patients having undergone PD. There was no significant difference in the number or type of complications between groups. The result is similar to other suggestions that routine postoperative drainage after major upper abdominal operations is not needed (Conlon et al. 2001). Formerly it has also been suggested that such drains may not be useful as a therapeutic method if leakage occurs. They may also be hazardous as they create a pathway for contamination (Jeekel 1992). According to a recent randomized study comparing early (3rd postoperative day) and standard (5th postoperative day or later) drain removal, results showed that prolonged period of drain insertion is associated with a higher rate of postoperative complications with increased hospital stay and costs (Bassi et al. 2010).

4.3. Other ways to protect the anastomosis

The use of somatostatin in preventing postoperative pancreatic anastomotic fistulas has been controversial. According to a randomised, controlled study performed on healthy individuals, pancreatic exocrine secretion was significantly reduced by somatostatin when measured with magnetic resonance cholangiopancreatography (MRCP). In a large RCT, somatostatin analogue octreotide was found to reduce severe postoperative complications in high risk stratum (pancreatic and periampullary tumours) but not in low risk stratum (Büchler et al. 1992). On the other hand, according to another large, randomised, controlled study, the use of prophylactic octreotide did not decrease the rate of pancreatic fistula in any diagnostic group. Avoiding the use of octreotide means cost savings (Yeo et al. 2000). Two systematic reviews and meta-analyses have been performed. According to Alghamdi et al. (2007), use of octreotide is associated with a significant reduction in the incidence of pancreatic fistulas after elective pancreatic surgery but not with postoperative mortality. Zeng et al. (2008), on the other hand, did not find use of octreotide to result in reduction of the incidence of pancreatic fistula, pancreas-specific postoperative complications or mortality.

5 Impacts of hospital and surgeon on short-term and long-term complications following pancreatic head resections

5.1. Impact of surgeon on postoperative morbidity and mortality

The concept of surgeon-related variability and the difficulties of surgical research have been discussed by Fielding (1988), though his examples were not of pancreatic resections. Forty years ago Howard published a study of his 41 consecutive Whipple resections without mortality. He concluded that a low mortality rate may be a result of a clinical team with a continued interest in these problems, and mentioned that high mortality rates place the responsibility on the profession to centralize or regionalize the care (Howard 1968).

A multi-institution database of 26 American university hospitals considering 168 PDs performed 1989–90 showed that in this period PDs were done by 91 surgeons, whose case loads varied from 1 to 15 resections per year (median 1). The mortality rate was 6 % with major complications in 21 %. The mortality rate did not correlate with case load, but surgeons performing 1 to 3 resections per year had significantly more complications than those performing 4 or more (Edge et al. 1993). In a Finnish university hospital, 89 patients underwent PD in a 20-year period 1968–1987 (Kairaluoma et al. 1990). Hospital mortality decreased from 33 % in 1968–1972 to 0 % in 1983–1987, and this decline was explained to be a result of centralizing the resections to the same group of surgeons. Morbidity remained the same in both periods. Incidence of pancreatic fistulas was 4.4 %. An example of good results in an American community hospital, where 29 patients underwent PD during the period 1981–1996, showed mortality of 3 % and pancreatic fistula of 3.4 %. The authors point out that the surgeons must be adequately trained in the procedure and that in low-volume hospitals the case load should be restricted to a minimal number of trained surgeons (Chew and Attiyeh 1997).

However, the results from Johns Hopkins Hospital between 1990 and 1995 considering 496 pancreatic resections showed that the outcome was mainly dependent on hospital volume but not on surgeon volume (Sosa et al. 1998). Similar results were published on New York State, where both hospital and surgeon volume were significantly related to perioperative deaths in univariate analysis, but in multivariate analysis only hospital volume was significant (Lieberman et al. 1995).

A retrospective study of PDs at a teaching hospital showed more postoperative complications among surgeons performing less than one operation per year compared to those performing more. It also showed that pancreatic resections can be taught safely provided that the surgeons supervising the operations have a personal caseload of at least one resection per year to maintain their own skills (Wamser et al. 2002). According to a study considering results of major operations performed in the United States over one year 1998-1999, (pancreatic resection being one of these operations) surgeon volume was inversely related to operative mortality in multivariate analysis (Birkmeyer et al. 2003).

Shrikhande et al. (2005) published a review considering factors associated with pancreatic anastomotic leakage and management of the pancreatic remnant after PD. They concluded that the surgeon is perhaps the most important factor in the prevention of pancreatic anastomotic leakage. They also emphasized that collaborative multi-centre trials from high-volume centres may provide data and guidelines regarding the best techniques for specific intraoperative findings and scenarios.

5.2. Impact of hospital on postoperative morbidity and mortality

Since the early nineties, many studies have been published in which centralization of PDs has been supported. PD has been of special interest because it is a typical high-risk procedure and because a large proportion of American patients with PD have undergone their operation at hospitals performing less than one procedure per year. As survival numbers have been accessible through the Internet, there have also been financial incentives to encourage the use of high-volume hospitals (Birkmeyer 2002).

Thirty-day mortality in major operations performed in the United States between 1994 and 1999 was studied, pancreatic resection being one of those operations. The results of multivariate analysis showed in all of the operations that mortality decreased as volume increased. Considering pancreatic resection, absolute differences in adjusted mortality rates between very-low-volume hospitals (< 1 resection per year) and very-high-volume hospitals (> 16 resections per year) ranged from 16.3 % to 3.8 % (Birkmeyer et al. 2002). Many investigators have shown that high-volume hospitals have better process control, including better intensive care support. It is possible that these institutional processes may drive the low mortality, and not simply the case volume (Orr 2010). Urbach et al. (2003) studied data on all patients undergoing five major surgical procedures in Ontario, one operation being PD. In a five-year period (1994–1999) over 31 000 patients underwent

these operations, 686 were pancreaticoduodenectomies. Hospital mortality was 10 %. They concluded that in Ontario a small number of operative deaths are potentially avoidable by performing complex operations at high-volume hospitals, but in determining health policy, prevention of a large number of such deaths must not be the most compelling argument.

According to an evidence-based review, the most important factor affecting mortality is the emergence of specialized centres focusing on pancreatic surgery. This means not only a restricted number of surgeons but also multidisciplinary experienced teams caring postoperatively (Schäfer et al. 2002). The results favouring the centralization of PDs are conclusive in two studies using multivariate analysis (Lieberman et al. 1995, Sosa et al. 1998), the results in the latter also being favourable to centralization from an economic perspective. These results were also replicated in a large, single-institution, retrospective study of a prospectively collected database. According to Gordon et al. (1995), hospital mortality, length of hospital stay and costs were significantly less at the high-volume regional medical centre than in other hospitals. Barnes et al. (1996) reported the results of 108 patients operated on for benign disease and found mortality less than 1 %. In the same institution, 616 patients with pancreatic adenocarcinoma underwent surgical resection from 1984 to 1999. Perioperative mortality was 2.3 % and postoperative pancreatic fistulas were found in 5 % of the patients (Sohn et al. 2000b). In Johns Hopkins Hospital, one thousand PDs were performed in the period 1969–2003, and hospital mortality was only 1 %. It was also observed in this period that median operative time has dropped from 8.8 to 5.5 hours, postoperative length of stay from 17 to 9 days and blood loss also decreased significantly (Cameron et al. 2006). Length of stay also dropped similarly although the mean age of patients rose in a 10-year study (1990–2000) performed in a high-volume university hospital in Massachusetts (Balcom et al. 2001). In this study there were 489 patients who underwent pancreatic resection. During this period, however, mortality remained unchanged (1 %) and so did pancreatic fistulas (11 %).

In Europe, centralization of pancreatic surgery has not been routine. A Dutch study compared mortality following PD in high-volume and low-volume hospitals (Gouma et al. 2000). The results showed increased hospital mortality in low-volume hospitals. The institutional mortality rate in an academic medical centre was 1 % and incidence of pancreatic fistulas 7.7 %. In this study, differences in mortality according to the surgeon were not seen. In Taiwan, an epidemiologic study considering the period 2000–2003 was conducted to compare surgical mortality rates in five cancer-related gastrointestinal resections (Lin et al. 2006) . There too, it could be noted that patients treated in high-volume hospitals had lower in-hospital mortality than those treated in low-volume hospitals,

although mortality rates were not directly comparable to those obtained from American studies, probably partly due to cultural differences. The impact of hospital volume on operative mortality has been studied in an American epidemiological study, according to which equal trends in mortality were observed in five major operations, PD being one of them (Begg et al. 1998). Operative mortality in a 10-year period (1984–1993) was 13 % in low-volume hospitals and 5.8 % in high-volume hospitals.

There has also been criticism of centralization. According to a 29-patient retrospective study the results in a university-affiliated community hospital were comparable to the results in high-volume centres, providing the surgeons performing PDs were trained for these operations (Chew and Attiyeh 1997). Similarly, centralization of PDs to high-volume hospitals did not influence either hospital procedure, volume or revenue according to a study performed in New York State (Chappel et al. 2006). In this study, there was discussion as to whether regionalization of colectomies might lead to loss of surgeons but not in the case of cardiothoracic procedures, cystectomies or PDs. It was speculated that centralization results in losing certain elective cases, but as their number is small, it was considered unlikely that rural surgeons rely on these high-risk procedures to maintain viable practices. According to a European study performed in a middle-volume centre (4.7 PDs per year), major pancreatic resections can be performed safely with acceptable morbidity and mortality. However, experience is required of the operating surgeon. In this study, mortality was 2 % and pancreatic fistulas were seen in 12 % (Peros et al. 2010).

The number of the nation-wide studies evaluating the effect of hospital volume and status on postoperative mortality and morbidity is relatively small. Status in Finland has not been studied.

6 Anastomotic strictures and long-term postoperative pancreatic exocrine insufficiency after pancreatic head resections

6.1. Enzymatic methods of measuring pancreatic exocrine function

Direct function tests with duodenal intubation are considered to be the most accurate pancreatic function tests. However, after PDs they are seldom successful. In secretin-cholecystokinin test, the specificity and sensitivity in the diagnosis of chronic pancreatitis are actually over 90 % (Domínguez-Muñoz et al. 1998). The secretin-cholecystokinin test has been the gold standard in the

evaluation of pancreatic exocrine insufficiency, but it is an invasive procedure as the test requires aspiration of duodenal and gastric juice (Walkowiak et al. 1999). Another direct function test is the Lundh test, which has lower accuracy, especially in cases of mild chronic pancreatitis. In this test, the exocrine pancreatic secretion is endogenously stimulated by a test meal, and this test, too, entails duodenal incubation (Domínguez-Muñoz et al. 1998).

Exocrine pancreatic function can also be measured indirectly by assessing the concentration of pancreatic enzymes in serum or faeces or evaluating the digestive capability of the gland on a test meal. Serum concentration of different pancreatic enzymes in chronic pancreatitis may be increased, decreased or normal. A decreased serum enzyme concentration is a very specific finding in advanced disease with pancreatic insufficiency, but has low sensitivity. Measuring chymotrypsin activity in faeces is a simple, cheap and non-invasive method of assessing the exocrine pancreatic function, but has low sensitivity (Domínguez-Muñoz et al. 1998). Faecal elastase-1 is a specific human protease synthesized by the acinar cells. It is unaffected by exogenous pancreatic enzyme treatment (Dominici and Franzini 2002). It has high specificity and sensitivity for detecting definite chronic pancreatitis, sensitivity being higher than with the faecal chymotrypsin test (Naruse et al. 2006). In severe and moderate exocrine pancreatic insufficiency it is specific, but rather unspecific in milder forms of pancreatic insufficiency (Walkowiak et al. 1999). Faecal elastase-1 test is widely used, and the result is expressed as normal (> 200 μg/gram stool), moderately reduced (100-200 μg/gram) or severely reduced (< 100 μg/gram).

Other function tests are based on the oral administration of a substrate, and on the determination in serum or urine of the concentration of their products that are liberated after pancreatic digestion and absorbed from the gut. Such tests include the NBT-PABA test and the pancreolauryl test (PLT), which is a cheap test and easy to perform and has high reliability to identify severe exocrine pancreatic insufficiency, but has low sensitivity in mild cases. It also yields a relatively large number of false positives in gastrointestinal diseases that have a marked influence on gastrointestinal transit and intestinal absorption (Domínguez-Muñoz et al. 1998).

Residual pancreatic exocrine function was studied clinically in a group of patients with periampullary carcinoma using NBT-PABA before and after pancreatic operations (Tanaka et al. 1988). According to these results, six-hour excretion of NBT-PABA to urine was significantly lowered preoperatively and within two months of the operation but not after 12 months of the operation. This study also had an experimental part, where the effect of the ligation of the minor

pancreatic duct and subsequent insertion of a polyethylene tube to the major pancreatic duct on urinary NBT-PABA were studied in adult mongrel dogs. Urinary NBT-PABA levels showed a reduction from the preoperative level but returned to almost the same level four to five months postoperatively. The authors concluded that postoperative pancreatic function was well preserved if pancreatic duct drainage was effectively performed, even after 50 percent resection of the pancreas.

6.2. Imaging of the pancreas

Ultrasonography is often used in the initial evaluation of patients with abdominal pain or suspected obstructive jaundice. It is a fast and cheap method for diagnosis, but it is in 15 % of patients inadequate due to intestinal gas and obesity (Clark et al. 1985, Brambs and Claussen 1993, Michl et al. 2006). It is very sensitive in showing biliary dilatation. The sensitivity of ultrasonography is 95 % in tumours > 3 cm in diameter but decreases rapidly with smaller tumours (Michl et al. 2006). Endoscopic ultrasonography was developed in the early 1980s and is highly sensitive in experienced hands to detect vascular infiltration of the major abdominal vessels (Michl et al. 2006).

Computed tomography (CT) enables superior assessment of the retroperitoneum and higher anatomic resolution for the extent of the tumour beyond its margins when compared to ultrasound (Thoeni and Blankenberg 1993). It needs oral contrast medium to demonstrate the interfaces between the stomach, duodenum and pancreas. CT cholangiography can be used if obstructive biliary disease is suspected (Fleischmann et al. 1996). Multi-detector CT is now the most widely available and best validated tool for pancreatic imaging (Michl et al. 2006).

Magnetic resonance imaging (MRI) and especially magnetic resonance cholangiopancreatography (MRCP) are nowadays useful diagnostic tools but they allow no therapeutic procedures. On the other hand, risk of pancreatitis associated with ERCP in diagnostics is avoided when using MRCP. Formerly MRI itself did not have a significant role in evaluating patients with signs of biliary obstruction, but the availability of heavily T2w breath hold sequences changed the value of MRI. Currently MRCP is an important addition to more conventional MRI of the pancreaticobiliary system by providing valuable information on pancreatic and biliary ducts. Its weakness is in analysing the aetiology of strictures (Friedrich et al. 1998).

Secretin-stimulated MRCP is a non-invasive, non-operator dependent technique that also produces high-quality images in patients with surgically modified anatomy (Sugiyama et al. 2003). It has the

advantage of delineating ductal pathology (benign strictures and duct leaks) as it helps to diagnose acute and chronic pancreatitis and neoplasms (Kinney et al. 2007). Images taken following intravenous injection of secretin may help in diagnosing pancreatic papillary stenosis and also in detecting reduced pancreatic function reserve (Matos et al. 1997). Sho et al. (1998) presented a three-grade classification of pancreatic exocrine secretion (grade I = poor secretion, grade II = moderate secretion, grade III = good secretion) in 34 patients who had undergone PD. These grades correlated significantly with the results of glucose tolerance tests and clinical symptoms. They could confirm the patency of the anastomotic site in 24 patients (71 %) (Sho et al. 1998). A study to evaluate the patency of pancreatogastrostomy after PD and to determine a correlation between pancreatic endocrine and exocrine functions has been performed (Pessaux et al. 2002). The results of secretin-stimulated MRCP were graded into four grades. Faecal elastase-1 samples were analysed to determine exocrine function and fasting blood glucose concentrations to determine endocrine function. There was a significant correlation between secretin-stimulated MRCP results and faecal elastase-1 concentrations. No correlation was found between endocrine function and secretin-stimulated MRCP. As the patency of the pancreatogastrostomy was 68 % and exocrine insufficiency 95 %, the authors concluded that these results may be partly explained by neutralization of pancreatic enzymatic secretion by gastric acid. One study has been published focusing on morphologic and functional evaluation with secretin stimulated MRCP. The patients had undergone PD with PJ anastomosis. The exocrine pancreatic function was evaluated by the Van de Kamer method (Monill et al. 2004). There are only few studies comparing faecal elastase-1 levels and secretin stimulated MRCP findings after pancreatic head resections.

Endoscopic retrograde cholangiopancreatography (ERCP) with brush cytology is still widely used in the diagnosis and particularly treatment of periampullary tumours and bile duct strictures. It is, however, difficult to perform on patients with jejunal or Roux-en-Y loops (Tang et al. 2000, Farrell et al. 2006). ERCP combined with intraductal ultrasonography may as a diagnostic tool, give a more accurate differentiation of malignant from benign lesions, than MRCP (Domagk et al. 2004).

In the future, positron emission tomography (PET) combined with CT may be an important improvement in diagnostic sensitivity for malignant tumours and preoperative planning of treatment. According to a prospective study comparing ^{18}F-fluorodeoxyglucose PET combined with CT (FDG-PET/CT) to multidirectional CT and MRI in patients with suspicion of pancreatic malignancy, FDG-PET/CT was more sensitive in the diagnosis of both primary pancreatic adenocarcinoma and distant metastases but not local lymph node metastases (Kauhanen et al. 2009).

In the light of these results, FDG-PET is recommended in the evaluation of diagnostically challenging cases, especially in patients with biliary strictures without evidence of malignancy in conventional imaging.

6.3. Postoperative pancreatic exocrine insufficiency

Postoperative exocrine insufficiency of the pancreas may be a result of shortage of pancreatic tissue, subnormal function of the pancreatic remnant and stenosis of the anastomosis. Exact knowledge of the functional status of the gland is mandatory for a correct therapeutic approach, as well as for follow-up (Domínguez-Muñoz et al. 1998).

Remnant pancreatic function after PD has a crucial effect on postoperative quality of life. However, evaluating the exocrine remnant pancreatic function is difficult (Sho et al. 1998). The histological grade of fibrosis in the cut-end of the pancreatic remnant has been found to correlate inversely with the exocrine pancreatic function when the amount and amylase activity of the pancreatic juice were measured on the 7th postoperative day via a tube exteriorised from the pancreatic duct (Uchida et al. 2002). In long-term follow-up studies comparing pancreaticogastrostomy and pancreaticojejunostomy, abnormal exocrine function could be shown after both anastomoses, but it was statistically poorer after pancreaticogastrostomy, when faecal elastase-1 test (Jang et al. 2002) or severe steatorrhoea were considered (Rault et al. 2005). The results of an RCT performed in a non-selected patient group having periampullary malignancy did not show statistical differences in postoperative exocrine insufficiency when anastomosis and occlusion of the pancreatic duct were compared (follow-up 12 months after surgery) and the results 12 months after surgery considered the aspect of stools and use of enzyme substitution (Tran et al. 2002). However, significantly more patients with pancreatic duct occlusion used pancreatic enzyme supplementation during the first year. Also, the incidence of diabetes was significantly higher in the patients with duct occlusion.

Chronic pancreatitis also leads to exocrine pancreatic insufficiency together with pain. According to a retrospective follow-up study of 335 patients and median duration of 9.8 years, pancreatic surgery often reduced pain postoperatively, but later the pain course between patients operated on and patients with no operation had no significant differences (Lankisch et al. 1993). In the same study, repeated exocrine pancreatic function tests in 143 patients showed that functional exocrine impairment came to a standstill in 46 % and improved in 11 % of patients. It is not well known how

frequent exocrine pancreatic insufficiency is among patients before PD, but enzyme substitution is recommended for all patients with pancreatic cancer (Matsumoto and Traverso 2006).

7 Health-related quality of life in patients having undergone pancreatic head resection

7.1. Different instruments for measuring HRQoL

There is growing interest in assessing the impact of a disease and the effect of a treatment on patients' lives, expressed as health-related quality of life (HRQoL). Three types of HRQoL instruments can be distinguished: generic, disease-specific and symptom-specific (Langenhoff et al. 2001). The results of HRQoL studies depend on the instruments used. Generic instruments may detect factors such as co-morbidity more accurately, disease or symptom specific instruments have the advantage of better clinical interpretability (Scheingraber et al. 2005). There are several studies on HRQoL specifically attributed to different treatments.

One example of generic instruments for measuring HRQoL is the 15D, which is a generic, comprehensive, 15-dimensional measure of HRQoL that can be used both as a profile and as a single index score measure (Sintonen 2001). The reliability, validity, sensitivity and discriminatory power, and responsiveness to change has been well tested in Finnish population. In many respects the properties of the 15D are considered superior to existing and generally used profile and single index score quality of life instruments (Sintonen 2001).

An example of the use of the 15D in gastrointestinal surgery was a prospective, observational study involving both curative and some palliative procedures (Räsänen et al. 2001). In this study there were 131 patients, of whom 77 had cholecystectomy, 20 fundoplication, 20 incisional herniorraphy, 12 large bowel resection and 2 construction of a stoma because of unresectable colorectal cancer. In this study, surgical treatment improved HRQoL and its various dimensions two months postoperatively, and HRQoL was comparable with that of the general population. The authors concluded, however, that as the pattern of recovery was dependent on the diagnostic subgroup and preoperative condition of the patients, a generic measure should be separated into dimensions when estimating the outcome (Räsänen et al. 2001). Another example of 15D was its use to evaluate postoperative HRQoL in a prospective study of patients who had undergone laparoscopic gastric bandage for morbid obesity. The results showed improvement of HRQoL 12 months

postoperatively both in the single index score and in the dimensions of mobility, respiratory function, sleep, functioning ability, vitality and sexuality (Tolonen et al. 2004). There are also many other generic instruments with numerous applications within both diagnoses and procedures.

McLeod (1999) has recommended the use of disease specific quality of life instruments based on better sensitivity than generic instruments. An example of a symptom specific HRQoL instrument is the McGill Pain Questionnaire, which consists of three different measures of pain. Data obtained from the questionnaire can be analysed statistically. It can detect differences among different methods of treating pain (Melzack 1975).

7.2. Pancreatic resection and HRQoL

A total of 192 patients having undergone PD (PPPD and classic Whipple) with various indications responded to a visual analogue scale (VAS) type of index (Huang et al. 2000). Controls were patients with laparoscopic cholecystectomy and healthy controls. Many patients reported weight loss and symptoms consistent with pancreatic exocrine and endocrine insufficiency, but as a group, patients who survived PD had HRQoL values similar to cholecystectomy patients and healthy controls. According to a 45-patient study (24 PPPD and 21 classic Whipple), there were some differences in the subgroups when compared to normal controls, i.e. classical Whipple patients had lower scores for vitality and general health than PPPD patients (Melvin et al. 1998). The patients had both benign and malignant diseases. HRQoL was measured with a generic instrument (SF-36). Comparison of HRQoL after PPPD and Whipple resection has also been determined on the basis of a questionnaire including questions on physical and psychosocial items (Ohtsuka et al. 2003). There were two measurement points, the first two months and the second 6-12 months postoperatively. According to this study, quality of life is better after PPPD than after Whipple resection, but long-term mental health care is necessary in patients of both groups.

When considering pancreatic cancer, both PPPD and double bypass (cholecystectomy, hepaticojejunostomy, gastroenterostomy and celiac plexus block) patients tended to have a temporary decrease in HRQoL after the operation, but it returned to its preoperative values by about three months after surgery until it decreased in the last 8 weeks before death (Nieveen van Dijkum et al. 2005). HRQoL was measured with four different questionnaires. Of these, the Medical Outcomes Study 24 acute-phase questionnaire was generic, the Rotterdam Symptom Checklist and VAS were symptom-specific and the Gastrointestinal Quality of Life Index (GIQLI) was disease-

specific. A generic, though cancer-specific HRQoL questionnaire often used is the Quality of Life Index C30 of the European Organization for the Research and Treatment of Cancer (EORTC QLQ-C30). According to a prospective, single-centre study comparing classic Whipple or PPPD with regional or extended lymphadenectomy, resection techniques did not affect HRQoL, but extended lymphadenectomy was associated with impairment of HRQoL, especially in terms of pain and diarrhoea (Schniewind et al. 2006). However, the follow-up was only 24 months after surgery. This could also be observed when single parameters were evaluated (weight gain, pain) (Ishikawa 1996). Based on the EORTC QLQ-C30, the EORTC QLQ-PAN26 was developed. This is a questionnaire specific to pancreatic cancer, and takes steatorrhoea into account better than EORTC QLQ-C30 (Fitzsimmons and Johnson 1998, Fitzsimmons et al. 1999). Besides survival rates, clinical benefit response as well as HRQoL measurements using the EORTC QLQ-C30 are of importance in evaluating survival data in series with multimodality treatment (Beger et al. 2003).

There are more RCTs of HRQoL in chronic pancreatitis than in pancreatic cancer. Bloechle et al. (1995) compared the EORTC QLQ-C30 index with Spitzer's quality of life index (both generic instruments) and with pain score (VAS). After follow-up of 18 months they found that the EORTC QLQ-C30 scores correlated well with the scores of Spitzer's quality of life index. They also found significant improvement of HRQoL in all these 25 patients, who were treated with duodenum-preserving resection of the head of the pancreas (Beger's operation). This study also showed the validity and reliability of the EORTC QLQ-C30 in chronic pancreatitis (Bloechle et al. 1995). According to a prospective trial of 65 patients comparing PD and Beger's operation and using two different disease-specific scores for measuring HRQoL, both procedures showed significant improvement in HRQoL, especially regarding pain (Witzigmann et al. 2002). During a later stage (18 to 24 months postoperatively), better quality of life was found in the Beger's operation group than in the PD group. It was also noted that after PD more patients seemed to develop diabetes mellitus. The indices used in this study were the EORTC QLQ-C30 and GIQLI, the content validity of which was found to be low compared to the EORTC QLQ-C30.

An RCT compared long-term results of LR-LPJ or Frey's procedure and PPPD in 61 patients (Izbicki et al. 1998). Pain relief, control of complications from adjacent organs and quality of life were studied with the EORTC QLQ-C30. Median follow-up time was 24 months. The pain score decreased by 95 % after PPPD and by 94 % after LR-LPJ, but global quality of life was improved by 43 % in the PPPD group and by 71 % in the LR-LPJ group. Compared to a German population

after follow-up of 18 – 24 months, HRQoL scores according to the EORTC QLQ-C30 were similar after Beger's operation but lower after PD (Witzigmann et al. 2003).

The results of Beger's operations, Frey's procedures and PPPDs were compared in a retrospective study using GIQLI scores (Kelemen and Horváth 2002). No significant differences between the total scores could be detected during the follow-up, but there were some differences between the operations, which may be explained with different follow-up times. Mean follow-up time was 41.5 months in the Beger group, 20.6 months in the Frey group and 31.1 months in the PPPD group. Early morbidity was higher after PPPDs, and there were significantly more new cases of diabetes after PPPD (43 %) than after Beger's operation (3.7 %).

One problem impairing postoperative HRQoL is exocrine insufficiency. One possible way to improve postoperative quality of life might be preoperative supplementation of pancreatic enzymes as recommended by Ohtsuka et al. (2001). The effect of type of anastomosis (pancreaticogastrostomy or pancreaticojejunostomy) following PPPD on HRQoL has been studied by using the EORTC QLQ-PAN26 and a self-developed non-validated questionnaire in 104 patients with a mean follow-up time of 6.4 years (Schmidt et al. 2005). These patients had both malignant and benign diseases. The general quality of life was identical in both groups of patients though there were some differences in the subgroups. McLeod et al. (1995) compared the HRQoL of post-Whipple patients to that of post-cholecystectomy patients using six different instruments. Follow-up time was 5.1 $\pm$ 4.2 years in the Whipple group and 4.9 $\pm$ 3.8 years in the control group. It was concluded that the quality of life of the Whipple patients was excellent and not significantly different from that of the control subjects.

In a prospective study in Johns Hopkins Hospital, 106 patients responded to 5-year follow-up with a VAS-type questionnaire (Sohn et al. 2000a). There were many different procedures, PD being the most common. The patients reported improvements in all aspects of quality of life, though they often became insulin-dependent diabetics and required pancreatic enzyme supplementation after surgical intervention.

In general, there are few studies investigating the possible long term changes in HRQoL after pancreatic head resections. The consequences especially of the problems in pancreatic anastomosis, such as early leakage and late stenosis on late HRQoL, are poorly understood.

AIMS OF THE STUDY

This study focuses on the association of pancreaticojejunostomy with the early complications and late clinical results after pancreatic head resection.

The specific aims were:

1. To evaluate the incidences and particularly co-incidence of pancreaticoenteric and bilioenteric leakages in patients who have undergone pancreatic head resection (I).
2. To study the effect of hospital and surgeon volume on the short-term and long-term results of pancreatic head resections performed in Finland (II).
3. To study whether pancreatic exocrine insufficiency late after pancreatic head resection is due to obstructed pancreaticoenteric anastomosis or poor parenchymal secretion (III).
4. To evaluate postoperative health-related quality of life in patients who have undergone pancreatic head resection at two different time points after the operation (IV).
5. To develop a prototype of an x-ray positive, biodegradable intraductal stent for the pancreaticojejunal anastomosis, and to test it in pilot patients (V).

PATIENTS AND METHODS

1 Study I – Pancreaticoenteric and bilioenteric leakages

This retrospective study included 46 patients, on whom resection of the head of the pancreas was performed in Tampere University Hospital during a four-year period, 1991–1994. Of the 46 patients, 19 were men and 27 were women. Their age ranged from 31 to 82 years, the median age being 65 years.

The final diagnosis was malignancy in 36 patients. Of these, 19 had ductal adenocarcinoma of the head of the pancreas, 10 had adenocarcinoma of the ampulla of Vater, two had adenocarcinoma of the distal common bile duct and two had duodenal carcinoma. In one case it remained uncertain whether the adenocarcinoma was of pancreatic or duodenal origin. One patient had malignant insulinoma and one had retroperitoneal liposarcoma that penetrated the duodenal wall.

Pancreaticoduodenal resection with antrectomy was performed on 17 patients (37 %), PPPD on 24 patients (52 %) and PPPD with extensive retroperitoneal lymphadenectomy on five patients (11 %). The hepatic duct was transsected above the cystic duct junction and the pancreas on the left of the portal vein in all patients. The pancreaticoenteric anastomosis was performed end to end in two layers with interrupted 4-0 braided nylon (Surgilon^{R}, Davis-Geck, USA) sutures, invaginating 2 cm of the pancreas into the jejunum. Bilioenteric end to side anastomoses were performed in one layer with interrupted 4-0 polydioxanon (PDS^{R}, Ethicon, Germany) sutures. Soft sump drains were left beside both anastomoses. The drain on the patient's right side was next to the bilioenteric and that on the left side next to the pancreaticojejunal anastomosis.

Early postoperative pancreaticobiliary complications were evaluated. The pancreatic fistula was classified as subclinical or clinical according to the amylase activity (more than three times the upper normal serum value) and the amount of secretion (> 50 ml) on day seven postoperatively and whether or not the patient had signs of intra-abdominal infection. The biliary fistula was considered subclinical according to the colour of the secrete from the right drain on day four, or if the postoperative cholangiogram showed signs of leakage, but the patients had no signs of intra-abdominal infection. It was deemed clinical if the patients had signs of intra-abdominal infection.

2 Study II – Results of resections of the head of the pancreas with pancreaticojejunal anastomosis in Finland

For this retrospective analysis, data of a total of 374 patients were collected from 33 Finnish hospitals, in which resections of the head of the pancreas were performed during a five-year period (1990-1994). The patients were identified from the national hospital discharge database, to which every patient must be reported on discharge. To obtain the right patients the code of pancreaticoduodenectomy from ICD-9 was used. To collect the data, each of these hospitals was visited by the author.

The case records of 350 patients (94 %) could be obtained for further analysis. There were 182 men and 168 women with a median age of 64 years (range 31–84 years). The following parameters were recorded: preoperative diseases, surgeon, hospital, age of the patient, preoperative biliary stent, type of operation, histological diagnosis, extent of the disease, adjuvant therapy, postoperative complications, re-operations, hospital stay and hospital mortality.

The hospitals were categorized as low (average < 5 annual resections), medium (average 5-10 annual resections) and high (average > 10 annual resections) volume hospitals and the surgeons as low (average < 1 annual resections), medium (average 1-3 annual resections) and high (average > 3 annual resections) volume surgeons.

The long-term results were based on actual five-year survival assessed using data from the hospital case records and from the National Registry for Causes of Death.

3 Study III – Postoperative exocrine insufficiency after pancreatic head resection

Twenty-six patients (10 men, 16 women; mean age 61 years, range 34–81 years), participated in this retrospective study, with a median follow-up of 55 months (range 3–76 months). These patients were examined in 2001, and some of them also participated in Study IV. Fourteen of the patients had benign disease. Fifteen patients had undergone PPPD and six had undergone pancreaticoduodenal resection with antrectomy. In these operations, the pancreaticojejunostomy was always an end-to-end invaginated telescopic type two-layer anastomosis. When duodenum-

preserving pancreatic head resection had been undertaken (five patients), Beger-type resection was used.

During the operation, the surgeon assessed the pancreatic duct diameter to one of three categories (small when below 3 mm, normal when between 3 and 5 mm, and wide when over 5 mm). The pancreatic parenchyma was divided into two groups, either normal or hard.

During examination, VAS was used to describe the patients' experience of diarrhoea. According to a test on a few pilot patients, 0–1.0 was considered minimal diarrhoea, 1.1–4.0 moderate diarrhoea and 4.1–10 severe diarrhoea. Previous use of any enzyme preparations was recorded. Pancreatic function was measured by analysing the faecal elastase-1 concentration with a commercial ELISA using an antibody highly specific to human enzyme. A faecal elastase-1 concentration > 200 μg/g was considered normal, 100–200 μg /g moderate and < 100 μg /g severe pancreatic insufficiency.

The pancreatic glandular size was studied from transverse sections obtained with MRI. The glandular and ductal responses on secretin stimulation and the ductal morphology were studied with dynamic magnetic resonance cholangiopancreatography (D-MRCP). For the interpretation of the results, previously used secretin-stimulated D-MRCP categories originally developed for the intact pancreas were used (Matos et al. 1997). These categories are shown in Table 2.

Table 2. Secretin-stimulated D-MRCP grading of the pancreatic secretory function (Nordback et al. 2007)

Grade	Finding	Interpretation
Grade 0	Impossible to evaluate due to excessive intestinal fluid	Discharged from analysis
Grade 1	No secretion into the jejunum, pancreatic duct not visible	Glandular malfunction
Grade 2	No secretion into the jejunum, pancreatic duct visible but remains large	Total obstruction of the anastomosis
Grade 3	Secretion into the jejunum detected, pancreatic duct visible but remains large	Partial obstruction of the anastomosis
Grade 4	Secretion into the jejunum detected, pancreatic duct visible, diameter changes with secretin stimulus	Normal glandular function and open anastomosis

4 Study IV – Early and late postoperative quality of life following pancreatic head resections with pancreaticojejunal anastomosis

This study included 27 patients, on whom resection of the head of the pancreas had been performed during 1994 and 1997. Of these, 13 were males and 14 females, with median age 66 years (range 31–85). Twelve patients (44 %) had a malignant and 15 (56 %) a benign disease. This exceptional distribution is explained by the fact that at the first point of interview (2 years postoperatively) some of the patients with malignant diseases were no longer alive. Of the malignancies, five (42 %) were ductal adenocarcinomas of the head of the pancreas, five (42 %) adenocarcinomas of the ampulla of Vater, one (8 %) adenocarcinoma of the distal bile duct and one (8 %) carcinoid tumour of the pancreatic head. Four of the 12 patients (33 %) with malignant disease were treated with extended lymphadenectomy and the rest with standard local lymphadenectomy. Eleven of the benign diseases were chronic pancreatitis, two were serous cystadenomas, one retention cyst and one ulcerative inflammation of the common bile duct. All the patients used digestive enzyme supplementation.

Of the operations performed, 19 (70 %) were PPPDs, two (7 %) were classic Whipple's resections and six (22 %) were duodenum preserving pancreatic head resections (Beger's operations). The patients were interviewed in the late 1990s at median 24 (range 3–43) months after the operation (early stage evaluation). During the interview a normal clinical examination was performed and blood tests were taken. Chest x-ray and upper abdominal ultrasound were also performed to eliminate the possibility of tumour recurrence or metastasis of a malignant tumour.

The interview was conducted using a questionnaire with a general part, which included the 15D questionnaire. This yields a 15-dimensional profile of level values on a 0–1 scale (0 = being dead, 1 = no problems on the dimension) and an overall HRQoL score (15D score) on a 0–1 scale (0 = being dead, 1 = no problems on any dimension). The HRQoL of the patients was compared to that of a sample representative of the over 15-year-old Finnish non-institutionalized population from the National Health Survey in 1995/96.

To evaluate possible late changes in HRQoL, those 17 patients who were still alive in September 2004 were invited to a new 15D interview for late stage evaluation. The median follow-up time from surgery was 110 (range 87–126) months. Two of the patients did not attend the second interview, so the possible change in HRQoL during the long-term follow-up could be assessed in 15 patients. Of these, ten had a benign and five a malignant diagnosis. The benign diagnoses were

seven chronic pancreatitis, one retention cyst of the pancreatic head, one ulcerative inflammation of the distal bile duct and one serous cystadenoma of the pancreatic head. The malignant diagnoses were three carcinomas of the ampulla of Vater, one carcinoma of the distal bile duct and one carcinoid tumour of the pancreatic head. The HRQoL of the patients was compared to that of a sample representative of over 30-year-old Finnish population from the National Health 2000 Health Examination Survey.

Before testing whether there were statistically significant differences between the patients and general population samples in the total 15D scores and on different dimensions (level values), the population samples were matched with the age and gender distribution of the patients with appropriate weighting.

As separate additional objectives, the effect of early complications on HRQoL was examined in these two time points (median 24 and 110 months postoperatively). The effect of the nature of the disease (benign vs. malignant) and the possible abnormal results in the laboratory or imaging tests were also compared in the first step evaluation.

5 Study V – A new biodegradable stent for the pancreaticojejunal anastomosis

This study had two parts, an *in vitro* study to follow biodegradability of gamma sterilized 0.4 mm spiral stents and an *in vivo* study, where the degradability of these stents was followed-up in two pilot patients. Originally, our idea was to have a stent manufactured of a poly-L,D-lactide (PLA 96, L/D ratio 96/4) spiral covered by a polyglycolide (PGA) membrane, the latter being intended to protect the anastomosis from leakage and the former of stricture. There were different sizes of stents to fit the pancreatic ducts with the use of a metal guide. We soon noticed that this two-part stent was too stiff and almost impossible to insert into the human pancreatic duct. Thus, the PGA cover was abandoned.

In the *in vitro* studies the biodegradability of the stents was studied at two different pH values, the first resembling that of pancreatic juice and the other resembling that of bile. The effects of barium sulphate on the stents and the enzymoactivity of the solution were also monitored for degradability. The temperature of the solutions was 37°C. *In vitro* enzyme substitution consisted of distilled water mixed with crushed granules of Pankreon^{R} (Kali-Chemie GmbH, Hannover, Germany) enterocapsules, which contained lipase, amylase and protease. Salts were added to simulate body

fluids and the pH values of the new solutions were measured and titrated to the desired level using 2 – 6 M NaOH and HCl solutions and electrolyte concentrations. The solutions were changed twice a week.

After a certain number of weeks three stents were randomly chosen and the compression stability of each stent was tested using Lloyd LR30K Materials Testing Machine (Lloyd Instruments PLC, Fareham, U.K.). The buckling force of the incubated stents and the compression modulus was measured. The experiment was continued until all stents had degraded.

Stents of this type were inserted using a tailor-made applicator (Fig 1) into the pancreatic duct of two pilot patients during pancreaticoduodenal resection. The length of these stents was 5 cm, outer diameter 3 mm and inner diameter 2.2 mm. These patients were a 66-year-old woman and a 67-year-old man, who had had PPPD for periampullary carcinoma. Both of them had fibrosis in the resection line of the pancreas. Neither of them had any postoperative complications during hospitalization. The degradation of the stents could be followed with plain radiograph controls.

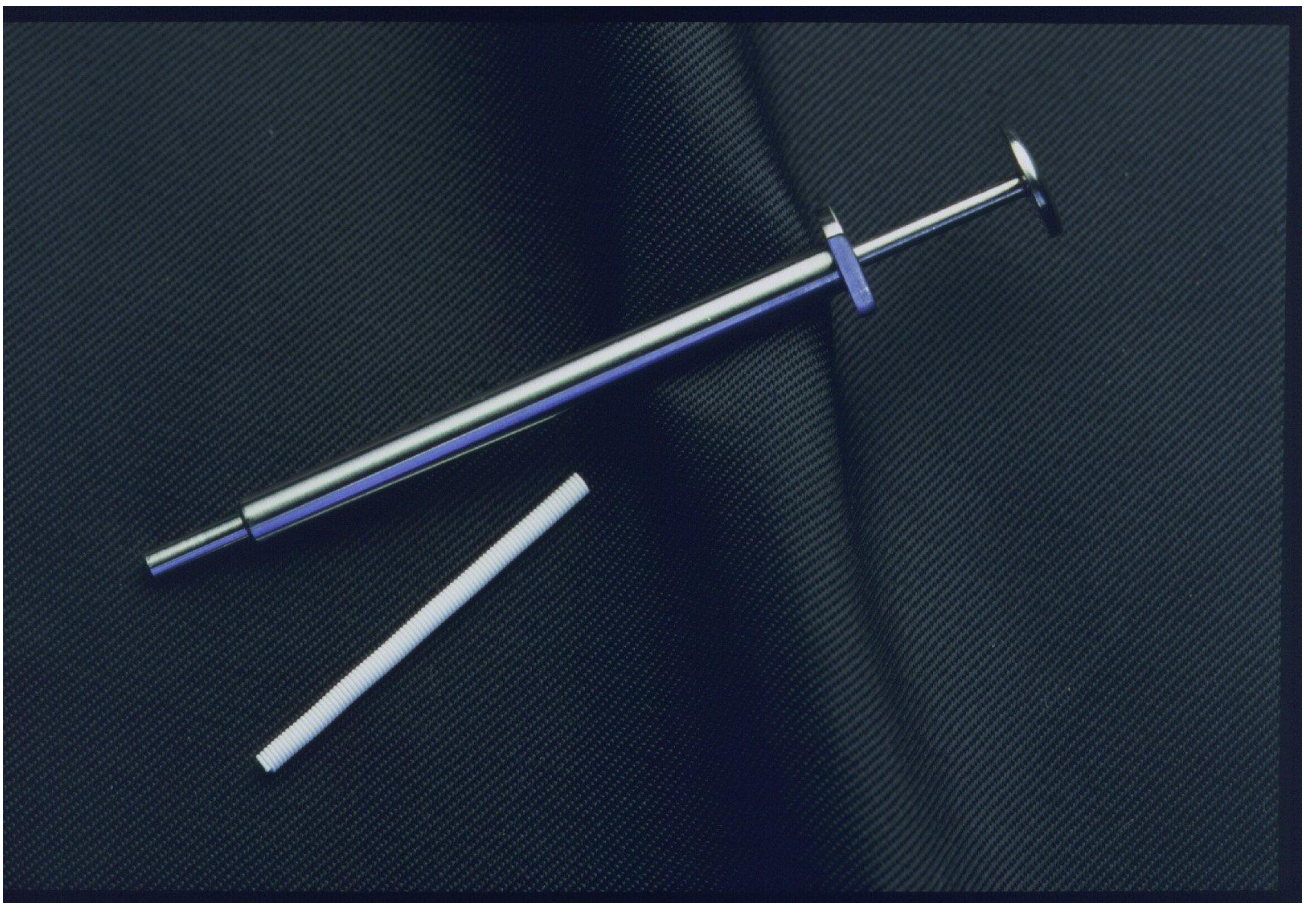

Figure 1. A biodegradable stent and an applicator to be used in inserting the stent into the pancreatic duct

6 Statistics

Fisher's exact t-test was used to evaluate the statistical significance of the differences within groups in Study I. Chi-square test and Mann-Whitney U-test were used to compare significance for univariate analysis in Studies II and III. Bonferroni correction and for multivariate analysis backward stepwise multiple logistic regression analysis were used for statistical calculations in Study II, and forward stepwise logistic regression analysis in Study III, then Kaplan-Meier method to create survival curves in Study II. Independent samples t-test was used to compare the means of patients and population samples and paired t-test was used to compare the means of study groups at different time points. Correlations of different study parameters were calculated with Pearson's correlation coefficient test in Study IV. Bonferroni Multiple Comparisons Test was used to test the statistical significance of the results between groups in Study V. A p-value < 0.05 was considered statistically significant.

7 Ethical considerations

The protocols were approved by the Ethical Committee of Tampere University Hospital. The general permit for Study II was obtained from the Ministry of Social Affairs and Health likewise individual permits to study the case records from each participating hospital.

In addition, all patients included in re-examination studies (III and IV) and the two pilot patients participating in Study V gave informed written consent.

RESULTS

1 Study I – Pancreaticoenteric and bilioenteric leakages

All patients had pancreaticojejunal anastomosis after resection of the pancreatic head. Hospital mortality was 4 % (2/46) in these patients operated on between 1991 and 1994. These two patients had no anastomotic leakages in autopsy. Eight patients (17 %) had pancreatic and four (9 %) biliary fistulas. Biliary fistula was significantly ($p = 0.014$) more common in patients with simultaneous pancreatic fistula (3/8 = 38 %) than in patients without pancreatic fistula (1/38 = 3 %) (Table 3). When only clinical fistulas were studied, biliary fistula was more common ($p < 0.01$) in patients with clinical pancreatic fistula (2/3 = 67 %) than in those without (1/43 = 2 %). Of these patients, two were operated on again. One of them recovered after revision and re-suturing of both anastomoses, the other had to undergo caudal resection and splenectomy.

Three of the eight patients who had pancreaticoenteric anastomosis leakage had firm and fibrous tissue in the pancreatic resection line according to the notes of the operating surgeon. In the remaining five patients the tissue was considered soft and normal. The patients with both pancreatic and biliary fistulas tended to have ($p = 0.05$) soft tissue in the pancreatic resection line (3/3 = 100 %) compared to those without simultaneous fistulas (15/43 = 35 %).

Table 3. The coincidence of postoperative biliary and pancreatic fistulas (clinical plus subclinical) (Parviainen et al. 1996).

			Biliary fistula	
		Yes		No
	Yes	3		5
Pancreatic fistula				
	No	1		37

2 Study II – Results of pancreatic head resections in Finland

When considering the short-term results, during this study period, resection of the head of pancreas was performed in 33 hospitals by 98 surgeons. The operations were performed in 6 university hospitals (5 separate universities), 16 central hospitals and 11 district or city hospitals. The most experienced surgeon had performed 24 resections during the 5-year study period.

Hospital mortality was 10 % (36/350 patients) and was related to hospital volume, surgeon volume and to the age of the patient, as can be seen in Table 4. Most of the deaths were directly related to surgical complications. Leakage of the pancreaticojejunal anastomosis could be found in the autopsies of 14 patients (39 %). Re-operations were also related to hospital volume and to surgeon volume. Of the patients surviving the resection, 103/314 (33 %) suffered from non-lethal but serious complications, most of which were directly related to the surgical procedure.

A multivariate analysis was performed to study the effect of patients' age, surgeon volume, hospital volume, preoperative palliation (stent versus no stent) and histological diagnosis on hospital mortality, re-operation and complications. The results are shown in Table 5. It revealed that younger age of the patient decreased the likelihood of hospital mortality (OR = 0.94, $p = 0.004$). It also showed that low annual surgeon volume increased hospital mortality and need for re-operation, low annual hospital volume increased re-operations. Significantly fewer complications were found in patients who had undergone preoperative stenting of the biliary tract, also when only clinically jaundiced patients were included.

Fifty-one out of 271 (20 %) patients with periampullary adenocarcinoma survived more than 5 years. There were no differences in relation to hospital or surgeon volume or type of operation or preoperative stenting (Fig. 2). However, patient survival was better when the recovery was uncomplicated compared to those who had suffered from postoperative complications.

Table 4. Mortality, re-operations and recovery after the resection of the head of the pancreas (Nordback et al. 2002)

	Hospital mortality	Re-operation	Uncompl. recovery	Hosp. stay (survivors) in days
	n (per cent)	n (per cent)	n (per cent)	median (range)
Hospital volume				
Low (<5)	26/201 (13)*	43/201 (21)*	119/201(59)	23 (8-100)**
Medium (5-10)	8/ 93 (7)	18/ 93 (19)	55/ 93 (59)	23 (7-81)**
High (>10)	2/ 56 (4)*	5/ 56 (9)*	40/ 56 (71)	18 (8-58)**
Surgeon volume				
Low (<1)	18/125 (14)*	28/125 (22)*	72/125 (58)*	24 (9-70)**
Medium (1-3)	16/164 (10)	33/164 (20)*	96/164 (59)*	23 (7-100)**
High (>3)	2/ 61 (3)*	5/ 61 (8)*	46/ 61 (75)*	18 (8-63)**
Age of the patient				
<60 years	5/122 (4)*	23/122 (19)	78/122 (64)	22 (8-81)
≥60 years	31/228 (14)*	43/228 (19)	136/228(60)	23 (7-100)
Preoperative diseases				
Yes	19/185 (10)	38/185 (21)	113/185(61)	26 (24-28)
No	17/165 (10)	28/165 (17)	101/165(61)	26 (24-28)
Histology				
Chronic pancreatitis	4/ 35 (11)	6/ 35 (17)	22/ 35(63)	19 (8-52)
Pancreatic ductal adenocarcinoma	21/163 (13)	27/163 (17)	104/163(64)	24 (9-100)
Other	11/152 (7)	33/152 (22)	88/152(58)	22 (7-70)
Preoperative palliation				
Stent	4/ 51 (8)	5/ 51 (10)	39/ 51(77)*	23 (7-100)
No stent	32/299 (11)	61/299 (20)	175/299(59)*	22 (7-70)
Operation				
Standard PD	28/270 (10)	54/270 (20)	162/270(60)	23 (7-100)
Pylorus preserving	7/ 76 (9)	12/ 76 (16)	49/ 76(65)	22 (9-70)
Duodenum preserving	1/ 4 (25)	0/ 4 (0)	3/ 4(75)	16 (10-34)

*p<0.05 (χ^2 –test), ** p< 0.05 (Bonferroni correction)

Table 5. The effect of age, surgeon volume, hospital volume, preoperative palliation and histology (chronic pancreatitis / ductal adenocarcinoma) on the hospital mortality, re-operations and complications (Nordback et al. 2002)

	Hospital mortality		Re-operations		Complications	
	p*	OR**	p*	OR**	p*	OR**
Age	0.004	0.94 (0.91-0.98)	0.90	1.00 (0.98-1.03)	0.69	0.69 (0.99-1.03)
Surgeon volume	0.04	1.30 (0.94-1.80)	0.05	1.10 (0.88-1.35)	0.11	0.92 (0.79-1.08)
Hospital volume	0.12	0.97 (0.85-1.10)	0.05	1.03 (0.93-1.14)	0.19	1.02 (0.94-1.10)
Stent	0.52	1.60 (0.5-5.10)	0.08	1.83 (0.66-5.04)	0.02	0.45 (0.22-0.94)
Histology	0.10	0.51 (0.24-1.10)	0.30	1.28 (0.74-2.21)	0.30	0.82 (0.53-1.27)

* Stepwise multiple logistic regression analysis, ** Odds ratio (95 % confidence interval)

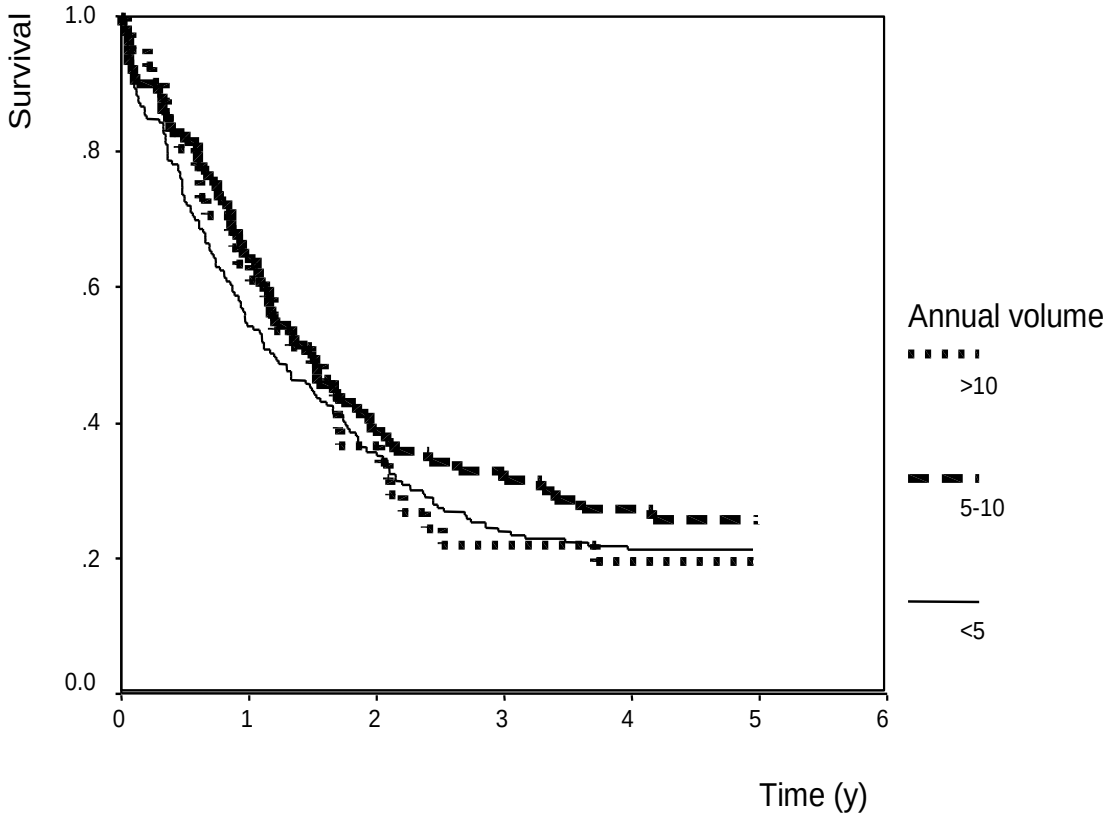

Figure 2. The effect of annual hospital volume on the actual five-year survival of 271 patients undergoing the resection of the head of the pancreas for periampullary carcinoma (mass around the head of the pancreas the final histology being ductal adenocarcinoma, ampullary adenocarcinoma, distal bile duct adenocarcinoma or duodenal adenocarcinoma) (Nordback et al. 2002).

None of the patients with malignancy had tumour recurrence in MRI examination. Twenty-four patients out of 26 (92 %) had severe pancreatic exocrine insufficiency, measured by faecal elastase-1 assay. Of these, 16 had elastase-1 concentration below 15 μg/g. The diagnosis of chronic pancreatitis or pancreatic ductal adenocarcinoma was significantly associated with the most decreased faecal elastase-1 concentration, whereas postoperative leakage of the anastomosis was not.

Eight patients (31 %) had minimal diarrhoea, 12 patients (46 %) moderate diarrhoea and six patients (23 %) reported severe diarrhoea. The median severity of diarrhoea was 2.2 (range 0–9.4) on a scale of 0–10. Seven patients (27 %) used enzyme supplementation, but one of these patients still suffered from severe diarrhoea.

According to a univariate analysis, the patients experienced more severe diarrhoea if the operation had been performed more than three years previously, if the primary diagnosis was chronic pancreatitis, if the pancreatic gland was considered hard with a small duct and if the duodenum was preserved. In the multivariate analysis the only independent risk factor for developing severe diarrhoea was hard parenchyma ($p = 0.02$, odds ratio = 16; 95 % CI 1.5–166).

According to MRI imaging of the pancreatic remnant, the size of the remnant gland was not significantly associated with the reported diarrhoea or the measured faecal-1 concentration. D-MRCP could be evaluated in 16 patients, as in three patients interpretation of the examination was not possible due to excessive fluid in the intestine prior to secretin injection (Grade 0) and in seven patients there was severe glandular malfunction (Grade 1), which means there was not enough fluid in the duct making it impossible to evaluate the anastomosis (Table 6). Five patients (22 %) had total obstruction of the anastomosis (Grade 2), six (26 %) partial obstruction (Grade 3) and in five patients (22 %) their anastomoses were considered fully open (Grade 4). The 23 patients with informative D-MRCP examinations were analysed further to determine whether diarrhoea and faecal elastase-1 concentration correlated with the glandular or anastomotic malfunction. There was no significant difference between patients with severe pancreatic glandular malfunction (Grade 1) and with patients with anastomotic malfunction (Grades 2–3) in the reported diarrhoea and measured elastase-1 concentration. On the other hand, patients with normal postoperative pancreatic

secretion in the D-MRCP (Grade 4) had the highest measured median faecal elastase-1 concentration (68 μg/g).

Factors associated with either glandular or anastomotic malfunction were analysed and the results are shown in Table 6. In the univariate analysis, none of the parameters studied was associated with glandular malfunction. Age over 60 years at the time of the operation and resection of the duodenum were significantly associated with an increased prevalence of obstructed anastomosis. Also, there was a trend towards an association between small duct size and late anastomotic obstruction. No independent risks could be found in multivariate analysis.

Table 6. Effect of patient, disease and the extent of operation on the pancreatic exocrine secretion assessed by D-MRCP (Nordback et al. 2007)

	N	Grade 1	2	3	4	Malfunction of remnant gland (Grade 1 vs. 2+3+4)	Obstructed anastomosis (Grade 2+3 vs. 4)
Men	10	2	2	2	4	NS	NS
Women	13	5	3	4	1		
Age							
< 60 years	11	2	2	2	5	NS	0.028
≥ 60 years	12	5	3	4	0		
Resected							
<36 mo ago	8	4	3	1	0	NS	NS
>36 mo ago	15	3	2	5	5		
Chr. pancr.	9	2	2	1	4	NS	NS
Ductal adenoca.	5	2	2	1	0		
Other	9	3	1	4	1		
Small/norm. duct	11	4	3	3	1	NS	0.09
Large duct	12	3	2	3	4		
Normal gland	9	3	3	2	1	NS	NS
Hard gland	14	4	2	4	4		
Duodenum							
Preserved	5	0	1	0	4	NS	0.013
Removed	18	7	4	6	1		
Pancreatic complication							
None	19	6	4	5	4	NS	NS
Fistula	4	1	1	1	1		
Pancreatic remnant size							
Small	6	1	2	0	3	NS	NS
Moderate	9	4	2	3	0		
Large	6	2	1	1	2		

4 Study IV – Early and late postoperative quality of life following pancreatic head resections

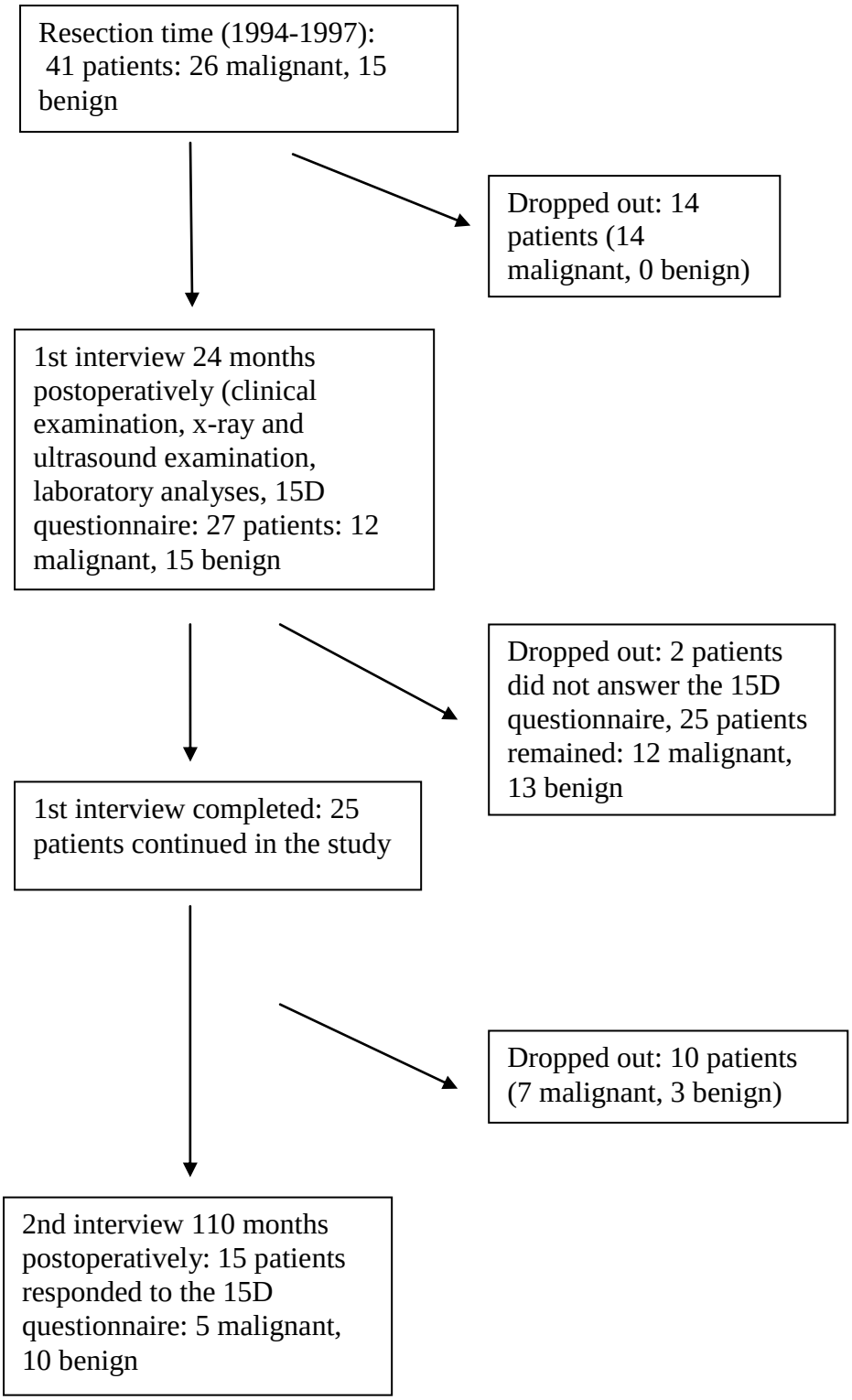

Figure 3. Distribution of patients participating in the early and late interviews using 15D-questionnaire

The distribution of the patients participating in the interviews is shown in Figure 3. Twenty-five out of 27 patients attended the first interview. All but one of the patients had faecal elastase-1 concentration < 15 μg/g. One patient with elevated Ca 19-9 value had signs of recurrent carcinoma, but no others had any such signs in thoracic plain x-ray examination or in the abdominal ultrasound.

In the first interview (24 months postoperatively), HRQoL was significantly lower in the study group than in the general population sample (0.8284 vs. 0.8784, $p = 0.03$) (Table 7). The patients were statistically significantly worse off than general population on the dimensions of sleeping (0.7042 vs. 0.8501, $p < 0.01$), elimination (i.e. bladder and bowel function) (0.7299 vs. 0.8772, $p < 0.01$) and sexual activity (0.6999 vs. 0.8160, $p = 0.04$) (Table 7). In the first interview we did not find any differences in HRQoL when the patients were divided into groups according to the nature of the disease (benign or malignant), but the patient with recurrent pancreatic carcinoma had low scores on 15D.

Nine of the 25 patients (36 %) had experienced severe early postoperative complications. Of these, seven had had postoperative pancreatic fistula, of which one had needed reoperation. Two more patients needed reoperation due to postoperative haemorrhage. When the results of these patients were compared to those with uneventful recovery, there were, however, no differences in HRQoL between these subgroups (data not shown).

In the second interview (110 months postoperatively), there was no longer any difference in the HRQoL of the 15 study patients compared to that of the population sample (Table 8). Also, experience of an early postoperative complication did not correlate with HRQoL at the second evaluation (data not shown). When HRQoL was compared between the two evaluations (median 24 and 110 months) in the 15 surviving patients, there were no significant differences in any parameters of HRQoL (Table 9).

Table 7. Comparison of HRQoL between patients after pancreaticoduodenal resection and general population sample (median 24 mo postoperatively, National Health Survey 1995/96) (Parviainen et al. 2008)

	HRQoL according to 15D				
	study group n=25		population sample n=2768		
15D dimensions	x ±	SEM	x ±	SEM	p*
D15 score	**0.8284**	**0.1286**	**0.8784**	**0.1166**	**0.03**
Mobility	0.8774	0.1776	0.8869	0.1850	0.80
Vision	0.9278	0.1306	0.9138	0.1179	0.70
Hearing	0.8668	0.1709	0.9234	0.1491	0.06
Breathing	0.8019	0.2244	0.8637	0.2201	0.16
Sleeping	**0.7042**	**0.2186**	**0.8501**	**0.1932**	**< 0.01**
Eating	0.9717	0.0980	0.9891	0.6731	0.20
Speech	0.9763	0.0822	0.9731	0.0942	0.89
Elimination (ability to defecate and urinate)	**0.7299**	**0.2523**	**0.8772**	**0.1946**	**< 0.01**
Usual activities	0.7699	0.2384	0.8367	0.2266	0.14
Mental function	0.8466	0.1986	0.8726	0.1851	0.49
Discomfort and symptoms	0.7418	0.1860	0.7622	0.2301	0.66
Depression	0.8384	0.1659	0.8893	0.1654	0.11
Distress	0.8385	0.1875	0.8828	0.1635	0.18
Vitality	0.7742	0.2013	0.8294	0.1770	0.12
Sexual activity	**0.6999**	**0.3041**	**0.8160**	**0.2785**	**0.04**

*Independent samples t-test

Table 8. Comparison of HRQoL between the 15 survived patients after pancreaticoduodenal resection and general population sample (median 110 mo postoperatively, National Health 2000 Health Examination Survey) (Parviainen et al. 2008)

	HRQoL according to 15D				
	study group n=15		population sample n=4602		
15D dimensions	x ±	SEM	x ±	SEM	p*
D15 score	0.86854	0.11797	0.8747	0.11360	0.83
Mobility	0.8883	0.17328	0.8893	0.18545	0.98
Vision	0.9424	0.09887	0.9177	0.17138	0.58
Hearing	0.8990	0.21037	0.9239	0.15402	0.53
Breathing	0.8754	0.23508	0.8604	0.21532	0.79
Sleeping	0.7670	0.25608	0.8295	0.19085	0.21
Speech	0.9802	0.07661	0.9688	0.10602	0.68
Elimination	0.7968	0.27256	0.8584	0.20745	0.25
Usual activities	0.9051	0.17781	0.8517	0.22150	0.35
Mental function	0.9049	0.16323	0.8475	0.20376	0.28
Discomfort and symptoms	0.7278	0.24857	0.7546	0.20717	0.62
Depression	0.8424	0.14739	0.8968	0.15109	0.16
Distress	0.8370	0.16947	0.8970	0.15456	0.13
Vitality	0.8134	0.16171	0.8335	0.17091	0.65
Sexual activity	0.7596	0.30780	0.8152	0.26899	0.42

* Independent samples t-test

Table 9. Comparison of HRQoL in the early (24 mo) and late (110 mo) stage evaluation of the 15 survived patients after pancreaticoduodenal resection (Parviainen et al. 2008)

	HRQoL according to 15D				
	24 mo		110 mo		
15D dimensions	x ±	SEM	x ±	SEM	p*
D15 score	0.8716	0.13847	0.8685	0.11797	0.86
Mobility	0.9234	0.13142	0.8883	0.17328	0.36
Vision	0.9568	0.08943	0.9424	0.09887	0.58
Hearing	0.9140	0.16201	0.8990	0.21037	0.61
Breathing	0.8551	0.22172	0.8754	0.23508	0.73
Sleeping	0.7306	0.23306	0.7670	0.25608	0.65
Speech	1.0000	0.00000	0.9802	0.07661	0.33
Elimination	0.7950	0.24830	0.7968	0.27256	0.97
Usual activities	0.8455	0.24350	0.9051	0.17781	0.18
Mental function	0.8811	0.17400	0.9049	0.16323	0.58
Discomfort and symptoms	0.7885	0.21784	0.7278	0.24857	0.27
Depression	0.8570	0.17729	0.8424	0.14739	0.70
Distress	0.8611	0.23178	0.8370	0.16947	0.65
Vitality	0.8274	0.22812	0.8134	0.16171	0.80
Sexual activity	0.8110	0.22906	0.7596	0.30780	0.31

*Paired t-test

5 Study V – A new biodegradable stent for the pancreaticojejunal anastomosis

Degradation of the stents was studied by measuring both compression modulus and buckling force in physiologic temperature. Statistical differences in the results are shown in Tables 10 and 11. Alkaline milieu and the presence of pancreatic enzymes accelerated degradation of the stents. In alkaline milieu and in the presence of pancreatic enzymes there was no significant difference in the degradation time of the stents containing barium sulphate. Complete degradation of the stents occurred between 24 and 52 weeks.

Table 10. Statistical difference (p values) of the effect of pH (study groups 1 and 2), barium sulphate (study groups 2 and 3) and enzymes (study groups 2 and 4) when compression modulus of the stents is considered at different time points (Parviainen et al. 2000)

Weeks	pH	barium sulphate	enzymes
0	ns	ns	ns
2	ns	ns	ns
4	ns	ns	ns
8	ns	ns	ns
12	< 0.05	ns	< 0.01
16	< 0.001	ns	< 0.001
20	< 0.01	ns	< 0.01
24	< 0.001	ns	< 0.001
28	< 0.001	ns	< 0.001
32	< 0.001	ns	< 0.001
40	< 0.001	ns	< 0.001
52	< 0.001	ns	< 0.001

Table 11. Statistical difference (p values) of the effect of pH (study groups 1 and 2), barium sulphate (study groups 2 and 3) and enzymes (study groups 2 and 4) when the buckling force of the stents is considered at different time points (Parviainen et al. 2000)

weeks	pH	barium sulphate	Enzymes
0	ns	< 0.01	ns
2	ns	ns	ns
4	ns	ns	< 0.05
8	ns	ns	< 0.05
12	< 0.01	ns	< 0.001
16	< 0.001	ns	< 0.001
20	< 0.001	ns	< 0.001
24	< 0.001	ns	< 0.001
28	< 0.001	ns	< 0.001
32	< 0.001	ns	< 0.001
40	< 0.001	ns	< 0.001
52	< 0.001	ns	< 0.001

Neither of the pilot patients experienced any early postoperative complications. Early postoperative plain x-ray photos showed the stents to be correctly placed. The stent had completely disappeared in the male and partially in the female in the radiographs taken 8 weeks postoperatively. The male was symptomless, but the female complained of slight diarrhoea. Both patients had faecal elastase value < 15 μg/g indicating pancreatic insufficiency, and both took enzyme substitution.

DISCUSSION

1 Finnish experience of pancreaticoduodenectomies with special reference to early complications (Studies I and II)

PD is associated with considerable technical difficulties, excessive postoperative morbidity and mortality and dismal long-term survival when the procedure is performed for ductal adenocarcinoma of the pancreas. Whether radical PD should be abandoned, possibly in favour of total pancreatectomy (van Heerden et al. 1981) was under discussion at the beginning of the 1980s. More recently, large series of PDs without mortality have been reported (Schmidt et al. 2004). Many authors support the idea of centralizing or regionalizing major operations, including PDs, to certain specialized hospitals. Results of studies performed in such centres show that centralization reduces early mortality and morbidity following pancreatic resections. The role of the surgeon especially has been emphasized in the prevention of pancreatic leakage (Edge et al. 1993, Shrikhande et al. 2005), but so also has the use of experienced teams caring for the patients postoperatively (Schäfer et al. 2002, Riall et al. 2008). The benefit of centralization may be gained by institutional processes that drive the low mortality in high volume hospitals, not simply the case volume (Orr 2010).

Pancreaticojejunal anastomosis is said to be the Achilles' heel of PD and a major cause of morbidity and mortality. The incidence of pancreaticojejunal leakage varies according to published series, but it leads to abscess formation, peritonitis, sepsis and haemorrhage, with a high mortality rate (de Castro et al. 2005). Certain predisposing factors are known that may result in anastomotic leakage. A narrow pancreatic duct ($\leq$ 2 mm) makes anastomosis more difficult to perform (van Berge Henegouwen et al. 1997, de Castro et al. 2005). There is also a strong association between pancreatic texture and anastomotic leakage, so that anastomosis is usually easier to perform in patients with chronic pancreatitis than in those with neoplasms but normal residual pancreas (Yeo et al. 2000, de Castro et al. 2005, Yang et al. 2005). Prolonged duration of surgery (over 285 minutes) also carries a significant risk of anastomotic leakage (de Castro et al. 2005). Other risk factors include age, gender, possible malnutrition and intraoperative blood loss (Yang et al. 2005). Age alone should not be a contraindication to pancreatic resection in elderly patients with pancreatic cancer (Riall 2009).

A retrospective study was performed on patients who had undergone PD or PPPD during a 3-year period (1991–1994) (Study I). The case records of all 46 patients operated on during this period were available. The classification of pancreatic fistulas into groups "none", "subclinical" or "clinical" was according to Büchler et al. (1992). In this study, biliary leakage was found more frequently in patients with simultaneous pancreatic leakage. A limitation in the definition of the co-incidence of the leakages is that one cannot be sure of the biliary leakage only by following the right drain. Simultaneous biliary stain of the secretion in both drains is suspicious, and the possible occurrence of biliary leakage can usually be examined by percutaneous cholangiography if the drain had been left in place. In the present study the biliary stain and amylase activity assessments were performed separately for both drains to distinguish between biliary and pancreatic leakage. In addition, in severe cases when patients were reoperated, the preoperative diagnosis was confirmed during surgery. According to the findings of this study, pancreatic and biliary leakages were as common as in former studies, although the definition of pancreatic leakage has changed. This study was quite small, but co-incidence of biliary and pancreatic leakages has subsequently been confirmed in a larger retrospective study (Aranha et al. 2003). This supports the idea of a possibly common mechanism, which may be postoperative pancreatitis, as has recently been proposed (Lämsä et al. 2006, Räty et al. 2006).

The effect of hospital and surgeon volume on postoperative morbidity and mortality was studied in all Finnish hospitals performing resections of the pancreatic head in the 5-year period 1990–1994 (Study II). Each of these 33 hospitals was visited by the author, and the data of interest was collected from the case records of all 350 patients into special formulas for later analysis. In this way, much more information could be obtained than by using databases only. The retrospective nature of the study made it difficult to classify some complications and there was some missing data. However, regarding the major findings the data could be reliably recognised. Most of the fatal complications were related to the procedure: anastomotic leakage (39 %), abscess / peritonitis / MOF (20 %), liver or intestinal necrosis (14 %), intra-abdominal haemorrhage (11 %); likewise the non-fatal complications: leakage (fistula) (32 %), DGE (23 %), abscess (14 %), wound infection (13 %), hyperglycaemia (6 %), intra-abdominal haemorrhage (4 %), pancreatitis (3 %), cholangitis (0.6 %). In Finland, hospital and surgeon volumes in pancreatic operations are generally low, but mortality especially decreased as volume increased, as it did elsewhere. In high-volume hospitals internationally acceptable and comparable results could be achieved. Studies favouring centralization of pancreatic resections have been published in many countries, one European example being the Netherlands (Gouma et al. 2000, van Heek et al. 2005, van Oost et al. 2006). In

Finland, the Ministry of Social Affairs and Health has recommended pancreatic resections for curative purposes to be further regionalized within a population of more than 500 000 inhabitants, which means a considerable reduction in the hospitals providing pancreatic resections. Similar recommendations concern resections of the oesophagus and cardia, likewise bariatric surgery. In the present study (1990-1994), 33 hospitals for 5 million inhabitants means that the mean current population for a centre was 150 000 inhabitants at that time. Since then, there has been a significant centralization of pancreatic head resections.

Centralizing PDs and PPPDs to high volume hospitals increases the probability of a technically successful resection. According to the results of our national study, centralization to high-volume hospitals did not improve 5-year survival, although it did significantly improve immediate postoperative survival. This may be explained by the differences in the biological nature of the periampullary malignancies. It was not known how many patients had angioinvasion or perineural growth, which has been shown to be an important prognostic factor in periampullary tumours (van Roest et al. 2008). The lymph node ratio, however, is the strongest prognostic factor after resection of pancreatic cancer (Riediger et al. 2009). The patients in the national study were operated on during a period before the European Study for Pancreatic Cancer (ESPAC-1) (Neoptolemos et al. 1997, Link et al. 1998, Ghaneh and Neoptolemos 2004) had taken place, thus postoperative chemotherapy was not yet routine. On the basis of the results of the ESPAC-3 trials, adjuvant chemotherapy with 5-fluorouracil or gemcitabine is recommended after radical resection of periampullary tumours (Neoptolemos et al. 2003, Neoptolemos et al. 2009, Saif 2009). Reoperations and other surgery-related major complications impair the efficacy of R0 pancreatectomy (Kang et al. 2009). Centralization of pancreatic head resections lowers the risk of serious early complications and reoperations, thus increasing the opportunity for adjuvant therapies. In future, this kind of centralization with lower complication rates and improved adjuvant therapy will probably also show improved long-term survival.

One independent factor that was found to reduce the risk of postoperative complications was endoscopic preoperative biliary stenting. Use of preoperative biliary stenting is still controversial. Despite the widespread use of biliary stenting in patients with potentially resectable pancreatic cancer, their use has recently been criticized (Aly and Johnson 2001, Hodul et al. 2003, Smith et al. 2008, Herzog et al. 2009), as biliary stenting may be associated with bile colonization and also with wound infection, and even with postoperative intra-abdominal abscess formation (Hodul et al. 2003). The controversial results published so far regarding preoperative stenting may be explained

by the fact that preoperative infection needs appropriate treatment, and as a result decisive treatment of the cancer cannot be provided in time.

Recently it has also been noted in a large American retrospective study that complication rates have not decreased during the last decade, although mortality rates have. The authors pointed out that general postoperative complications involving the cardiovascular and pulmonary systems are very important. They also noticed that patients experiencing one complication have been shown to be at increased risk for subsequent complications (Simons et al. 2009). The importance of cardiovascular diseases in relation to postoperative complications in PDs has been pointed out in the studies by Aranha et al. (2003), Räty et al. (2006) and Balcom et al. (2009). This may partly explain the steadily high morbidity rates, while the patients operated on are older and may have more co-morbidities than a decade ago (Balcom et al. 2009, Hardacre et al. 2009). The effect of cardiovascular diseases on pancreaticojejunal leakage, however, was not specifically investigated in these studies.

2 Pancreaticojejunostomy and long-term consequences of pancreaticoduodenectomies (Studies III–IV)

In addition to early postoperative complications, the majority of patients surviving PD suffer from symptoms of pancreatic insufficiency (weight loss, diarrhoea), and this has been thought to affect their quality of life (Armstrong et al. 2002, Jang et al. 2002). Long-term follow-up of patients having undergone pancreaticoduodenal resection can usually only be performed on patients who have been operated on for a benign disease. Many of these have chronic pancreatitis, the symptoms of which are similar to those of anastomotic stricture (Reid-Lombardo et al. 2007b). The symptoms in those patients who have pancreaticogastric anastomosis are especially significant (Aubé et al. 2003, Kahl and Malfertheiner 2004). Pancreaticojejunostomy is more difficult to examine and treat than pancreaticogastrostomy, as it can seldom be reached with endoscopy, and stricture may need operative treatment, e.g. redo the anastomosis (Reid-Lombardo et al. 2007b). One possible way to examine the patency of pancreaticojejunal anastomosis is secretin stimulated MRCP.

Stricture can be considered a long-term complication of pancreaticojejunostomy. It is not easily known when stricture occurs, since the symptoms are similar to those resulting from pancreatic exocrine insufficiency. In the present study a formerly presented classification of D-MRCP findings was used (Study III), which, however, was originally developed on the basis of the function of a

normal gland. The study group was quite small, and included both patients with chronic pancreatitis and periampullary malignancies. According to the present results the classification used seems to be reliable to divide the results of D-MRCP findings into different categories. Postoperative exocrine pancreatic insufficiency was diagnosed in all of our patients re-examined after pancreaticoduodenal resection, 92 % of them having severe insufficiency. PD has been reported to cause postoperative exocrine insufficiency in 20 - 72 % and drainage procedures in up to 35 % of patients (Metzger and DiMagno, 1998). According to the classification used, out of the successful 23 D-MRCP examinations, seven patients (30 %) showed severe glandular malfunction (Grade 1) not allowing the evaluation of the anastomosis because too little fluid accumulated in the duct. Anastomoses could thus be evaluated in 16 patients. Five (22 %) showed total obstruction of the anastomosis (Grade 2), six (26 %) showed partial obstruction of the anastomosis (Grade 3) and five anastomoses (22 %) were considered to be fully open (Grade 4). Pessaux et al. (2002) obtained better results in a prospective study with 19 patients, but the anastomosis was pancreaticogastric.

The patients who had fully open anastomosis in D-MRCP had the highest faecal elastase-1 values. As the anastomosis was considered fully open in only 22 % of the patients, this result indicates that the surgical technique should be further developed to keep the anastomoses open. The current findings showed that narrow ducts seem more often to lead to anastomotic obstruction. The anastomosis which is done by invaginating the pancreas into the jejunum may not be the best in long-term results, as so many patients had poorly open anastomoses in MRCP. Prospective studies from this point of view, too, are needed to develop the surgical technique. However, given the results of both D-MRCP and faecal elastase-1 values enzyme substitution is recommended for all PD patients as also suggested by others (Armstrong et al. 2002). It is also noteworthy that patients may have diarrhoea and need enzyme substitution even though the anastomosis is open, due to the impaired function of the pancreatic gland.

As postoperative mortality following PD has fallen in experienced centres and anastomotic complications have also become rarer in such centres, HRQoL has become an increasingly important issue. The present study to examine HRQoL following PPPD or PD was performed at two different time points (Study IV). The generic instrument used enabled easy comparison of our study group with general population. In the late-stage evaluation there were 15 patients who responded, five of them having been operated on due to a malignant disease. The main finding regarding long-term quality of life was that there is no difference in general quality of life compared to healthy people. The result concurred with those of other studies (Huang et al. 2000, Witzigmann

et al. 2003). The present follow-up time was exceptionally long (110 months). In the current study the presence of early postoperative complications did not affect long-term HRQoL. The study population was, however, small, and it was not known what quality of life was like in these patients before the operation. Certain parameters (hearing, sexual activity) of the generic instrument we used (15D) showed a slight deterioration in the course of time, although not statistically significant, and these may be a result of aging. Another study using 15D showed that after gastrectomy long-term HRQoL was also generally similar to that of normal population (Tyrväinen et al. 2008). In obesity surgery, HRQoL is significantly improved, but there is a decline over time (Tolonen et al. 2004). In pancreatic surgery, a combination of a generic and an organ-specific HRQoL instrument might be more suitable for prospective studies.

3 How to develop pancreaticojejunal anastomosis (Study V)

There are numerous studies focusing on pancreaticojejunal anastomosis, evincing solutions as to how early postoperative complications especially can be reduced by new methods of performing anastomosis. According to an overview of RCTs, systemic meta-analyses and clinical trials, the surgeons' experience with one or the other technique appears to be more important than the technique itself (Kleespies et al. 2008). This conclusion also favours centralization of pancreatic resections on a few surgeons. Lai et al. (2009) in their review studied different ways of preventing pancreatic fistula following PD using a Medline database from 1990 to 2008. They considered pancreatic texture, pancreatic duct size, blood supply of the stump and volume of pancreatic juice output to be the most significant. Others are patient associated risk factors (age, sex, bilirubin level, co-morbid illness) and operative risk factors (duration of surgery, blood loss, type of anastomosis and stent use). They concluded that there is no conclusive evidence for or against a particular type of pancreaticoenteric anastomosis. They also found that pancreaticogastrostomy is equivalent to pancreaticojejunostomy in perioperative morbidity and mortality and that pancreaticoenterostomy cannot be replaced with pancreatic ductal obliteration (Lai et al. 2009).

The possibility of postoperative pancreatitis as a risk factor for anastomotic leakage has been briefly discussed. It had been considered impossible to show which comes first, pancreatitis or anastomotic leakage (Bassi et al. 2001). Associations between postoperative pancreatitis and anastomotic leakage have been reported on the basis of a prospective study (Räty et al. 2006). According to these results, postoperative pancreatitis may be a pathogenetic factor for anastomotic leakage. Thus finding new methods, either medical or technical, to reduce the risk of postoperative pancreatitis

and to develop anastomosis to be more resistant to such a pancreatitis is perhaps the most important future challenge.

According to the idea of protecting the pancreticojejunostomy with a biodegradable stent, it was first planned to develop a two-part stent (Study V). It would have had a PLA-96 spiral to prevent possible strictures and a PGA cover to prevent possible leakages. The PGA cover proved to be too stiff, so it was abandoned, and development went on with the PLA-96 spiral stent. Stents can be developed to be biodegradable and x-ray positive to help monitor the position and possible degradation by means of plain x-ray photos. The experiment was performed with stents with outside diameters 3 ± 0.2 mm, the diameter of the wire being 0.4 ± 0.05 mm. The study showed that pancreatic enzymes and the pH of the environment both affect the degradation time of these stents, so the composition of the stents must be studied separately for different purposes. In this *in vitro* study, the effects of pH, pancreatic enzymes and presence of barium sulphate on buckling force and compression modulus were tested. The solutions were changed twice a week to keep pH within physiological limits. All changes were performed in the same way. The temperature was held constant at 37°C using incubators. Pilot studies showed that such a stent can indeed be inserted into the human pancreatic duct during pancreatic resection. Follow-up with plain x-ray photos showed that the stents had disappeared in these patients. It is not known, however, if the stents had disappeared by degradation or if they had fallen from the anastomosis into the bowel. It could be concluded, however, that such stents are not suitable in narrow ducts (≤ 2 mm).

The safety of such biodegradable stents has subsequently been studied further in rat pancreatic parenchyma and in swine pancreatic duct (Lämsä et al. 2006, Laukkarinen et al. 2008). The use of such stents in novel anastomosis has also been reported (Nordback et al. 2008), but long-term results in respect of the patency of the anastomosis and exocrine function are not available. Radiopaque biodegradable stents (PLA 96-$BaSO_4$) have been examined in an animal model and have been found to have as little toxicity as steel (Lämsä et al. 2006). They have also been applicable in pilot patients (Nordback et al. 2008). By using such stents clogging, which can be a drawback in plastic stents, and difficulties in changing the stent, which can be a drawback in metal stents, may be avoided (Laukkarinen et al. 2008). Occlusion of biodegradable PLA stents could not be detected in animal studies either in the hepatic duct (Laukkarinen et al. 2007) or in the pancreatic duct (Laukkarinen et al. 2008). Occlusion of biodegradable stents has not been reported in urological experiments, either (Schlick and Planz 1998). Such stents, however, showed increased

neointimal formation and reduced patency in an animal study considering their use in iliac arteries (Uurto et al. 2004).

According to the results of a recent systematic search, there is insufficient data to support or refute claims of improved outcomes after transpancreatic ductal stent insertion on patients with PJ or PG with small ducts (< 3 mm) or soft pancreata. More evidence of benefit is needed before the use of stents can be recommended (Shukla et al. 2010).

To conclude, although experimental studies have been promising concerning the use of biodegradable stents in protecting the pancreaticojejunal anastomosis, further clinical studies are warranted to determine their usefulness, feasibility and safety in clinical use.

SUMMARY AND CONCLUSIONS

In the present study postoperative early and late complications related to pancreaticojejunal anastomosis were studied. Attention was paid to postoperative health-related quality of life and to the possible ways of reducing these complications.

The major findings and conclusions were as follows:

1. Pancreatic anastomotic leakage is a common and serious complication after pancreatic head resection. Biliary leakage is rare, but when it occurs, it often coincides with pancreatic leakage.
2. Hospital volume and surgeon's volume are related to early postoperative mortality and morbidity after pancreatic head resections in Finland, too. The majority of both fatal and non-fatal complications were consequences of pancreaticojejunal anastomotic leakage. However, no direct connection could be found between hospital volume or surgeon's volume and five-year survival in periampullary cancer.
3. Pancreatic exocrine insufficiency after pancreatic head resection results partly from the inability of the pancreas to produce digestive enzymes and partly from the stenosis of the pancreatic anastomosis.
4. In the early stage after pancreatic head resection, health-related quality of life was significantly poorer than in general population, but there was no difference in the late stage. No correlation was found between postoperative complications and health related quality of life.
5. A prototype of a biodegradable stent for pancreaticojejunal anastomosis was developed and tested both *in vitro* and *in vivo*. pH and enzyme activity of the milieu affected degradability. The spiral stent developed is not, however, optimal, because of low inner/outer diameter ratio allowing it to be used only in fairly large ducts.

ACKNOWLEDGEMENTS

This thesis was carried out at the Department of Gastroenterology and Alimentary Tract Surgery in Tampere University Hospital, the Medical Faculty of the University of Tampere and also with the collaboration of Tampere University of Technology.

I wish to express my most profound gratitude to Professor Teuvo Tammela, M.D., Ph.D., who provided excellent facilities especially to complete my work.

My warmest thanks are due to my supervisor and the Director of the Division of Surgery, Gastroenterology and Oncology Docent Juhani Sand, M.D., Ph.D., whose profound knowledge in both clinical and scientific fields as well as his patience and encouraging guidance have been of utmost importance for the completion of this work.

I am deeply grateful to my co-supervisor and the Director of Development, Pirkanmaa Hospital District Docent Isto Nordback, M.D., Ph.D., who introduced me to the interesting field of pancreatic surgery and especially to the fascinating subject of pancreaticojejunostomy and planned the subjects for the original publications.

I gratefully acknowledge the developer of the 15D instrument, Professor Harri Sintonen, Ph.D., of the University of Helsinki, Department of Public Health, for collaboration in the study concerning health-related quality of life.

I am also deeply grateful to the expert in biomaterials, Professor Pertti Törmälä, Ph.D., of Tampere University of Technology, for arranging facilities to carry out the fifth study in the laboratory of the Institute of Biomaterials of the University of Technology.

I would like to express my deepest thanks to Professor Pekka Pikkarainen, M.D., Ph.D., for the valuable follow-up of this study and critical comments throughout the study.

I wish to thank Docent Juha Grönroos, M.D., Ph.D., and Professor Jyrki Mäkelä, M.D., Ph.D., for pre-examining my work and for all the constructive criticism which helped me to complete my manuscript.

My sincere thanks go to all co-workers, Docent Sari Räty, M.D., Ph.D., Dr. Anneli Piironen, M.D., Ph.D., Docent Aimo Harmoinen, Ph.D., Docent Heikki Kainulainen, Ph.D., Dr. Pentti Vehkalahti, M.D., Dr. Heikki Kolehmainen, M.D. and Dr. Tero Välimaa, Ph.D.

Special thanks are to Mrs. Taina Ahlgren and Mrs. Maarit Mäki for all their practical advice and help. I also thank Mrs. Eija Kulo, R.N., for help in inviting the patients to participate in my studies. I thank also the laboratory personnel for their help. I thank Mrs. Heini Huhtala, M.Sc. for her help in the statistics. Thanks also belong to the personnel of the library of the Medical School for help in collecting the references and to the personnel who helped to collect the medical histories of the patients. Mrs. Virginia Mattila, M.A., is thanked for revision of the English language.

I wish to express my thanks to all my colleagues in all the hospitals where I have ever worked. I owe a special debt of gratitude to Medical Major-General, Docent Timo Sahi, M.D., Ph.D., the former Head of the Medical Service of the Finnish Defence Forces, for encouraging me in my work.

I wish to express my sincere thanks to my loving wife Hannele, who also is a co-worker in my studies, for help and patience during all these years.

My warmest thanks go to my dear parents, my mother Amalia Condou-Parviainen and my late father Erkki Parviainen for all the love and support I have received from them in all my endeavours from the time before I went to school until now. I also thank my brother Johannes Parviainen for his encouraging attitude. My deep thanks belong also to my other relatives who have supported me in every possible way throughout all years.

Last but not least, my love and thanks go to my three children, Pauliina, Markus and Joonas, for the patience they have shown while I have been writing my study.

This study was financially supported by grants from the Medical Research Fund of Pirkanmaa Hospital District.

Espoo, October 2010

Mickael Parviainen

REFERENCES

Abete M, Ronchetti V, Casano A and Pescio G (2005): Pancreatic fistula after pancreaticoduodenectomy: Risk factors and treatment. Minerva Chir 60: 99-110.

Adam U, Makowiec F, Riediger H, Benz S, Liebe S und Hopt UT (2002): Pankreasleckage nach Pankreasresektion. Eine Analyse von 345 Operierten. Chirurg 73: 466-473.

Adams DB (2009): The pancreatic anastomosis: The danger of a leak, which anastomotic technique is better? J Gastrointest Surg 13: 1182-1183.

Alghamdi AA, Jawas AM and Hart RS (2007): Use of octreotide for the prevention of pancreatic fistula after elective pancreatic surgery: A systematic review and meta-analysis. Can J Surg 50: 459-465.

Aly EAH and Johnson CD (2001): Preoperative biliary drainage before resection in obstructive jaundice. Dig Surg 18: 84-89.

Andivot T, Cardoso B, Dousset O, Soubrane O, Bonnichon P et Chapuis Y (1996): Complications de deux types d'anastomoses pancréatiques après duodéno-pancréatectomie céphalique. Ann Chir 50: 431-437.

Aranha GV, Hodul P, Golts E, Oh D, Pickleman J and Creech S (2003): A comparison of pancreaticogastrostomy and pancreaticojejunostomy following pancreaticoduodenectomy. J Gastrointest Surg 7: 672-682.

Armstrong T, Walters E, Varshney S and Johnson CD (2002): Deficiencies of micronutrients, altered bowel function, and quality of life during late follow-up after pancreaticoduodenectomy for malignancy. Pancreatology 2: 528-534.

Arnaud JP, Casa C, Serra-Maudet V, Georgeac C and Ronceray J (1993): Pancreato-gastric anastomosis after cephalic duodenopancreatectomy. Apropos of 36 cases. Chirurgie 119: 317-319.

Aubé C, Lebigot J, Pessaux P, Tuech JJ, Kapel N, Burtin P, Arnaud JP and Caron C (2003): Evaluation of the permeability of pancreaticogastric anastomoses (PGA) with dynamic magnetic

resonance pancreatography after secretin stimulation (secretin MRCP). Abdom Imaging 28: 563-570.

Bachellier P, Nakano H, Oussoultzoglou PD, Weber JC, Boudjema K, Wolf PD and Jaeck D (2001): Is pancreaticoduodenectomy with mesentericoportal venous resection safe and worthwhile? Am J Surg 182: 120-129.

Balcom JH 4th, Rattner DW, Warshaw AL, Chang Y and Fernandez-del Castillo C (2001): Ten-year experience with 733 pancreatic resections: Changing indications, older patients, and decreasing length of hospitalization. Arch Surg 136: 391-398.

Barnes SA, Lillemoe KD, Kaufman HS, Sauter PK, Yeo CJ, Talamini MA, Pitt HA and Cameron JL (1996): Pancreaticoduodenectomy for benign disease. Am J Surg 171: 131-134.

Bassi C, Butturini G, Molinari E, Mascetta G, Salvia R, Falconi M, Gumbs A and Pederzoli P (2004): Pancreatic fistula rate after pancreatic resection. Dig Surg 21: 54-59.

Bassi C, Dervenis C, Butturini G, Fingerhut A, Yeo C, Izbicki J, Neoptolemos J, Sarr M, Traverso W, Büchler M and International Study Group on Pancreatic Fistula, Definition (2005): Postoperative pancreatic fistula: An international study group (ISGPF) definition. Surgery 138: 8-13.

Bassi C, Falconi M, Salvia R, Mascetta G, Molinari E and Pederzoli P (2001): Management of complications after pancreaticoduodenectomy in a high volume centre: Results in 150 consecutive patients. Dig Surg 18: 453-458.

Bassi C, Molinari E, Malleo G, Crippa S, Butturini G, Salvia R, Talamini G and Pederzoli P (2010): Early versus late drain removal after standard pancreatic resections: results of a prospective randomized trial. Ann Surg 252: 207-14.

Beger HG, Rau B, Gansauge F, Poch B and Link KH (2003): Treatment of pancreatic cancer: Challenge of the facts. World J Surg 27: 1075-1084.

Beger HG, Schlosser W, Friess HM and Büchler MW (1999): Duodenum-preserving head resection in chronic pancreatitis changes the natural course of the disease: A single-center 26-year experience. Ann Surg 230: 512-519.

Begg CB, Cramer LD, Hoskins WJ and Brennan MF (1998): Impact of hospital volume on operative mortality for major cancer surgery. See comment. JAMA 280: 1747-1751.

Berger AC, Howard TJ, Kennedy EP, Sauter PK, Bower-Cherry M, Dutkevitch S, Hyslop T, Schmidt CM, Rosato EL, Lavu H, Nakeeb A, Pitt HA, Lillemoe KD and Yeo CJ (2009): Does type of pancreaticojejunostomy after pancreaticoduodenectomy decrease rate of pancreatic fistula? A randomized, prospective, dual-institution trial. J Am Coll Surg 208: 738-749.

Berney T, Rüdisühli T, Oberholzer J, Caulfield A and Morel P (2000): Long-term metabolic results after pancreatic resection for severe chronic pancreatitis. Arch Surg 135: 1106-1111.

Birkmeyer JD (2002): Raising the bar for pancreaticoduodenectomy. Comment. Ann Surg Oncol 9: 826-827.

Birkmeyer JD, Siewers AE, Finlayson EVA, Stukel TA, Lucas FL, Batista I, Welch HG and Wennberg DE (2002): Hospital volume and surgical mortality in the United States. N Engl J Med 346: 1128-1137.

Birkmeyer JD, Stukel TA, Siewers AE, Goodney PP, Wennberg DE and Lucas FL (2003): Surgeon volume and operative mortality in the United States. N Eng J Med 349: 2117-2127.

Bloechle C, Izbicki JR, Knoefel WT, Kuechler T and Broelsch CE (1995): Quality of life in chronic pancreatitis - results after duodenum-preserving resection of the head of the pancreas. Pancreas 11: 77-85.

Brambs H-J and Claussen CD (1993): Pancreatic and ampullary carcinoma. Ultrasound, computed tomography, magnetic resonance imaging and angiography. Endoscopy 25: 58-68.

Brozzetti S, Mazzoni G, Miccini M, Puma F, De Angelis M, Cassini D, Bettelli E, Tocchi A and Cavallaro A (2006): Surgical treatment of pancreatic head carcinoma in elderly patients. Arch Surg 141: 137-142.

Büchler M, Friess H, Klempa I, Hermanek P, Sulkowski U, Becker H, Schafmayer A, Baca I, Lorenz D and Meister R (1992): Role of octreotide in the prevention of postoperative complications following pancreatic resection. Am J Surg 163: 125-130.

Büchler MW, Friess H, Wagner M, Kulli C, Wagener V and Z'graggen K (2000): Pancreatic fistula after pancreatic head resection. Br J Surg 87: 883-889.

Cameron JL (1990): Pancreaticoduodenectomy (Pylorus-preserving Whipple procedure). In: Atlas of Surgery, pp. 386-413. Ed. JL Cameron, B.C. Decker Inc. Toronto, Canada.

Cameron JL, Pitt HA, Yeo CJ, Lillemoe KD, Kaufman HS and Coleman J (1993): One hundred and forty-five consecutive pancreaticoduodenectomies without mortality. Ann Surg 217: 430-435, discussion 435-438.

Cameron JL, Riall TS, Coleman J and Belcher KA (2006): One thousand consecutive pancreaticoduodenectomies. See comment. Ann Surg 244:10-15.

Ceyhan GO, Michalski CW, Demir IE, Müller MW and Friess H (2008): Pancreatic pain. Best Pract Res Clin Gastroenterol 22: 31-44.

Ceyhan GO, Bergmann F, Kadihasanoglu M, Altintas B, Demir IE, Hinz U, Müller MW, Giese T, Büchler MW, Giese NA and Friess H (2009): Pancreatic neuropathy and neuropathic pain – a comprehensive pathomorphological study of 546 cases. Gastroenterology 136: 177-186.

Chappel AR, Zuckerman RS and Finlayson SR (2006): Small rural hospitals and high-risk operations: How would regionalization affect surgical volume and hospital revenue? J Am Coll Surg 203: 599-604.

Chew DK and Attiyeh FF (1997): Experience with the Whipple procedure (pancreaticoduodenectomy) in a university-affiliated community hospital. Am J Surg 174: 312-315.

Clark LR, Jaffe MH, Choyke PL, Grant EG and Zeman RK (1985): Pancreatic imaging. Radiol Clin North Am 23: 489-501.

Collier DStJG and Pollard SG (1992): Whipple's Operation or Pancreaticoduodenectomy. In: Operative Surgery, pp. 4.38-4.40. Eds. R Calne and SG Pollard. Gover Medical Publishing, London, UK.

Conlon KC, Labow D, Leung D, Smith A, Jarnagin W, Coit DG, Merchant N and Brennan MF (2001): Prospective randomized clinical trial of the value of intraperitoneal drainage after pancreatic resection. Ann Surg 234: 487-494.

Cooperman AM (1990): Pancreatic and Periampullary Carcinoma. In: Maingot's Abdominal Operations, 9th ed, vol. II, pp.1633-1669. Eds. SI Schwartz and H Ellis. Appleton & Lange, Connecticut

Cullen JJ, Sarr MG and Ilstrup DM (1994): Pancreatic anastomotic leak after pancreaticoduodenectomy: incidence, significance and management. Am J Surg 168: 295-298.

De Castro SMM, Busch ORC, van Gulik TM and Gouma DJ (2005): Incidence and management of pancreatic leakage after pancreatoduodenectomy. Br J Surg 92: 1117-1123.

DeOliveira ML, Winter JM, Schafer M, Cunningham SC, Cameron JL, Yeo CJ and Clavien PA (2006): Assessment of complications after pancreatic surgery: A novel grading system applied to 633 patients undergoing pancreaticoduodenectomy. Ann Surg 244: 931-937.

Di Carlo V, Zerbi A and Balzano G (1998): Surgical treatment: Whipple-Kausch pancreatoduodenectomy with or without pylorus preservation. In: The Pancreas, pp. 1028-1040. Eds. HG Beger, AL Warshaw, MW Büchler, DL Carr-Locke, JP Neoptolemos, C Russell and MG Sarr, Blackwell Science Ltd. Cambridge, Great Britain.

Diener MK, Knaebel HP, Heukaufer C, Antes G, Büchler MW and Seiler CM (2007): A systematic review and meta-analysis of pylorus-preserving versus classical pancreaticoduodenectomy for surgical treatment of periampullary and pancreatic carcinoma. Ann Surg 245: 187-200.

Diener MK, Rahbari NN, Fischer L, Antes G, Büchler MW and Seiler CM (2008): Duodenum-preserving pancreatic head resection versus pancreatoduodenectomy for surgical treatment of chronic pancreatitis. Ann Surg 247: 950-961.

Diller R, Senninger N, Kautz G and Tübergen D (2003): Stent migration necessitating surgical intervention. Surg Endosc 17: 1803-1807.

Domagk D, Wessling J, Reimer P, Hertel L, Poremba C, Senninger N, Heinecke A, Domschke W and Menzel J (2004): Endoscopic retrograde cholangiopancreatography, intraductal ultrasonography, and magnetic resonance cholangiopancreatography in bile duct strictures: A prospective comparison of imaging diagnostics with histopathological correlation. See comment. Am J Gastroenterol 99: 1684-1689.

Domínguez-Muñoz JE, Manes G and Malfertheiner P (1998): Laboratory diagnosis of inflammatory pancreatic disease. In: The Pancreas, pp. 169-179. Eds. HG Beger, AL Warshaw, MW Büchler, DL Carr-Locke, JP Neoptolemos, C Russell and MG Sarr, Blackwell Science Ltd. Cambridge, Great Britain.

Dominici R and Franzini C (2002): Fecal elastase-1 as a test for pancreatic function: A review. See comment. Clin Chem Lab Med 40: 325-332.

Duffas JP, Suc B, Msika S, Fourtanier G, Muscari F, Hay JM, Fingerhut A, Millat B, Radovanowic A, Fagniez PL and The French Associations for Research in Surgery (2005): A controlled randomized multicenter trial of pancreatogastrostomy or pancreatojejunostomy after pancreatoduodenectomy. Am J Surg 189: 720-729.

Edge SB, Schmieg RE Jr., Rosenlof LK and Wilhelm MC (1993): Pancreas cancer resection outcome in American university centers in 1989-1990. Cancer 71: 3502-3508.

Fallick JS, Farley DR, Farnell MB, Ilstrup DM and Rowland CM (1999): Venting intraluminal drains in pancreaticoduodenectomy. J Gastrointest Surg 3: 156-161.

Farrell J, Carr-Locke D, Garrido T, Ruymann F, Shields S and Saltzman J (2006): Endoscopic retrograde cholangiopancreatography after pancreaticoduodenectomy for benign and malignant disease: Indications and technical outcomes. Endoscopy 38: 1246-1249.

Fielding LP (1988): Surgeon-related variability in the outcome of cancer surgery. J Clin Gastroenterol 10: 130-132.

Fitzsimmons D and Johnson CD (1998): Quality of life after treatment of pancreatic cancer. Langenbecks Arch Surg 383: 145-151.

Fitzsimmons D, Johnson CD, George S, Payne S, Sandberg AA, Bassi C, Beger HG, Birk D, Büchler MW, Dervenis C, Fernandez Cruz L, Friess H, Grahm AL, Jeekel J, Laugier R, Meyer D, Singer MW and Tihanyi T (1999): Development of a disease specific quality of life (QoL) questionnaire module to supplement the EORTC core cancer QoL questionnaire, the QLQ-C30 in patients with pancreatic cancer. EORTC study group on quality of life. Eur J Cancer 35: 939-941.

Fleischmann D, Ringl H, Schöfl R, Pötzi R, Kntrus M, Henk C, Bankier AA, Kettenbach J and Mostbeck GH (1996): Three-dimensional spiral CT cholangiography in patients with suspected

obstructive biliary disease: comparison with endoscopic retrograde cholangiography. Radiology 198: 861-868.

Frey CF and Mayer KL (2003): Comparison of local resection of the head of the pancreas combined with longitudinal pancreaticojejunostomy (Frey procedure) and duodenum-preserving resection of the pancreatic head (Beger procedure). World J Surg 27: 1217-1230.

Friedrich J, Tomczak R and Brambs H (1998): Magnetic resonance imaging of the pancreas. In: The Pancreas, pp. 247-259. Eds. HG Beger, AL Warshaw, MW Büchler, DL Carr-Locke, JP Neoptolemos, C Russell and MG Sarr, Blackwell Science Ltd. Cambridge, UK.

Fuks D, Piessen G, Huet E, Tavernier M, Zerbib P, Michot F, Scotte M, Triboulet JP, Mariette C, Chiche L, Salame E, Segol P, Pruvot FR, Mauvais F, Roman H, Verhaeghe P and Regimbeau JM (2009): Life-threatening postoperative pancreatic fistula (grade C) after pancreatcoduodenectomy: incidence, prognosis, and risk factors. Am J Surg 197: 702-709.

Ghaneh P and Neoptolemos JP (1999): Exocrine pancreatic function following pancreatectomy. Ann N Y Acad Sci 880: 308-318.

Ghaneh P and Neoptolemos JP (2004): Conclusions from the European Study Group for Pancreatic Cancer adjuvant trial of chemoradiotherapy and chemotherapy for pancreatic cancer. Surg Oncol Clin N Am 13: 567-587.

Goh BKP, Tan YM, Chung YFA, Cheow PC, Ong HS, Chan WH, Chow PKH, Soo KC, Wong WK and Ooi LLPJ (2008): Critical appraisal of 232 consecutive distal pancreatectomies with emphasis on risk factors, outcome, and management of the postoperative pancreatic fistula. A 21-year experience at a single institution. Arch Surg 143: 956-965.

Gordon TA, Burleyson GP, Tielsch JM and Cameron JL (1995): The effects of regionalization on cost and outcome for one general high-risk surgical procedure. See comment. Ann Surg 221: 43-49.

Gouma DJ, van Geenen RC, van Gulik TM, de Haan RJ, de Wit LT, Busch OR and Obertop H (2000): Rates of complications and death after pancreaticoduodenectomy: Risk factors and the impact of hospital volume. Ann Surg 232: 786-795.

Hardacre JM, Simo K, McGee MF, Stellato TA and Schulak JA (2009): Pancreatic resection in octogenarians. J Surg Res 156: 129-132.

Heidt DG, Burant C and Simeone DM (2007): Total pancreatectomy: Indications, operative technique, and postoperative sequelae. J Gastrointest Surg 11: 209-216.

Herzog T, Belyaev O, Muller CA, Mittelkotter U, Seelig MH, Weyhe D, Felderbauer P, Schlottmann R, Schrader H, Schmidt WE and Uhl W (2009): Bacteribilia after preoperative bile duct stenting. J Clin Gastroenterol 43: 457-462.

Heslin MJ, Brooks AD, Hochwald SN, Harrison LE, Blumgart LH and Brennan MF (1998): A preoperative biliary stent is associated with increased complications after pancreatoduodenectomy. Arch Surg 133: 149-154.

Ho V, Heslin MJ, Yun H and Howard L (2006): Trends in hospital and surgeon volume and operative mortality for cancer surgery. Ann Surg Oncol 13: 851-858.

Hodul P, Creech S, Pickleman J and Aranha GV (2003): The effect of preoperative biliary stenting on postoperative complications after pancreaticoduodenectomy. Am J Surg 186: 420-425.

Hosotani R, Doi R and Imamura M (2002): Duct-to-mucosa pancreaticojejunostomy reduces the risk of pancreatic leakage after pancreatoduodenectomy. World J Surg 26: 99-104.

Howard JM (1968): Pancreatico-duodenectomy: Forty-one consecutive Whipple resections without an operative mortality. Ann Surg 168: 629-640.

Huang JJ, Yeo CJ, Sohn TA, Lillemoe KD, Sauter PK, Coleman J, Hruban RH and Cameron JL (2000): Quality of life and outcomes after pancreaticoduodenectomy. See comment. Ann Surg 231: 890-898.

Ihse I and Andrén-Sandberg Å (1998): Surgical treatment: Total pancreatectomy. In: The Pancreas, pp. 1047-1954. Eds. HG Beger, AL Warshaw, MW Büchler, DL Carr-Locke, JP Neoptolemos, C Russell and MG Sarr, Blackwell Science Ltd. Cambridge, Great Britain.

Ishikawa O (1996): Surgical technique, curability and postoperative quality of life in an extended pancreatectomy for adenocarcinoma of the pancreas. Hepato-Gastroenterol 43: 320-325.

Izbicki JR, Bloechle C, Broering DC, Knoefel WT, Kuechler T and Broelsch CE (1998): Extended drainage versus resection in surgery for chronic pancreatitis: A prospective randomized trial

comparing the longitudinal pancreaticojejunostomy combined with local pancreatic head excision with the pylorus-preserving pancreatoduodenectomy. Ann Surg 228: 771-779.

Jang JY, Kim SW, Park SJ and Park YH (2002): Comparison of the functional outcome after pylorus-preserving pancreatoduodenectomy: Pancreatogastrostomy and pancreatojejunostomy. World J Surg 26: 366-371.

Jeekel J (1992): No abdominal drainage after Whipple's procedure. Br J Surg 79: 182.

Jethwa P, Sodergren M, Lala A, Webber J, Buckels JAC, Bramhall SR and Mirza DF (2006): Diabetic control after total pancreatectomy. Dig Liver Dis 38: 415-419.

Kahl S and Malfertheiner P (2004): Exocrine and endocrine pancreatic insufficiency after pancreatic surgery. Best Pract Res Clin Gastroenterol 18: 947-955.

Kairaluoma MI, Stahlberg M and Kiviniemi H (1990): Pancreatic resection for carcinoma of the pancreas and the periampullary region. A twenty-year experience. HPB Surg 2: 57-66.

Kang CM, Kim DH, Choi GH, Kim KS, Choi JS and Lee WJ (2009): Detrimental effect of postoperative complications on oncologic efficacy of R0 pancreatectomy in ductal adenocarcinoma of the pancreas. J Gastrointest Surg 13: 907-914.

Karanicolas PJ, Davies E, Kunz R, Briel M, Koka HP, Payne DM, Smith SE, Hsu HP, Lin PW, Bloechle C, Paquet KJ and Guyatt GH (2007): The pylorus: Take it or leave it? Systematic review and meta-analysis of pylorus-preserving versus standard Whipple pancreaticoduodenectomy for pancreatic or periampullary cancer. Ann Surg Oncol 14: 1825-1834.

Kauhanen SP, Komar G, Seppänen MP, Dean KI, Minn HR, Kajander SA, Rinta-Kiikka I, Alanen K, Borra RJ, Puolakkainen PA, Nuutila P and Ovaska JT (2009): A prospective diagnostic accuracy study of ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography, multidetector row computed tomography, and magnetic resonance imaging in primary diagnosis and staging of pancreatic cancer. Ann Surg 250: 957-963.

Kazanjian KK, Hines OJ, Eibl G and Reber HA (2005): Management of pancreatic fistulas after pancreaticoduodenectomy: Results in 437 consecutive patients. Arch Surg 140: 849-854.

Keck H, Steffen R, Waluja W and Neuhaus P (1991): Anastomosenprotektion durch ein spezielles Drainageverfahren bei der Kausch-Whipple Operation. Chirurg 62: 561-564.

Kelemen D and Horváth ÖP (2002): Clinical experience with different techniques of pancreatic head resection for chronic pancreatitis. Dig Surg 19: 28-34.

Kim SW, Youk EG and Park YH (1997): Comparison of pancreatogastrostomy and pancreatojejunostomy after pancreatoduodenectomy performed by one surgeon. World J Surg 21: 640-643.

Kingsnorth AN (1989): Duct to mucosa isolated Roux loop pancreaticojejunostomy as an improved anastomosis after resection of the pancreas. Surg Gynecol Obstet 169: 451-453.

Kinney TP, Punjabi G and Freeman M (2007): Technology insight: Applications of MRI for the evaluation of benign disease of the pancreas. Nat Clin Pract Gastroenterol Hepatol 4: 148-159.

Kleespies A, Albertsmeier M, Obeidat F, Seeliger H, Jauch KW and Bruns CJ (2008): The challenge of pancreatic anastomosis. Langenbecks Arch Surg 393: 459-471.

Lai ECH, Lau SHY and Lau WY (2009): Measures to prevent pancreatic fistula after pancreatoduodenectomy. A comprehensive review. Arch Surg 144: 1074-1080.

Lämsä T, Jin H, Mikkonen J, Laukkarinen J, Sand J and Nordback I (2006): Biocompatibility of a new bioabsorbable radiopaque stent material ($BaSO_4$ containing poly-L,D-lactide) in the rat pancreas. Pancreatology 6: 301-305.

Langenhoff BS, Krabbe PF, Wobbes T and Ruers TJ (2001): Quality of life as an outcome measure in surgical oncology. Br J Surg 88: 643-652.

Lankisch PG, Lohr-Happe A, Otto J and Creutzfeldt W (1993): Natural course in chronic pancreatitis. Pain, exocrine and endocrine pancreatic insufficiency and prognosis of the disease. Digestion 54: 148-155.

Laukkarinen JM, Sand JA, Chow P, Juuti H, Kellomäki M, Kärkkäinen P, Isola J, Yu S, Somanesan S, Kee I, Song IC, Ng TH and Nordback IH (2007): A novel biodegradable biliary stent in the normal duct hepaticojejunal anastomosis: an 18-month follow-up in a large animal model. J Gastrointest Surg 11: 750-757.

Laukkarinen J, Lämsä T, Nordback I, Mikkonen J and Sand J (2008): A novel biodegradable pancreatic stent for human pancreatic applications: A preclinical study in a large animal model. Gastrointest Endosc 67: 1106-1112.

Levy MJ, Chari S, Adler DG, Clain JE, Gostout CJ, Harewood GC, Pearson RK, Petersen BT, Sarr MG and Farnell MB (2004): Complications of temporary pancreatic stent insertion for pancreaticojejunal anastomosis during pancreaticoduodenectomy. Gastrointest Endosc 59: 719-724.

Lieberman MD, Kilburn H, Lindsey M and Brennan MF (1995): Relation of perioperative deaths to hospital volume among patients undergoing pancreatic resection for malignancy. Ann Surg 222: 638-645.

Li-Ling J and Irving M (2001): Somatostatin and octreotide in the prevention of postoperative pancreatic complications and the treatment of enterocutaneous pancreatic fistulas: a systematic review of randomized controlled trials. Br J Surg 88: 190-199.

Lin HC, Xirasagar S, Lee HC and Chai CY (2006): Hospital volume and inpatient mortality after cancer-related gastrointestinal resections: The experience of an Asian country. Ann Surg Oncol 13: 1182-1188.

Lin JW, Cameron JL, Yeo CJ, Riall TS and Lillemoe KD (2004): Risk factors and outcomes in postpancreaticoduodenectomy pancreaticocutaneous fistula. J Gastrointest Surg 8: 951-959.

Lin PW, Shan YS, Lin YJ and Hung CJ (2005): Pancreaticoduodenectomy for pancreatic head cancer: PPPD versus Whipple procedure. Hepato-Gastroenterol 52: 1601-1604.

Link KH, Formentini A, Leder G, Fortnagel G, Sartori N, Schatz M and Beger HG (1998): Resection and radiochemotherapy of pancreatic cancer - the future? Langenbecks Arch Surg 383: 134-144.

Maki HS, Kolts RL and Kuehner ME (1990): Prevention of pancreatic fistula by modified pancreaticojejunal anastomosis. Am J Surg 160: 533-534.

Marcus SG, Cohen H and Ranson JH (1995): Optimal management of the pancreatic remnant after pancreaticoduodenectomy. Ann Surg 221: 635-645.

Martin RF, Rossi RL and Leslie KA (1996): Long-term results of pylorus-preserving pancreatoduodenectomy for chronic pancreatitis. Arch Surg 131: 247-252.

Martin RF and Rossi RL (1998): Pancreaticoduodenectomy with or without Pylorus Preservation. In: The Pancreas, pp. 863-869. Eds. HG Beger, AL Warshaw, MW Büchler, DL Carr-Locke, JP Neoptolemos, C Russell and MG Sarr, Blackwell Science Ltd. Cambridge, UK.

Martin RF and Zuberi KA (2010): The evidence for technical considerations in pancreatic resections for malignancy. Surg Clin N Am 90: 265-285.

Matos C, Metens T, Deviere J, Nicaise N, Braude P, Van Yperen G, Cremer M and Struyven J (1997): Pancreatic duct: Morphologic and functional evaluation with dynamic MR pancreatography after secretin stimulation. Radiology 203: 435-441.

Matsumoto J and Traverso LW (2006): Exocrine function following the Whipple operation as assessed by stool elastase. J Gastrointest Surg 10: 1225-1229.

Matsumoto Y, Fujii H, Miura K, Inoue S, Sekikawa T, Aoyama H, Ohnishi N, Sakai K and Suda K (1992): Successful pancreatojejunal anastomosis for pancreatoduodenectomy. Surg Gynecol Obstet 175: 555-562.

McLeod RS (1999): Quality of life, nutritional status and gastrointestinal hormone profile following the Whipple procedure. Ann Oncol 10: 281-284.

McLeod RS, Taylor BR, O'Connor BI, Greenberg GR, Jeejeebhoy KN, Royall D and Langer B (1995): Quality of life, nutritional status, and gastrointestinal hormone profile following the Whipple procedure. Am J Surg 169: 179-185.

Melvin WS, Buekers KS, Muscarella P, Johnson JA, Schirmer WJ and Ellison EC (1998): Outcome analysis of long-term survivors following pancreaticoduodenectomy. J Gastrointest Surg 2: 72-78.

Melzack R (1975): The McGill pain questionnaire: Major properties and scoring methods. Pain 1: 277-299.

Metzger A and DiMagno EP (1998) Enzymes and digestion. In: The Pancreas, pp. 147-159. Eds. HG Beger, AL Warshaw, MW Büchler, DL Carr-Locke, JP Neoptolemos, C Russell and MG Sarr, Blackwell Science Ltd. Cambridge, UK.

Michalski CW, Kleeff J, Wente MN, Diener MK, Büchler MW and Friess H (2007): Systematic review and meta-analysis of standard and extended lymphadenectomy in pancreaticoduodenectomy for pancreatic cancer. Br J Surg 94: 265-273.

Michl P, Pauls S and Gress TM (2006): Evidence-based diagnosis and staging of pancreatic cancer. Best Pract Res Clin Gastroenterol 20: 227-251

Monill J, Pernas J, Clavero J, Farré A, Morales A, Gonzáles M, Artigas V and Martínez-Noguera A (2004): Pancreatic duct after pancreatoduodenectomy: morphologic and functional evaluation with secretin-stimulated MR pancreatography. Am J Roentgenol 183: 1267-1274.

Mosca F, Giulianotti PC, Balestracci T, Di Candio G, Pietrabissa A, Sbrana F and Rossi G (1997): Long-term survival in pancreatic cancer: Pylorus-preserving versus Whipple pancreatoduodenectomy. Surgery 122: 553-566.

Müller MW, Friess H, Kleeff J, Dahmen R, Wagner M, Hinz U, Breisch-Girbig D, Ceyhan GO and Büchler MW (2007): Is there still a role for total pancreatectomy? Ann Surg 246: 966-975.

Nagakawa T, Konishi I, Ueno K, Ohta T, Kayahara M and Miyazaki I (1997): A comparison of the complication rate for three pancreaticojejunostomy techniques. Hepato-Gastroenterol 44: 1452-1456.

Naruse S, Ishiguro H, Ko SB, Yoshikawa T, Yamamoto T, Yamamoto A, Futakuchi S, Goto H, Saito Y and Takahashi S (2006): Fecal pancreatic elastase: A reproducible marker for severe exocrine pancreatic insufficiency. J Gastroenterol 41: 901-908.

Neoptolemos JP, Cunningham D, Friess H, Bassi C, Stocken DD, Tait DM, Dunn JA, Dervenis C, Laçaine F, Hickey H, Raraty MG, Ghaneh P and Büchler MW (2003): Adjuvant therapy in pancreatic cancer: Historical and current perspectives. Ann Oncol 14: 675-692.

Neoptolemos JP, Kerr DJ, Beger H, Link K, Pederzoli P, Bassi C, Dervenis C, Fernandez-Cruz L, Laçaine F, Friess H and Büchler M (1997): ESPAC-1 trial progress report: The European randomized adjuvant study comparing radiochemotherapy, 6 months chemotherapy and combination therapy versus observation in pancreatic cancer. Digestion 58: 570-577.

Neoptolemos JP, Stocken DD, Tudur Smith C, Bassi C, Ghaneh P, Owen E, Moore M, Padbury R, Doi R, Smith D and Büchler MW (2009): Adjuvant 5-fluorouracil and folinic acid vs. observation

for pancreatic cancer: Composite data from the ESPAC-1 and -3(v1) trials. Br J Cancer 100: 246-250.

Niedergethmann M, Farag Soliman M and Post S (2004): Postoperative complications of pancreatic cancer surgery. Minerva Chir 59: 175-183.

Nieveen van Dijkum EJ, Kuhlmann KF, Terwee CB, Obertop H, de Haes JC and Gouma DJ (2005): Quality of life after curative or palliative surgical treatment of pancreatic and periampullary carcinoma. Br J Surg 92: 471-477.

Nordback I, Lämsä T, Laukkarinen J, Leppiniemi J, Kellomäki M and Sand J (2008): Pancreatico-jejunostomy with a biodegradable stent and without stitches through the pancreas. Hepato-Gastroenterol 55: 319-322.

Nordback I, Parviainen M, Räty S, Kuivanen H and Sand J (2002): Resection of the head of the pancreas in Finland: effects of hospital and surgeon on short-term and long-term results. Scand J Gastroenterol 12: 1454-1460.

Nordback I, Parviainen M, Piironen A, Räty S and Sand J (2007): Obstructed pancreaticojejunostomy partly explains exocrine insufficiency after pancreatic head resection. Scand J Gastroenterol 42: 263-270.

Ogata Y and Hishinuma S (2002): The impact of pylorus-preserving pancreatoduodenectomy on surgical treatment for cancer of the pancreatic head. J Hepatobiliary Pancreat Surg 9: 223-232.

Ohtsuka T, Yamaguchi K, Chijiiwa K, Kinukawa N and Tanaka M (2001): Quality of life after pylorus-preserving pancreatoduodenectomy. Am J Surg 182: 230-236.

Ohtsuka T, Yamaguchi K, Ohuchida J, Inoue K, Nagai E, Chijiiwa K and Tanaka M (2003): Comparison of quality of life after pylorus-preserving pancreatoduodenectomy and Whipple resection. Hepato-Gastroenterol 50: 846-850.

Ohwada S, Ogawa T, Kawate S, Tanahashi Y, Iwazaki S, Tomizawa N, Yamada T, Ohya T and Morishita Y (2001): Results of duct-to-mucosa pancreaticojejunostomy for pancreaticoduodenectomy Billroth I type reconstruction in 100 consecutive patients. J Am Coll Surg 193: 29-35.

Orr RK (2010): Outcomes in pancreatic cancer surgery. Surg Clin N Am 90: 219-234.

Parviainen M, Räty S, Nordback I, Sintonen H, Vehkalahti P and Sand J (2008): Late postoperative quality of life following pancreatic head resections. Hepato-Gastroenterol 55: 711-716.

Parviainen MC, Sand JA and Nordback IH (1996): Coincidence of pancreatic and biliary leakages after pancreaticoduodenal resections. Hepato-Gastroenterol 43: 1246-1249.

Parviainen M, Sand J, Harmoinen A, Kainulainen H, Välimaa T, Törmälä P and Nordback I (2000): A new biodegradable stent for the pancreaticojejunal anastomosis after pancreaticoduodenal resection: in vitro examination and pilot experiences in humans. Pancreas 21: 14-21.

Patel AG, Toyama MT, Kusske AM, Alexander P, Ashley SW and Reber HA (1995): Pylorus-preserving Whipple resection for pancreatic cancer. Is it any better? Arch Surg 130: 838-843.

Pedrazzoli S, DiCarlo V, Dionigi R, Mosca F, Pederzoli P, Pasquali C, Klöppel G, Dhaene K and Michelassi F (1998): Standard versus extended lymphadenectomy associated with pancreaticoduodenectomy in the surgical treatment of adenocarcinoma of the head of the pancreas: A multicenter, prospective, randomized study. Ann Surg 228: 508-517.

Peng SY, Wang JW, Lau WY, Cai XJ, Mou YP, Liu YB and Li JT (2007): Conventional versus binding pancreaticojejunostomy after pancreaticoduodenectomy. A prospective randomized trial. Ann Surg 245: 692-698.

Peros G, Giannopoulos GA, Christodoulou S, Konstantoudakis G, Petropoulou K and Sakorafas GH (2010): Good results after major pancreatic resections in a middle-volume center. Pancreas 39: 411-414.

Pessaux P, Aubé C, Lebigot J, Tuech JJ, Regenet N, Kapel N, Caron C and Arnaud JP (2002): Permeability and functionality of pancreaticogastrostomy after pancreaticoduodenectomy with dynamic magnetic resonance pancreatography after secretin stimulation. J Am Coll Surg 194: 454-462.

Porter GA, Pisters PW, Mansyur C, Bisanz A, Reyna K, Stanford P, Lee JE and Evans DB (2000): Cost and utilization impact of a clinical pathway for patients undergoing pancreaticoduodenectomy. Ann Surg Oncol 7: 484-489.

Räsänen JV, Niskanen MM, Miettinen P, Sintonen H and Alhava E (2001): Health-related quality of life before and after gastrointestinal surgery. Eur J Surg 167: 419-425.

Räty S, Sand J, Lantto E and Nordback I (2006): Postoperative acute pancreatitis as a major determinant of postoperative delayed gastric emptying after pancreaticoduodenectomy. J Gastrointest Surg 10: 1131-1139.

Rault A, SaCunha A, Klopfenstein D, Larroudé D, Epoy FN, Collet D and Masson B (2005): Pancreaticojejunal anastomosis is preferable to pancreaticogastrostomy after pancreaticoduodenectomy for longterm outcomes of pancreatic exocrine function. J Am Coll Surg 201: 239-244.

Raut CP, Tseng JF, Sun CC, Wang H, Wolff RA, Crane CH, Hwang R, Vauthey JN, Abdalla EK, Lee JE, Pisters PW and Evans DB (2007): Impact of resection status on pattern of failure and survival after pancreaticoduodenectomy for pancreatic adenocarcinoma. Ann Surg 246: 52-60.

Reddy DM, Townsend Jr. CM, Kuo Y-F, Freeman JL, Goodwin JS and Riall TS (2009): Readmission after pancreatectomy for pancreatic cancer in Medicare patients. J Gastrointest Surg 13: 1963-1975.

Reid-Lombardo KM, Farnell MB, Crippa S, Barnett M, Maupin G, Bassi C and Traverso LW (2007a): Pancreatic anastomotic leakage after pancreaticoduodenectomy in 1,507 patients: A report from the Pancreatic Anastomotic Leak Study Group. J Gastrointest Surg 11: 1451-1458, discussion 1459.

Reid-Lombardo KM, Ramos-De la Medina A, Thomsen K, Harmsen WS and Farnell MB (2007b): Long-term anastomotic complications after pancreaticoduodenectomy for benign diseases. J Gastrointest Surg 11: 1704-1711.

Reissman P, Perry Y, Cuenca A, Bloom A, Eid A, Shiloni E, Rivkind A and Durst A (1995): Pancreaticojejunostomy versus controlled pancreaticocutaneous fistula in pancreaticoduodenectomy for periampullary carcinoma. Am J Surg 169: 585-588.

Riall TS (2009): What is the effect of age on pancreatic resection? Adv Surg 43: 233-249.

Riall TS, Nealon WH, Goodwin JS, Townsend CM Jr. and Freeman JL (2008): Outcomes following pancreatic resection: Variability among high-volume providers. Surgery 144: 133-140.

Richter A, Niedergethmann M, Sturm JW, Lorenz D and Post S (2003): Long-term results of partial pancreaticoduodenectomy for ductal adenocarcinoma of the pancreatic head: 25-year experience. World J Surg 27: 324-329.

Riediger H, Keck T, Wellner U, zur Hausen A, Adam U, Hopt UT and Makowiec F (2009): The lymph node ratio is the strongest prognostic factor after resection of pancreatic cancer. J Gastrointest Surg 13: 1337-1344.

Röher HD, Heise JW und Goretzki PE (2000): Die magenerhaltende Duodenopankreatektomie. Indikation und Kontraindikation. Die wichtigsten operativen Schritte. (Stomach saving duodenopancreatectomy. indications and contraindications. The most important surgical steps.). Zentralbl Chir 125: 961-965.

Rumstadt B, Schwab M, Korth P, Samman M and Trede M (1998): Hemorrhage after pancreatoduodenectomy. Ann Surg 227: 236-241.

Saif MW (2009): Adjuvant treatment of pancreatic cancer in 2009: Where are we? Highlights from the 45th ASCO Annual Meeting. Orlando, FL, USA. May 29 - June 2, 2009. JOP 10: 373-377.

Sato N, Yamaguchi K, Yokohata K, Shimizu S, Morisaki T, Mizumoto K, Chijiiwa K and Tanaka M (1998): Preoperative exocrine pancreatic function predicts risk of leakage of pancreaticojejunostomy. Surgery 124: 871-876.

Schäfer M, Müllhaupt B and Clavien PA (2002): Evidence-based pancreatic head resection for pancreatic cancer and chronic pancreatitis. Ann Surg 236: 137-148.

Scheingraber S, Scheingraber T, Brauckhoff M and Dralle H (2005): Comparison between a general and a disease-specific health-related quality-of-life questionnaire in patients after pancreatic surgery. J Hepatobiliary Pancreat Surg 12: 290-297.

Schlick RW and Planz K (1998): In vitro results with special plastics for biodegradable endoureteral stents. J Endourol 12: 451-455.

Schmidt CM, Powell ES, Yiannoutsos CT, Howard TJ, Wiebke EA, Wiesenauer CA, Baumgardner JA, Cummings OW, Jacobson LE, Broadie TA, Canal DF, Goulet RJ Jr., Curie EA, Cardenes H, Watkins JM, Loehrer PJ, Lillemoe KD and Madura JA (2004): Pancreaticoduodenectomy: A 20-year experience in 516 patients. Arch Surg 139: 718-725.

Schmidt CM, Choi J, Powell ES, Yiannoutsos CT, Zyromski NJ, Nakeeb A, Pitt HA, Wiebke EA, Madura JA and Lillemoe KD (2009): Pancreatic fistula following pancreaticoduodenectomy: clinical predictors and patient outcomes. HPB Surg 2009: 1-8.

Schmidt U, Simunec D, Piso P, Klempnauer J and Schlitt HJ (2005): Quality of life and functional long-term outcome after partial pancreatoduodenectomy: Pancreatogastrostomy versus pancreatojejunostomy. Ann Surg Oncol 12: 467-472.

Schniewind B, Bestmann B, Henne-Bruns D, Faendrich F, Kremer B and Kuechler T (2006): Quality of life after pancreaticoduodenectomy for ductal adenocarcinoma of the pancreatic head. Br J Surg 93: 1099-1107.

Scurtu R, Bachellier P, Oussoultzoglou E, Rosso E, Maroni R and Jaeck D (2006): Outcome after pancreaticoduodenectomy for cancer in elderly patients. J Gastrointest Surg 10: 813-822.

Shinchi H, Wada K and Traverso LW (2006): The usefulness of drain data to identify a clinically relevant pancreatic anastomotic leak after pancreaticoduodenectomy? J Gastrointest Surg 10: 490-498.

Sho M, Nakajima Y, Kanehiro H, Hisanaga M, Nishio K, Nagao M, Tatekawa Y, Ikeda N, Kanokogi H, Yamada T, Hirohashi S, Hirohashi R, Uchida H and Nakano H (1998): A new evaluation of pancreatic function after pancreatoduodenectomy using secretin magnetic resonance cholangiopancreatography. Am J Surg 176: 279-282.

Shrikhande SV, Qureshi SS, Rajneesh N and Shukla PJ (2005): Pancreatic anastomoses after pancreaticoduodenectomy: Do we need further studies? World J Surg 29: 1642-1649.

Shukla PJ, Barreto SG and Fingerhut A (2010): Do transanastomotic pancreatic ductal stents after pancreatic resections improve outcomes? Pancreas 39: 561-566.

Shyr YM, Su CH, Wu CW and Lui WY (2003): Does drainage fluid amylase reflect pancreatic leakage after pancreaticoduodenectomy? World J Surg 27: 606-610.

Simons JP, Shah SA, Ng SC, Whalen GF and Tseng JF (2009): National complication rates after pancreatectomy, beyond mere mortality. J Gastrointest Surg 13: 1798-1805.

Sintonen H (2001): The 15D instrument of health-related quality of life: Properties and applications. Ann Med 33: 328-336.

Smith RA, Dajani K, Dodd S, Whelan P, Raraty M, Sutton R, Campbell F, Neoptolemos JP and Ghaneh P (2008): Preoperative resolution of jaundice following biliary stenting predicts more favourable early survival in resected pancreatic ductal adenocarcinoma. Ann Surg Oncol 15: 3138-3146.

Sohn TA, Campbell KA, Pitt HA, Sauter PK, Coleman JA, Lillemoe KD, Yeo CJ and Cameron JL (2000a): Quality of life and long-term survival after surgery for chronic pancreatitis. J Gastrointest Surg 4: 355-364.

Sohn TA, Yeo CJ, Cameron JL, Koniaris L, Kaushal S, Abrams RA, Sauter PK, Coleman J, Hruban RH and Lillemoe KD (2000b): Resected adenocarcinoma of the pancreas - 616 patients: Results, outcomes, and prognostic indicators. See comment. J Gastrointest Surg 4: 567-579.

Sosa JA, Bowman HM, Gordon TA, Bass EB, Yeo CJ, Lillemoe KD, Pitt HA, Tielsch JM and Cameron JL (1998): Importance of hospital volume in the overall management of pancreatic cancer. Ann Surg 228: 429-438.

Sperti C, Pasquali C, Piccoli A and Pedrazzoli S (1996): Survival after resection for ductal adenocarcinoma of the pancreas. Br J Surg 83: 625-631.

Srinarmwong C, Luechakiettisak P and Prasitvilai W (2008): Standard Whipple's operation versus pylorus preserving pancreaticoduodenectomy: A randomized controlled trial study. J Med Assoc Thai 91: 693-698.

Strasberg SM, Linehan DC, Clavien PA and Barkun JS (2007): Proposal for definition and severity grading of pancreatic anastomosis failure and pancreatic occlusion failure. Surgery 141: 420-426.

Suc B, Msika S, Fingerhut A, Fourtanier G, Hay JM, Holmieres F, Sastre B, Fagniez PL and The French Associations for Surgical Research (2003): Temporary fibrin glue occlusion of the main pancreatic duct in the prevention of intra-abdominal complications after pancreatic resection: Prospective randomized trial. Ann Surg 237: 57-65.

Sugiyama M, Abe N, Tokuhara M, Masaki T, Mori T, Takahara T, Hachiya J and Atomi Y (2003): Magnetic resonance cholangiopancreatography for postoperative follow-up of intraductal papillary-mucinous tumors of the pancreas. Am J Surg 185: 251-255.

Tanaka T, Ichiba Y, Fujii Y, Kodama O and Dohi K (1988): Clinical and experimental study of pancreatic exocrine function after pancreaticoduodenectomy for periampullary carcinoma. Surg Gynecol Obstet 166: 200-205.

Tang Y, Yamashita Y, Arakawa A, Namimoto T, Mitsuzaki K, Abe Y, Katahira K and Takahashi M (2000): Pancreaticobiliary ductal system: Value of half-fourier rapid acquisition with relaxation enhancement MR cholangiopancreatography for postoperative evaluation. Radiology 215: 81-88.

Tarazi RY, Hermann RE, Vogt DP, Hoerr SO, Esselstyn CB Jr., Cooperman AM, Steiger E and Grundfest S (1986): Results of surgical treatment of periampullary tumors: A thirty-five-year experience. Surgery 100: 716-723.

Thoeni RF and Blankenberg F (1993): Pancreatic imaging. Radiol Clin North Am 31: 1085-1113.

Tolonen P, Victorzon M and Mäkelä J (2004): Impact of laparoscopic adjustable gastric banding for morbid obesity on disease-specific and health-related quality of life. Obes Surg 14: 788-795.

Touzios JG, Krzywda B, Nakeeb A and Pitt HA (2005): Exercise-induced cholangitis and pancreatitis. HPB 7: 124-128.

Tran K, Van Eijck C, Di Carlo V, Hop WC, Zerbi A, Balzano G and Jeekel H (2002): Occlusion of the pancreatic duct versus pancreaticojejunostomy: A prospective randomized trial. Ann Surg 236: 422-428.

Traverso LW and Longmire WPJ (1978): Preservation of the pylorus in pancreaticoduodenectomy. Surg Gynecol Obstet 146: 959-962.

Tyrväinen T, Sand J, Sintonen H and Nordback I (2008): Quality of life in the long-term survivors after total gastrectomy for gastric carcinoma. J Surg Oncol 97: 121-124.

Uchida E, Tajiri T, Nakamura Y, Aimoto T and Naito Z (2002): Relationship between grade of fibrosis in pancreatic stump and postoperative pancreatic exocrine activity after

pancreaticoduodenectomy: With special reference to insufficiency of pancreaticointestinal anastomosis. J Nippon Med Sch 69: 549-556.

Urbach DR, Bell CM and Austin PC (2003): Differences in operative mortality between high- and low-volume hospitals in Ontario for 5 major surgical procedures: Estimating the number of lives potentially saved through regionalization. CMAJ 168: 1409-1414.

Uurto I, Juuti H, Parkkinen J, Kellomäki M, Keski-Nisula L, Nevalainen T, Törmälä P and Salenius J-P (2004): Biodegradable self-expanding poly-L/D-Lactic Acid Vascular stent: a pilot study in canine and porcine iliac arteries. J Endovasc Ther 11: 712-718.

van Berge Henegouwen MI, De Wit LT, Van Gulik TM, Obertop H and Gouma DJ (1997): Incidence, risk factors, and treatment of pancreatic leakage after pancreaticoduodenectomy: Drainage versus resection of the pancreatic remnant. J Am Coll Surg 185: 18-24.

van Heek NT, Kuhlmann KFD, Scholten RJ, de Castro SMM, Busch ORC, van Gulik TM, Obertop H and Gouma DJ (2005): Hospital volume and mortality after pancreatic resection: A systematic review and an evaluation of intervention in the Netherlands. Ann Surg 242: 781-788; discussion 788-790.

van Heerden JA, McIlrath DC, Dozois RR and Adson MA (1981): Radical pancreatoduodenectomy - a procedure to be abandoned? Mayo Clin Proc 56: 601-606.

van Oost FJ, Luiten EJT, van de Poll-Franse LV, Coebergh JWW and van den Eijnden-van Raaij AJM (2006): Outcome of surgical treatment of pancreatic, periampullary and ampullary cancer diagnosed in the south of the Netherlands: A cancer registry based study. Eur J Surg Oncol 32: 548-552.

van Roest MHG, Gouw ASH, Peeters PMJG, Porte RJ, Slooff MJH, Fidler V and de Jong KP (2008): Results of pancreaticoduodenectomy in patients with periampullary adenocarcinoma: Perineural growth more important prognostic factor than tumor localization. Ann Surg 248: 97-103.

Walkowiak J, Cichy WK and Herzig KH (1999): Comparison of fecal elastase-1 determination with the secretin-cholecystokinin test in patients with cystic fibrosis. Scand J Gastroenterol 34: 202-207.

Wamser P, Stift A, Passler C, Goetzinger P, Sautner T, Jakesz R and Fuegger R (2002): How to pass on expertise: Pancreatoduodenectomy at a teaching hospital. World J Surg 26: 1458-1462.

Wente MN, Shrikhande SV, Müller MW, Diener MK, Seiler CM, Friess H and Büchler MW (2007): Pancreaticojejunostomy versus pancreaticogastrostomy: systematic review and meta-analysis. Am J Surg 193: 171-183.

Whipple A, Parsons WB and Mullens CR (1935): Treatment of carcinoma of the ampulla of Vater. Ann Surg 102: 763-776.

Winter JM, Cameron JL, Campbell KA, Chang DC, Riall TS, Schulick RD, Choti MA, Coleman J, Hodgin MB, Sauter PK, Sonnenday CJ, Wolfgang CL, Marohn MR and Yeo CJ (2006): Does pancreatic duct stenting decrease the rate of pancreatic fistula following pancreaticoduodenectomy? results of a prospective randomized trial. J Gastrointest Surg 10: 1280-1290.

Witzigmann H, Max D, Uhlmann D, Geissler F, Ludwig S, Schwarz R, Krauss O, Lohmann T, Keim V and Hauss J (2002): Quality of life in chronic pancreatitis: A prospective trial comparing classical Whipple procedure and duodenum-preserving pancreatic head resection. J Gastrointest Surg 6: 173-179.

Witzigmann H, Max D, Uhlmann D, Geissler F, Schwarz R, Ludwig S, Lohmann T, Caca K, Keim V, Tannapfel A and Hauss J (2003): Outcome after duodenum-preserving pancreatic head resection is improved compared with classic Whipple procedure in the treatment of chronic pancreatitis. Surgery 134: 53-62.

Yang YM, Tian XD, Zhuang Y, Wang WM, Wan YL and Huang YT (2005): Risk factors of pancreatic leakage after pancreaticoduodenectomy. World J Gastroenterol 11: 2456-2461.

Yeo CJ, Cameron JL, Maher MM, Sauter PK, Zahurak ML, Talamini MA, Lillemoe KD and Pitt HA (1995): A prospective randomized trial of pancreaticogastrostomy versus pancreaticojejunostomy after pancreaticoduodenectomy. Ann Surg 222: 580-588.

Yeo CJ, Cameron JL, Sohn TA, Lillemoe KD, Pitt HA, Talamini MA, Hruban RH, Ord SE, Sauter PK, Coleman J, Zahurak ML, Grochow LB and Abrams RA (1997): Six hundred fifty consecutive pancreaticoduodenectomies in the 1990s: Pathology, complications and outcomes. Ann Surg 226: 248-257.

Yeo CJ, Cameron JL, Sohn TA, Coleman J, Sauter PK, Hruban RH, Pitt HA and Lillemoe KD (1999): Pancreaticoduodenectomy with or without extended retroperitoneal lymphadenectomy for

periampullary adenocarcinoma: Comparison of morbidity and mortality and short-term outcome. See comment. Ann Surg 229: 613-622.

Yeo CJ, Cameron JL, Lillemoe KD, Sauter PK, Coleman J, Sohn TA, Campbell KA and Choti MA (2000): Does prophylactic octreotide decrease the rates of pancreatic fistula and other complications after pancreaticoduodenectomy? Results of a prospective randomized placebo-controlled trial. See comment. Ann Surg 232: 419-429.

Yeo CJ, Cameron JL, Lillemoe KD, Sohn TA, Campbell KA, Sauter PK, Coleman J, Abrams RA and Hruban RH (2002): Pancreaticoduodenectomy with or without distal gastrectomy and extended retroperitoneal lymphadenectomy for periampullary adenocarcinoma, part 2: randomized controlled trial evaluating survival, morbidity and mortality. Ann Surg 236: 355-368.

Yeo CJ, Sohn TA, Cameron JL, Hruban RH, Lillemoe KD and Pitt HA (1998): Periampullary adenocarcinoma: Analysis of 5-year survivors. See comment. Ann Surg 227: 821-831.

Zeng Q, Zhang Q, Han S, Yu Z, Zheng M, Zhou M, Bai J and Jin R (2008): Efficacy of somatostatin and its analogues in prevention of postoperative complications after pancreaticoduodenectomy. A meta-analysis of randomized controlled trials. Pancreas 36: 18-25.

Z'graggen K, Uhl W, Friess H and Büchler MW (2002): How to do a safe pancreatic anastomosis. J Hepatobiliary Pancreat Surg 9: 733-737.

Original Paper

Coincidence of Pancreatic and Biliary Leakages after Pancreaticoduodenal Resections

Mickael C. Parviainen, M.D., Juhani A. Sand, M.D. and Isto H. Nordback, M.D.

Department of Surgery, Tampere University Hospital and Medical School, University of Tampere, Tampere, Finland

Abstract

Background/Aims: *Pancreaticoenteric leakage is the most important complication after pancreaticoduodenal resection. Bilioenteric leakage, though rarer, may also complicate recovery after pancreaticoduodenal resection. Each of these complications may occur separately or simultaneously and may be treated conservatively or need reoperation. The possible coincidence of these complications has not been studied.*

Materials and Methods: *The case history of 46 patients, who underwent pancreaticoduodenal resection during 1991-1994 at Tampere University Hospital, Finland, was studied retrospectively.*

Results: *Pancreatic fistula occurred in eight patients (17%) and biliary fistula in four (9%). Biliary fistula was more common in the patients with simultaneous pancreatic fistula than in those without, which was also noted when only clinical fistulas were considered. The three patients with both fistulas had soft tissue in the pancreatic resection line, which is more often than those without fistulas. Two of the three patients who were reoperated had pancreatitis at the reoperation.*

Conclusions: *Biliary leakage after pancreaticoduodenal resection occurs usually together with pancreatic leakage. One important cause for those leakages might be postoperative pancreatitis.*

Key words: pancreas, surgery, complication, pancreaticoduodenal resection, anastomosis, leakage

Introduction

Pancreaticoduodenal resection was originally associated with a mortality rate in excess of 25% mainly due to leakage in the pancreaticoenteric anastomosis (1). While the mortality has dramatically decreased, pancreaticoenteric leakage is still the most important postoperative complication independently whether pancreaticojejunal or pancreaticogastric anastomosis is performed (2-4). Leakage may be subclinical or result in an intra-abdominal infection (5). Incidence of such a leakage varies between zero and 28 per cent (5-8) depending on the number of patients studied and the criteria used.

Postoperative biliary leakage is rarer. It has been reported in one to seven (2,9-11) per cent of the patients undergoing pancreaticoduodenal resection. Anastomotic leakage may be treated conservatively but may also result in intra-abdominal infection or even biliary peritonitis requiring reoperation (11,12).

The occurrence of pancreaticoenteric and bilioenteric leakages have usually been studied separately. The aim of this retrospective study was to evaluate the possible coincidence of the early pancreatic and biliary complications after the resection of the head of the pancreas.

Patients and Methods

During a four-year period, 1991-94, 46 patients underwent resection of the head of the pancreas in the Tampere University Hospital, Finland. Of these patients, 19 were men and 27 women. Their age ranged from 31 to 82 years, the median age being 65 years.

The final histology demonstrated a malignant disease in 36 patients. The most common diagnosis was ductal adenocarcinoma of the head of the pancreas (19 patients). Ten patients had adenocarcinoma of the ampulla of Vater, two patients had adenocarcinoma of the distal common bile duct and two patients had duodenal carcinoma. In one case it remained uncertain whether the adenocarcinoma was of duodenal or pancreatic origin. One patient had malignant insuloma and one had retroperitoneal liposarcoma that penetrated the duodenal wall. Ten patients had chronic pancreatitis. Twenty-eight patients had dilated bile ducts before the operation. Pancreaticoduodenal resection with antrectomy was performed in 17 patients (37%), pylorus-preserving pancreaticoduodenectomy in 24 patients (52%) and pylorus-preserving pancreaticoduodenectomy with extensive retroperitoneal lym-

Hepato-Gastroenterology 43 (1996) (Pages 1246-1249)
© H.G.E. Update Medical Publishing Ltd, Athens-Stuttgart

phadenectomy in 5 patients (11%). The hepatic duct was transected above the cystic duct junction and the pancreas on the left of the portal vein in all patients. Pancreaticojejunal end-to-end anastomosis was performed in two layers with interrupted 4-0 braided nylon (Surgilon®, Davis-Geck, USA) sutures, invaginating 2 cm of pancreas into the jejunum (13). Bilioenteric end to side anastomoses were performed in one layer with interrupted 4-0 polydioxanon (PDS®, Ethicon, Germany) sutures. Soft sump drains were left beside both anastomoses. The drain on the patient's right side was next to the bilioenteric and the one on the left side next to the pancreaticojejunal anastomosis.

Postoperative mortality and early pancreaticobiliary complications were evaluated. The pancreatic fistula was considered subclinical when the amylase activity in the secrete was more than three times the normal upper serum limit and the amount of the secrete was over 50 ml on the seventh postoperative day or later, when measured from the drain controlling the pancreaticojejunal anastomosis, but no clinical or laboratory signs of intra-abdominal infection were recognized (5). The biliary fistula was considered subclinical when the secrete coming from the drain controlling the bilioenteric anastomosis was bile stained on the fourth postoperative day or later, or when the postoperative cholangiogram demonstrated extravasation of contrast medium, but no clinical or laboratory signs of intra-abdominal infection were recognized. The pancreatic or the biliary fistula was named clinical if there were simultaneous signs of intra-abdominal infection.

Fischer's exact test was used to evaluate the statistical significance of the differences.

Results

Hospital mortality was 2/46 (4%). These patients did not have anastomotic leakages in the autopsy. Pancreatic fistula was detected in eight patients (17%). Five of them were classified subclinical (11%) and three (6%) clinical. Four patients (9%) had a biliary fistula. One of them was subclinical (2%) and three were clinical (6%). Biliary fistula was statistically more common in patients with simultaneous pancreatic fistula (3/8 = 38%) than in the patients without pancreatic fistula (1/38 = 3%) ($p=0.014$) **(Table 1).** Also, when only clinical fistulas were studied, biliary fistula was more common in the patients with clinical pancreatic fistula (2/3 = 67%) than in those without (1/43 = 2%) ($p<0.01$) **(Table 2).** Three of the eight patients who had pancreaticoenteric anastomotic leakage had firm and fibrous tissue in the pancreatic resection line, whereas the tissue was soft and normal in the gross appearance in the remaining five patients.

TABLE 1. THE COINCIDENCE OF POSTOPERATIVE BILIARY AND PANCREATIC FISTULAS (CLINICAL PLUS SUBCLINICAL).

		Biliary fistula	
		Yes	**No**
Pancreatic fistula	Yes	3	5
	No	1	37

Biliary fistula was more common in the patients with pancreatic fistula than with those without ($p=0.014$)

TABLE 2. THE COINCIDENCE OF CLINICAL POSTOPERATIVE BILIARY AND PANCREATIC FISTULAS

		Biliary fistula	
		Yes	**No**
Pancreatic fistula	Yes	2	1
	No	1	42

Clinical biliary fistula was more common in the patients with clinical pancreatic fistula than in those without ($p<0.01$)

This difference was always described on the notes by the operating surgeon but not always in histology by the pathologist. All the patients with both biliary and pancreatic leakages had soft tissue in the pancreatic resection line **(Table 3).** Two out of three patients with clinical leakages of both pancreatic and biliary anastomoses were re-operated. They demonstrated postoperative pancreatitis and a breakdown of the both anastomoses. They recovered after revision and resuturing of the anastomoses in the other case, and after combined splenectomy plus pancreatic caudal resection in the other case, respectively. Also the remaining seven patients, who were treated conservatively for the leakages, recovered.

One of the patients with subclinical pancreaticojejunal leakage was operated for chronic pancreatitis.

Discussion

Pancreaticoduodenal resection is the only treatment with a hope of cure in the malignant tumors of the periampullary region. While the mortality rate associ-

ated to the operation has decreased during the last decade to five per cent or less (four per cent in the present series) the procedure has more widely been accepted for benign diseases such as chronic pancreatitis, pancreatic cyst adenomas and islet cell tumors, too (14). Although the mortality rate is low, postoperative morbidity is still common (15).

TABLE 3. THE DISTRIBUTION OF BOTH PANCREATIC AND BILIARY LEAKAGES ACCORDING TO THE GROSS APPEARANCE OF PANCREATIC RESECTION LINE.

		Pancreas normal (soft)	
		Yes	No
Both fistulas	Yes	3	0
	No	15	28

The patients with both pancreatic and biliary leakages tended to have soft tissue in the pancreatic resection line ($p = 0.05$)

Pancreaticoenteric leakage, the most important postoperative complication, occurred in overall eight patients (17%), being clinical in three and subclinical in five patients. The present leakage rate is in concord with previous reports between zero and 28 per cent (5-8). Bilioenteric leakage occurred in overall four patients (9%), being clinical in three and subclinical in one patient. The present leakage rate is close to the upper range of previous reports between one and seven per cent (2,9-11).

In the present series bilioenteric leakages occurred more frequently in patients who had concomitant pancreaticoenteric leakage. The difference was significant when either all leakages were considered or when only clinical leakages were considered. All the pancreaticojejunal and hepaticojejunal anastomoses were performed by the same technique to the same place and almost all of the 46 patients were operated on by a team of two surgeons. Thus the differences in the operative technique do not explain the coincidence of pancreatic and biliary leakages in these patients. Also the preoperative nutritional state as estimated by serum albumin concentrations (data not shown) did not differ in the patients with leakages as compared with those without leakages.

An explanation for the coincidence of pancreatic and biliary leakages might be postoperative pancreatitis in the remaining tail of the pancreas. This theory is supported by the observation that all the three patients who demonstrated both leakages had soft and "normal" tissue in the pancreatic resection line, as assessed at the operation, and the two of those patients who were re-operated demonstrated postoperative pancreatitis in the remaining tail of the pancreas. It has also previously been observed that if the resection line is soft, the risk of anastomotic leakage is increased when compared to the firm and fibrous resection line (1). The exact diagnosis of postoperative pancreatitis after pancreaticoduodenal resection is difficult. Currently the best way to investigate the prevalence of postoperative pancreatitis might be a daily CT-control. However, postoperative peripancreatic oedema might be observed without clinical pancreatitis.

In conclusion, bilioenteric leakage after pancreaticoduodenal resection coincides with the pancreaticoenteric leakage. One important cause for these leakages might be postoperative pancreatitis.

References

1 *Lerut JP, Gianello PR, Otte JB, Kestens PJ.* Pancreaticoduodenal resection - surgical experience and evaluation of risk factors in 103 patients. Ann Surg 1984; 199: 432-437.

2 *Crist DW, Sitzmann JV, Cameron JL.* Improved hospital morbidity, mortality and survival after the Whipple procedure. Ann Surg 1987; 206: 358-365.

3 *Roder JD, Stein HJ, Hövttland W, Siewert JR.* Pylorus-preserving versus standard pancreaticoduodenectomy: an analysis of 110 pancreatic and periampullary carcinomas. Br J Surg 1992; 79: 152-155.

4 *Yeo CJ, Cameron JL, Maher MM, Sauter PK, Zahurak ML, Talamini MA, Lillemoe KD, Pitt HA.* A prospective randomized trial of pancreaticogastrostomy versus pancreaticojejunostomy after pancreaticoduodenectomy. Ann Surg 1995; 222: 580-592.

5 *Bövchler M, Friess H, Klempa I, Hermanek P, Sulkowski U, Becker H, Schafmayer A, Baca I, Lorenz D, Meister R, Kremer B, Wagner P, Witte J, Zurmayer EL, Saeger H-D, Rieck B, Dollinger P, Glaser K, Teichmann R, Konradt J, Gaus W, Dennler H-J, Welzel D, Beger HG.* Role of octreotide on the prevention of postoperative complications following pancreatic resection. Am J Surg 1992; 163: 125-131.

6 *Biehl T, Traverso LW.* Is stenting necessary for a succesful pancreatic anastomosis? Am J Surg 1992; 163: 530-532.

7 *Kingsnorth AN.* Duct to mucosa isolated Roux loop pancreaticojejunostomy as an improved anastomosis after resection of the pancreas. Surg Gynecol Obstet 1989; 169: 451-453.

8 *Maki HS, Kolts RL, Kuehner, ME.* Prevention of pancreatic fistula by modified pancreaticojejunal anastomosis. Am J Surg 1990; 160: 533-534.

9 *Bismuth H, Franco D.* Long term results of Roux-en-Y hepaticojejunostomy. Surg Gynecol Obstet 1978; 164: 161-167.

10 *Braasch JW, Rossi, RL, Watkins E, Deziel DJ, Winter PF.* Pyloric and gastric preserving pancreatic resection. Ann Surg 1986; 204: 411-418.

11 *Parrilla P, Ramirez P, Sanchez Bueno F, Perez JM, Candel MF, Muelas MS, Robles R.* Long-term results of choledochoduodenostomy in the treatment of choledocholithiasis: assessment of 225 cases. Br J Surg 1991; 78: 470-472.

12 *Genoni M, Decurtins M, Largiadèr F.* Postoperative Komplikationen nach bilidigestiven Anastomosen. Helv Chir Acta 1989; 56: 903-906.

13 *Cameron JL:* Pancreaticoduodenectomy (Pylorus-preserving Whipple Procedure). In Atlas of Surgery, vol. I. B.C. Decker Inc. Toronto, Philadelphia, 1990

14 *Matsumoto Y, Fujii H, Miura K, Inove S, Sekikawa T, Aoyama H, Ohnishi N, Sakai K, Suda K.* Succesful pancreatojejunal anastomosis for pancreatoduodenectomy. Surg Gynecol Obstet 1992; 175: 555-562.

15 *Cameron JL, Pitt HA, Yeo CJ, Lillemoe KD, Kaufman HS, Coleman J.* One hundred and forty-five consecutive pancreaticoduodenectomies without mortality. Ann Surg 1993; 217: 430-438.

Corresponding Author:
Juhani Sand, M.D.
Department of Surgery
Tampere University Hospital
P.O.B. 2000
FIN-33521 Tampere
Finland
Tel: +358-3-2475111
Fax: +358-3-2474358

ORIGINAL ARTICLE

Taylor & Francis
healthsciences

Resection of the Head of the Pancreas in Finland: Effects of Hospital and Surgeon on Short-term and Long-term Results

I. Nordback, M. Parviainen, S. Räty, H. Kuivanen & J. Sand
Dept. of Surgery, Tampere University Hospital, Tampere, Finland

Scand J Gastroenterol Downloaded from informahealthcare.com by University of Tampere on 06/24/10
For personal use only.

Nordback I, Parviainen M, Räty S, Kuivanen H, Sand J. Resection of the head of the pancreas in Finland: effects of hospital and surgeon on short-term and long-term results. Scand J Gastroenterol 2002;37:1454–1460.

Background: To study the effect of hospital volume and surgeon volume on postoperative hospital mortality, morbidity and long-term survival after resection of the head of the pancreas in a nationwide study (case record study), taking into a consideration risk factors found important in series based on experience in one hospital. **Method:** The case record investigation of 374 patients identified from the National Hospital Discharge Database as having undergone resection of the head of the pancreas between 1990 and 1994 in Finland. **Results:** The records of 350 patients were obtained for analysis. Operations were performed in 33 hospitals by 98 surgeons (average 2.1/year/hospital and 0.7/year/surgeon). Hospital mortality was 36/350 (10%), increasing from 4 and 7 to 13% with decreasing hospital volume from >10 and 5–10 to <5 respectively ($P < 0.05$) and increasing from 3 and 10 to 14% with decreasing surgeon volume from >3 and 1–3 to <1, respectively ($P < 0.05$). Most deaths were caused by surgical or technical complications (31/36 = 86%). Besides hospital mortality, postoperative complications, re-operations and hospital stay were also affected by surgeon volume. In the univariate analysis, also the age of the patient had an effect on the hospital mortality, and preoperative biliary stenting on the uncomplicated recovery, but in the multivariate analysis hospital mortality was independently affected by age (OR 0.94, $P = 0.004$) and surgeon volume (OR 1.3, $P = 0.04$), re-operations by surgeon volume (OR 1.10, $P = 0.05$) and hospital volume (OR 1.03, $P = 0.05$), postoperative complications by using the preoperative stent (OR 0.45, $P = 0.02$). Long-term survival was dependent on the histology of the specimen and by uncomplicated recovery, but not by hospital volume or surgeon volume. **Conclusion:** To decrease postoperative morbidity, mortality and hospital stay, pancreatic head surgery needs to be concentrated to only a few hospitals and to a few surgeons.

Key words: Histology; hospital load; morbidity; mortality; pancreas surgery; results; risk factors; surgeon experience; survival; Whipple

Isto Nordback, M.D., Dept. of Surgery, Tampere University Hospital, P.O. Box 2000, FI-33521 Tampere, Finland (fax. +358 3 247 4358, e-mail. isto.nordback@tays.fi)

Resection of the head of the pancreas was originally meant for treatment of periampullary malignancies (1, 2). Although increasing numbers of these operations were done during the 1960s and 1970s, it was suggested that the whole operation should be abandoned because it was accompanied by high postoperative mortality (up to 25%) and very high morbidity (3). Later, during the 1980s and 1990s, better postoperative results were published showing hospital mortality to have decreased in most series below 5%, and in many even to 1–2% (5, 6).

Important factors affecting the early results in individual hospitals have been whether the operation has been made for chronic pancreatitis with or without concomitant malignant disease ('soft versus hard pancreas'), the age of the patient and the preoperative health condition of the patient (7, 8). The long-term results in individual hospitals have been largely dependent on the histology and stage of the malignant disease, possibly accompanied by postoperative adjuvant therapy (9–11).

However, great variations between hospitals have been noticed when statewide or nationwide surveys have been made. These differences probably cannot be explained by the patient-dependent or treatment-dependent variables. In fact, during the past decade, reports have been increasingly published on the effect of hospital annual volume of the resections on the short-term results (Fig. 1).

Hospital volume has been considered an even more important factor than the number of operations carried out by individual surgeons (12). Most of these surveys have been based on the registry data. Case records of individual patients have seldom been studied. It has therefore not been possible to study in detail the risk factors that have been found important in series based on the experience in one hospital. Long-term survival has not been analysed either.

The aim of this study was to investigate the effect of hospital volume and surgeon volume on the short-term and long-term results of resection of the head of the pancreas

© 2002 Taylor & Francis

RIGHTSLINK

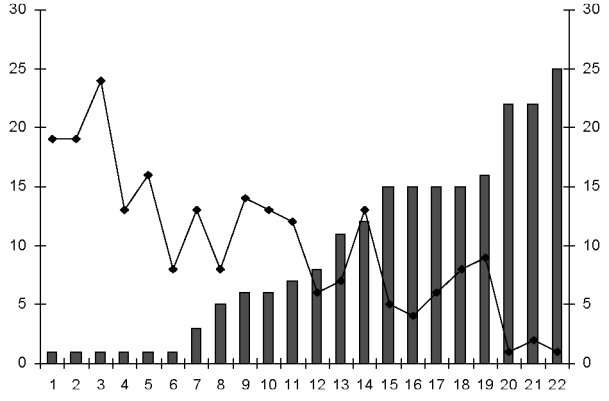

Fig. 1. Hospital mortality in percentages according to the annual number of resections of the head of the pancreas performed in the hospital (references 12–17) (columns = number of resections; line = mortality).

performed in Finland during a 5-year period, taking into account general and disease-specific risk factors.

Methods

The patients for this retrospective analysis were identified from the national hospital discharge database. All public and private hospitals in Finland need to report each patient discharged from hospital after being admitted as an inpatient. This registry contains patient identification data, diagnosis, operations performed and discharge status (dead, alive). To obtain patients who had undergone resection of the head of the pancreas during a 5-year period (1.1.1990 to 31.12.1994), code 6706 in ICD-9 was used. Thereafter, each hospital was visited by one of the investigators, who collected the data from the case records.

The following parameters were recorded as the possible risk factors for results: surgeon, hospital, age of the patient, preoperative illnesses, preoperative palliation, the type of the operation, histological diagnosis, the extent of the disease, adjuvant therapy. The short-term results were based on the postoperative complications, re-operations, hospital stay and hospital mortality.

The long-term results were based on actual 5-year survival assessed using data from the hospital case records and from the National Registry for Causes of Death. This was undertaken after the end of May 2000 to ensure collection of complete information by the end of 1999. The chi-square test, Mann-Whitney U-test, Bonferroni correction and backward stepwise multiple logistic regression analysis were used for statistical calculations, as identified in the Results. The Kaplan-Meier method was used to create the survival curves.

The general permit for the study was obtained from the Ministry of Social and Health Affairs and individual permits to study the case records were obtained from each participating hospital.

Table I. Preoperative illnesses recorded before the operation in 350 patients undergoing the resection of the head of the pancreas

Disease	*n*	%
Previous malignancy	28	8
General arteriosclerosis	20	5.7
Prior myocardial infarction	4	1.1
Prior cerebral infarction	1	0.3
Compensated cardiac insufficiency	4	1.1
High blood pressure, stabile under medication	29	8.3
COPD	3	0.9
Diabetes	9	2.6
Renal insufficiency	1	0.3
Rheumatic disease	4	1.1
Hypothyreosis	2	0.6
Ulcerative colitis	1	0.3
Hepatic cirrhosis	1	0.3
Bronchial asthma	6	1.7
Hyperparathyreosis	1	0.3
MEN 1	2	0.6
Multiple venous thrombosis	2	0.6
Patients with any of the above illnesses but no previous malignancy	67	19

Patients

A total of 374 patients were collected from the discharge database as having had resection of the head of the pancreas during the 5-year study period. Of these, 36 had been discharged dead after having PD during this hospitalization (10%). The case records of 350 patients (94%) obtained for further analysis included those of all 36 patients identified as hospital mortalities according to the discharge database.

There were 182 men and 168 women with a median age of 64 years (range 31–84 years). Table I summarizes the preoperative illnesses. Two-hundred-and-sixteen patients (62%) were jaundiced at the time of diagnosis, and 51 of these (24%) had had either percutaneous transhepatic or endoscopic stent to relieve bile duct obstruction prior to resection.

Most patients (270/350 or 77%) had a standard resection of the head of the pancreas, including partial gastric resection, whereas 76 (22%) had a pylorus-preserving resection of the head of the pancreas and 4 (1%) a duodenum-preserving resection (Beger's resection).

The final histological diagnoses are presented in Table II. None of the resections for malignant diseases were performed with the presence of distant metastases. Margins were studied in only a small proportion of specimens, which is why this could not be recorded. Nodal growth is reported in each histological category in Table II.

Thirty patients (10%) out of the total 292 with a malignant disease had adjuvant therapy after the resection. This included radiotherapy in 7 and chemotherapy in 23. None of the patients had neoadjuvant therapy.

Results

Short-term results

During the study period, the resection of the head of the

Scand J Gastroenterol Downloaded from informahealthcare.com by University of Tampere on 06/24/10
For personal use only.

Scand RIGHTSLINK

Table II. Histology of the specimen and the respective nodal status

Histology	$n = 350$ (%)	Nodal growth
Periampullary malignant tumours		
Pancreatic ductal adenocarcinoma	163 (47)	43/163 (26)
Ampullary adenocarcinoma	81 (23)	21/81 (26)
Bile duct adenocarcinoma	13 (3.7)	2/13 (15)
Duodenal adenocarcinoma	14 (4)	2/14 (14)
Other malignant tumours		
Pyloric adenocarcinoma	4 (1)	3/4 (75)
Pancreatic cystic adenocarcinoma	3 (0.9)	2/3 (67)
Pancreatic oncocytoma	1 (0.3)	
Pancreatic carcinoid tumour	1 (0.3)	
Pancreatic apudoma	1 (0.3)	
Malignant insulinoma	1 (0.3)	
Pancreatic adenosquamous carcinoma	1 (0.3)	
Retroperitoneal liposarcoma	1 (0.3)	
Duodenal leiomyosarcoma	2 (0.6)	
Duodenal Schwannoma	1 (0.3)	
Duodenal carcinoid tumour	1 (0.3)	1/1 (100)
Duodenal mesenchymal tumour	1 (0.3)	
Metastatic renal cell carcinoma	2 (0.6)	½ (50)
Metastatic colonic adenocarcinoma	1 (0.3)	1/1 (100)
Neoplastic benign		
Cystadenoma	6 (1.7)	
Benign pancreatic schwannoma	1 (0.3)	
Benign insulinoma	1 (0.3)	
Glucagonoma	1 (0.3)	
Duodenal adenoma	5 (1.4)	
Tubular adenoma of ampulla Vateri	1 (0.3)	
Duodenal fibroneuroleiomyomatosis	1 (0.3)	
Peutz-Jegher polyp of ampulla Vateri	1 (0.3)	
Non-neoplastic		
Chronic pancreatitis	35 (10)	
Duodenal ulcer		3 (0.9)
Duodenal xantelasma	1 (0.3)	
Duodenal Crohn disease	1 (0.3)	
Benign bile stricture	1 (0.3)	

pancreas was performed in 33 hospitals by 98 surgeons. More than 10 resections annually were performed in only one hospital. The operations were performed in 6 university departments (5 separate universities), 16 central hospitals and 11 district or city hospitals. The most experienced surgeon had performed 24 resections during the 5-year study period. The annual number of hospitals and resections performed per surgeon are summarized in Table III. With this distribution

Table III. Number of hospitals and surgeons according to number of resections of the head of the pancreas performed during the 5-year study period

Total no. of resections during 5-year period	No. of hospitals $n = 33$	No. of surgeons $n = 98$
0–5	13	74
6–10	11	20
11–15	4	1
16–20	1	2
21–30	1	1
31–40	2	
41–50	0	
>50	1	

Table IV. The reason for hospital mortality in the patients who had undergone resection of the head of the pancreas

Reason for death	*n* (%)
Surgical complications	
Leakages	14 (39)
Abscesses/peritonitis/MOF	7 (20)
Hepatic or intestinal necrosis	5 (14)
Intra-abdominal haemorrhage	4 (11)
Gastrointestinal haemorrhage	1 (3)
General complications	
Cardiac or cerebral insults	4 (11)
Unknown reason	1 (3)

we categorized the hospitals for low (average <5 annual resections), medium (average 5–10 annual resections) and high (average >10 annual resections) volume hospitals and low (average <1 annual resections), medium (average 1–3 annual resections) and high (average >3 annual resections) volume surgeons.

Thirty-six patients died during hospitalization, with a hospital mortality of 10%. In addition, one of the patients died during the second hospitalization within 30 days of the operation as a result of complications that had appeared during the first hospitalization. The reasons for death are given in Table IV. Most of the deaths were related directly to surgical complications.

Hospital mortality was related to hospital volume, to surgeon volume and to age of the patient (Table V). Mortality was not dependent on the status of the hospital (data not shown). A total of 66 (19%) patients required a re-operation. Re-operations were also related to hospital volume and to surgeon volume (Table V). Of the 314 patients surviving the resection, 103 (33%) suffered from non-lethal complications (listed in Table VI). Most of the complications were related directly to the surgical procedure. The number of uncomplicated recoveries was related to surgeon volume (Table V). Mean (95% CI) hospital stay of the patients surviving the resection was 26 (24–27) days. In the univariate analysis, this was dependent on hospital volume and also on surgeon volume (Table V).

We conducted a multivariate analysis in order to study the effect of patient age, surgeon volume, hospital volume, preoperative palliation (stent versus no stent) and histological diagnosis (pancreatic ductal adenocarcinoma versus others) (i.e. those with significant effect in the univariate analysis) on hospital mortality, re-operation and complications (Table VII). This demonstrated that younger age of the patient decreased the likelihood of hospital mortality (OR = 0.94, $P = 0.004$). Low annual surgeon volume increased hospital mortality and need for re-operation. Low annual hospital volume increased re-operations. Patients who had undergone preoperative stenting of the biliary tract had significantly fewer complications. Another analysis was done including only clinically jaundiced patients. This again indicated a significant association between stent and postoperative

Scand J Gastroenterol Downloaded from informahealthcare.com by University of Tampere on 06/24/10
For personal use only.

RIGHTSLINK

Table V. Mortality, re-operations and recovery after resection of the head of the pancreas

	Hospital mortality *n* (%)	Re-operation *n* (%)	Uncompl. recovery *n* (%)	Hospital stay (survivors) in days median (range)
Hospital volume				
Low (<5)	26/201 (13)*	43/201 (21)*	119/201 (59)	23 (8–100)**
Medium (5–10)	8/93 (7)	18/93 (19)	55/93 (59)	23 (7–81)**
High (>10)	2/56 (4)*	5/56 (9)*	40/56 (71)	18 (8–58)**
Surgeon volume				
Low (<1)	18/125 (14)*	28/125 (22)*	72/125 (58)*	24 (9–70)**
Medium (1–3)	16/164 (10)	33/164 (20)*	96/164 (59)*	23 (7–100)**
High (>3)	2/61 (3)*	5/61 (8)*	46/61 (75)*	18 (8–63)**
Age of the patient				
<60 years	5/122 (4)*	23/122 (19)	78/122 (64)	22 (8–81)
≥60 years	31/228 (14)*	43/228 (19)	136/228 (60)	23 (7–100)
Preoperative illnesses				
Yes	19/185 (10)	38/185 (21)	113/185 (61)	26 (24–28)
No	17/165 (10)	28/165 (17)	101/165 (61)	26 (24–28)
Histology				
Chronic pancreatitis	4/35 (11)	6/35 (17)	22/35 (63)	19 (8–52)
Pancreatic ductal adenoca	21/163 (13)	27/163 (17)	104/163 (64)	24 (9–100)
Other	11/152 (7)	33/152 (22)	88/152 (58)	22 (7–70)
Preoperative palliation				
Stent	4/51 (8)	5/51 (10)	39/51 (77)*	23 (7–100)
No stent	32/299 (11)	61/299 (20)	175/299 (59)*	22 (7–70)
Operation				
Stardard PD	28/270 (10)	54/270 (20)	162/270 (60)	23 (7–100)
Pylorus preserving	7/76 (9)	12/76 (16)	49/76 (65)	22 (9–70)
Duodenum preserving	1/4 (25)	0/4 (0)	3/4 (75)	16 (10–34)

* $P < 0.05$ (chi-squared test), ** $P < 0.05$ (Bonferroni correction).

Scand J Gastroenterol Downloaded from informahealthcare.com by University of Tampere on 06/24/10
For personal use only.

complications in favour of stent (Table VIII). The goodness of fit (Hosmer and Lemeshow test) in the backward multivariate analysis was good (hospital mortality ($P = 0.91$), re-operations ($P = 0.50$), complications ($P = 0.63$)).

Long-term results

Fifty-five of the 271 (20%) patients with periampullary adenocarcinoma survived more than 5 years. This did not differ in relation to hospital (Fig. 1) or surgeon volume (data not shown). Actual 5-year survival was 12% (20/163) in pancreatic ductal adenocarcinoma, 33% (27/81) in ampullary adenocarcinoma, 31% (4/13) in distal bile duct adenocarcinoma and 43% (6/14) in duodenal adenocarcinoma. The various parameters could be studied only in pancreatic ductal adenocarcinoma and ampullary adenocarcinoma with sufficient number of patients. Table VIII indicates that 5-year survival was not dependent significantly on hospital volume, surgeon volume, type of operation, preoperative stenting in pancreatic ductal adenocarcinoma or ampullary adenocarcinoma in the univariate analysis (Table VIII) or in the multivariate analysis (data not shown). Pancreatic ductal adenocarcinoma patients with uncomplicated recovery had better survival than the patients who had suffered from postoperative complications (Table IX).

Table VI. Postoperative complications after resection of the head of the pancreas in the patients surviving the operation (numbers in parentheses are percentages)

Complications related directly to the resection of the head of the pancreas	
Delayed gastric emptying	72 (23)
Leakage of anastomosis	53 (17)
Pancreatic fistula	46 (15)
Intra-abdominal abscess	45 (14)
Wound infection	42 (13)
Hyperglycaemia	19 (6)
GI-bleeding	17 (5)
Intra-abdominal bleeding	11 (4)
Acute pancreatitis	9 (3)
Cholangitis	2 (0.6)
General surgical complications	
Urinary infection	37 (12)
Pneumonia	35 (11)
Cardiac insufficiency	9 (3)
Urinary retention	4 (1)
Myocardial infarction	3 (1)
Pulmonary embolus	1 (0.3)
Low limb thrombosis	1 (0.3)

Non-lethal complications occurred in 103 patients out of 314 survivors (33%).

Discussion

In studying nationwide results on any disease, national registries are needed. In Finland, the conditions are favourable for performance this kind of study, because the hospital discharge database has proved reliable (18). The current study is a retrospective one, but unlike many other nationwide studies this one included the analysis of case records identified from the discharge database. To obtain actual rather than actuarial 5-year survival rates, the study period was chosen so that the status of all the operated patients could be checked 5

RIGHTSLINK

Table VII. The effect of age, surgeon volume, hospital volume, preoperative palliation and histology on the hospital mortality, re-operations and complications

	Hospital mortality		Re-operations		Complications	
	*P**	OR**	*P**	OR**	*P**	OR**
Age	0.004	0.94 (0.91–0.98)	0.90	1.00 (0.98–1.03)	0.69	1.01 (0.99–1.03)
Surgeon volume	0.04	1.30 (0.94–1.80)	0.05	1.10 (0.88–1.35)	0.11	0.92 (0.79–1.08)
Hospital volume	0.12	0.97 (0.85–1.10)	0.05	1.03 (0.93–1.14)	0.19	1.02 (0.94–1.10)
Stent	0.52	1.60 (0.5–5.10)	0.08	1.83 (0.66–5.04)	0.02	0.45 (0.22–0.94)
Chr. pancr/ductal adenoca	0.10	0.51 (0.24–1.10)	0.30	1.28 (0.74–2.21)	0.30	0.82 (0.53–1.27)

* Stepwise multiple logistic regression analysis. ** Odds ratio (95% confidence interval).

Scand J Gastroenterol Downloaded from informahealthcare.com by University of Tampere on 06/24/10
For personal use only.

years later. Thus, until prospective nationwide surveys are performed, the current study provides the best possible approach to the question.

We found that after resection of the head of the pancreas the immediate postoperative results, but not long-term survival, was associated with the number of operations performed in that hospital. This is not unexpected, since the impact of experience on the surgical results has been stressed for decades. Scientific proof supporting such opinions has been published, but not until during the last decade of the resection of the head of the pancreas. In this operation, hospital mortality has been used as a simple and readily defined scale of crude medical quality. As presented in Fig. 1, hospital mortality decreases from 8%–24% to 1%–2% when the annual number of operations in a hospital increases from 1–5 to over 20. The present results (mortalities 4%, 7% and 13% in over 10, 5–10 and fewer than 5 annual operations) fit well within the range of the previous studies.

An obvious explanation for the better results according to increased patient load would be better facilities. However, hospital status (university dept., central hospital or other) did not significantly affect the result; there were also university depts. with poorer results. It was the load, not the status that was important.

One possibility is that the larger patient load allows better concentration of these operations to few pancreatobiliary surgeons; this has been considered important for more than 10 years now (6). In hospitals with fewer pancreatic head resections, the alimentary tract surgeons may need to carry out the whole repertoire of general and alimentary tract surgery. In fact, our study showed that 98 surgeons performed the 350 analysed operations, giving an average annual number of operations of <1. Such a low figure could easily explain the different results according to hospital volume supported by the finding that surgeon volume was another important parameter affecting hospital mortality.

The explanation often offered by the low volume surgeons themselves for the variant results is that the patients, diseases and preoperative methods of treatment were different, thus affecting the results. Our study showed that all of the following parameters were associated with the postoperative results: age of the patient, hospital volume, surgeon volume and preoperative palliation. We could not find a significant effect of the preoperative illnesses, possibly because the most diseased patients had been excluded from the operation. However, when the effect of independent variables was extracted by multivariate analysis, patient age, hospital

Table VIII. The effect of preoperative use of biliary stent ($n = 51$) compared to no stent ($n = 165$) on the postoperative complications, re-operations and mortality in clinically jaundiced patients

	Stent $n = 51$ *n* (%)	No stent $n = 165$ *n* (%)	*P* (chi square)
Complications	12 (24)	67 (41)	0.03
Re-operations	5 (10)	36 (22)	0.06
Mortality	4 (8)	20 (12)	0.40

Table IX. Actual 5-year survival in patients with pancreatic ductal adenocarcinoma or ampullary adenocarcinoma according to the various operative conditions. Numbers in parentheses are percentages

	Pancreatic ductal adenocarcinoma $n = 163$	Ampullary adenocarcinoma $n = 81$
Hospital volume		
Low (<5)	10/94 (11)	20/64 (31)
Medium (5–10)	6/43 (14)	5/9 (56)
High (>10)	4/26 (15)	2/8 (25)
Surgeon volume		
Low (<1)	8/65 (12)	8/30 (27)
Medium (1–3)	8/74 (11)	15/42 (36)
High (>3)	4/24 (17)	4/9 (44)
Preoperative palliation		
Stent	6/32 (19)	2/8 (25)
No stent	14/131 (11)	25/73 (34)
Operation		
Standard PD	14/123 (11)	21/64 (33)
Pylorus preserving	4/40 (10)	6/17 (35)
Adjuvant therapy		
Yes	1/19 (5)	1/8 (13)
No	19/144 (13)	26/73 (36)
Uncomplicated recovery		
Yes	19/104 (18)*	17/52 (33)
No	1/59 (2)*	10/29 (34)
Nodal tumour growth		
Yes	3/44 (7)	3/21 (14)
No	17/119 (14)	22/60 (37)

* $P = 0.002$, chi-squared test.

RIGHTSLINK

volume, surgeon volume and preoperative stent became important. This is contrary to some previous studies (19), where an increased number of intra-abdominal and wound infections was observed, resulting in a longer hospital stay. One explanation for the difference could be that in our study the use of stent was selective (24% of jaundiced patients). Furthermore, it is not known in this retrospective study how many could have been withdrawn from any surgery because of stent complications.

What were the mistakes of non-experienced surgeons? Firstly, the reasons for death suggested vascular damage resulting in intestinal or liver necrosis. One could hypothesize, for example, undetected right replaced hepatic artery and difficulties in separating the uncinate process from the superior mesenteric artery. Postoperative haemorrhage suggests inadequate preparation techniques, and numerous lethal complications could be associated with pancreaticojejunal anastomosis, which on the one hand is the most vulnerable site for complications also in the case of the experienced pancreatic surgeon, but on the other hand should seldom result in the death of the patient. Thus, the more experienced the surgeon the better the immediate surgical results. In this study, however, only one or two surgeons had the expertise that is internationally accepted.

Why was hospital volume also an important independent nominator of short-term results, and not just via surgeon volume? When surgeon volume was associated with complications, re-operations and mortality, hospital volume was associated only with re-operations. This could be explained by saying that mortality and re-operation depend on the surgeon's skills, but that re-operation is more dependent on the 'hospital skills'. The term 'hospital skills' does not relate to status of the institution (university, central, other), since this was not associated with mortality. One could simply assume that in a hospital with a greater load of these patients the surgeon on call could recognize threatening complications that required intensive care, appropriate radiological examination and intervention, and have the possibility to consult an experienced pancreatic surgeon. There is therefore a strong need to concentrate these operations not just to a few surgeons but also to just a few hospitals. When taking into account the present and previous studies, more than 10, preferably more than 20, operations annually are needed if there is to be sufficient immediate medical quality to satisfy the patient. In Finland, if during this study period the operations had been concentrated within one department of each of the five university hospitals, and mortality had remained at the same 4% level as during the study period in the only hospital with over 10 annual operations (Tampere University Hospital), 14 patients would have died postoperatively compared to 36 in the current analysis, giving a saving of 22 avoidable postoperative deaths.

The long-term results (actual 5-year survivals) were not significantly associated with the surgeon or hospital experience, but only with the histology. This is contrary to what has been suggested for example by colorectal surgeons (19). In the current study, 5-year survival was better in the patients with uncomplicated postoperative recovery, giving rise, in neither univariate nor multivariate analysis, to better survival according to surgeon or hospital volume. Also, in a further analysis of ESPAC-1 trial, postoperative complications were not significantly associated with long-term survival (21). It is possible that the other important parameters affecting survival, i.e. histology, nodes and margins that could not be restudied in this retrospective analysis, would have masked any volume effects on survival. On the other hand, although

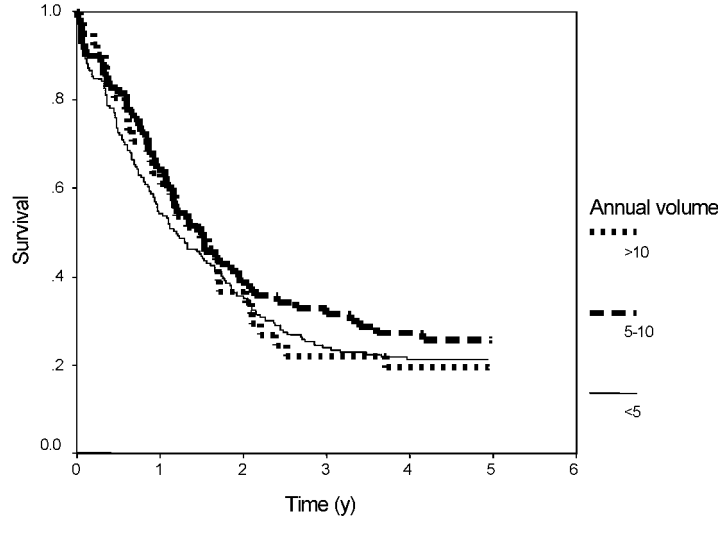

Fig. 2. The effect of annual hospital volume on the actual 5-year survival of 271 patients undergoing resection of the head of the pancreas for periampullary carcinoma (mass around the head of the pancreas the final histology being ductal adenocarcinoma, ampullary adenocarcinoma, distal bile duct adenocarcinoma or duodenal adenocarcinoma).

Scand J Gastroenterol Downloaded from informahealthcare.com by University of Tampere on 06/24/10
For personal use only.

Scand RIGHTSLINK

the effect of experience on long-term survival was not seen in this study, it cannot reliably be ruled out according to the present results.

Acknowledgements

Pirkanmaa Hospital District foundation for financial support to Dr. Parviainen and to Dr. Räty; Pekka Rissanen from STAKES for providing the data from the National Hospital Discharge Database and Heini Huhtala for statistical consultation.

References

1. Whipple AO, Parsons WB, Mullens CR. Treatment of carcinoma of the ampulla of vater. Ann Surg 1935;102:763–76.
2. van Heerden JA, McIlrath DC, Dozois RR, Adson MA. Radical pancreatoduodenectomy: a procedure to be abandoned? Mayo Clin Proc 1981;56:601–6.
3. Barnes SA, Lillemoe KD, Kaufman HS, Sauter PK, Yeo CJ, Talamini MA, et al. Pancreaticoduodenectomy for benign disease. Am J Surg 1996;171:131–5.
4. Howard JM. Pancreatico-duodenectomy: 41 consecutive Whipple resections without an operative mortality. Ann Surg 1968; 168:629–40.
5. Tarazi RY, Hermann RE, Vogt DP, Hoerr SO, Esselstyn CB Jr., Cooperman AM, et al. Results of surgical treatment of periampullary tumors: a thirty-five-year experience. Surgery 1986; 100:716–23.
6. Kairaluoma MI, Stahlberg M, Kiviniemi H. Pancreatic resection for carcinoma of the pancreas and the periampullary region. A twenty-year experience. HPB Surg 1990;2:57–66.
7. Balcom JH 4th, Rattner DW, Warshaw AL, Chang Y, Fernandez-de Castillo C. Ten-year experience with 733 pancreatic resections: changing indications, older patients, and decreasing length of hospitalization. Arch Surg 2001;136:391–8.
8. Porter GA, Pisters PW, Mansyur C, Bisanz A, Reyna K, Stanford PJE, et al. Cost and utilization impact of a clinical pathway for patients undergoing pancreaticoduodenectomy. Ann Surg Oncol 2000;7:484–9.
9. Sohn TA, Yeo CJ, Cameron JL, Koniaris L, Kaushal S, Abrams RA, et al. Resected adenocarcinoma of the pancreas: 616 patients: results, outcomes, and prognostic indicators. J Gastrointest Surg 2000;4:567–79.
10. Sperti C, Pasquali C, Piccoli A, Pedrazzoli S. Survival after resection for ductal adenocarcioma of the pancreas. Br J Surg 1996;83:625–31.
11. Yeo CJ, Sohn TA, Cameron JL, Hruban RH, Lillemoe KD, Pitt HA. Periampullary adenocarcinoma: analysis of 5-year survivors. Ann Surg 1998;227:821–31.
12. Sosa JA, Bowman HM, Gordon TA, et al. Importance of hospital volume in the overall management of pancreatic cancer. Ann Surg 1998;228:429–38.
13. Gordon TA, Burleyson GP, Tielsch JM, Cameron JL. The effects of regionalization on cost and outcome for one general high-risk surgical procedure. Ann Surg 1995;221:43–9.
14. Lieberman MD, Kilburn H, Lindsey M, Brennan MF. Relation of perioperative deaths to hospital volume among patients undergoing pancreatic resection for malignancy. Ann Surg 1995;222: 638–45.
15. Begg CB, Cramer LD, Hoskins WJ, Brennan MF. Impact of hospital volume on operative mortality for major cancer surgery. JAMA 1998;280:1747–51.
16. Gouma DJ, van Geenen RC, Van Gulik TM, de Haan RJ, De Wit LT, Busch OR, et al. Rates of complications and death after pancreaticoduodenectomy; risk factors and the impact of hospital volume. Ann Surg 2000;232:786–95.
17. Edge SB, Schmieg RE Jr, Rosenlof LK, Wilhelm MC. Pancreas cancer resection outcome in American University centers in 1989–1990. Cancer 1993;71:3502–8.
18. Poikolainen K. Accuracy of hospital discharge data: five alcohol related diseases. Drug Alcohol Depen 1983;12:315–22.
19. Heslin MJ, Brooks AD, Hochwald SN, Harrison LE, Blumgart LH, Brennan MF. A preoperative biliary stent is associated with increased complications after pancreatoduodenectomy. Arch Surg 1998;133:149–54.
20. Fielding LP. Surgeon-related variability in the outcome of cancer surgery. J Clin Gastroenterol 1988;10:130–2.
21. Neoptolemos JP, Stocken DD, Dunn JA, Bassi C, Dervenis C, Fernandez-Cruz L, et al. Influence of the type of surgery and surgical complications in the ESPAC-1 adjuvant trial. Pancreatology 2002;2:328.

Received 15 April 2002
Accepted 27 September 2002

Scand J Gastroenterol Downloaded from informahealthcare.com by University of Tampere on 06/24/10
For personal use only.

RIGHTSLINK

Scandinavian Journal of Gastroenterology, 2007; 42: 263–270

informa
healthcare

ORIGINAL ARTICLE

Obstructed pancreaticojejunostomy partly explains exocrine insufficiency after pancreatic head resection

ISTO NORDBACK[1], MICKAEL PARVIAINEN[1], ANNELI PIIRONEN[2], SARI RÄTY[1] & JUHANI SAND[1]

[1]*Department of Gastroenterology and Alimentary Tract Surgery, and* [2]*Department of Diagnostic Radiology, Tampere University Hospital, Tampere, Finland*

Scand J Gastroenterol Downloaded from informahealthcare.com by University of Tampere on 06/24/10
For personal use only.

Abstract

Objective. The majority of patients with long-term survival after pancreatic head resection suffer from pancreatic exocrine insufficiency. The objective of this study was to investigate whether this is due to glandular malfunction or obstructed pancreaticojejunal anastomosis. ***Material and methods.*** Twenty-six patients (10 M, 16 F, mean age 61 years, range 34–81 years) were re-examined a median of 52 months (range 3–76 months) after pancreatic head resection and end-to-end invaginated pancreaticojejunostomy. Pancreatic exocrine function was measured by fecal elastase-1 assay. The size of the pancreatic remnant, glandular secretion and the flow through the anastomosis were analyzed with secretin-stimulated dynamic magnetic resonance pancreatography (D-MRP). ***Results.*** All patients had pancreatic exocrine insufficiency, 24 (92%) of them having severe insufficiency. Eighteen patients (69%) reported moderate to severe diarrhea. Lowest fecal elastase-1 concentrations were associated with the initial diagnosis of chronic pancreatitis or ductal adenocarcinoma, suggesting preoperative primary or secondary chronic pancreatitis as important determinants. The size of the remnant gland did not correlate with the fecal elastase-1 concentrations. D-MRP failed in three patients. Severe glandular malfunctions were found in 7 (30%) of the 23 successful D-MRP examinations. The anastomosis was totally obstructed in 5 patients (22%) or partially obstructed in 6 (26%) but remained perfectly open in 5 patients (22%). The five patients with perfect anastomoses had the highest measured median fecal elastase-1 activity. ***Conclusions.*** Although late diarrhea and pancreatic exocrine insufficiency may be partly induced already by the disease treated with resection, at least half may be explained by obstructed anastomosis. To obtain better late functional results, improvements may be required in the surgical techniques.

Key Words: *Exocrine function, late complications, long-term follow-up, pancreas surgery, pancreatic insufficiency, pancreaticojejunostomy, Whipple operation*

Introduction

Along with the decrease in hospital mortality after pancreaticoduodenectomy, the indications for this operation have become more liberal and include a variety of diseases with considerable long-term survival [1]. The patients, however, often lose weight, have an increased number of daily bowel movements, and frequently need pancreatic enzyme supplementation [2], all of which reduces their quality of life [3,4]. Surprisingly, however, the mechanisms of reduced pancreatic exocrine function after pancreatic resection have scarcely been studied.

The overall exocrine pancreatic function depends on the pancreatic stimulus [5–8], the amount and the functional reserves of the pancreatic remnant, and on the pancreatic duct outflow. Pancreatic exocrine function tests, such as the N-benzoyl-1-tyrosyl-p-aminobenzoic acid (NBT-PABA) test, or the more sensitive and specific fecal elastase-1 assay, both of which are frequently employed because they are easy to use [9–11], cannot differentiate between ductal (obstructed anastomosis) or parenchymal (amount of tissue, tissue secretion capacity) etiology.

Correspondence: Isto Nordback, MD, Division of Surgery, Gastroenterology and Oncology, Tampere University Hospital, P.O. Box 2000, FIN-33521 Tampere, Finland. Tel: +358 3 3116 4608. Fax: +358 3 3116 4358. E-mail: isto.nordback@pshp.fi

(Received 2 January 2006; accepted 8 June 2006)

ISSN 0036-5521 print/ISSN 1502-7708 online © 2007 Taylor & Francis
DOI: 10.1080/00365520600849174

RIGHTSLINK

Some investigators have considered that the drainage of the remnant pancreas into the stomach results in good long-term functioning of the anastomosis [12], whereas others have observed less pancreatic insufficiency after drainage into the jejunum [3]. Pancreaticogastrostomy has been investigated to a greater extent [12,13] than pancreaticojejunostomy because of its easier access.

The visualization of the pancreatic secretion through pancreaticojejunostomy became possible after the introduction of secretin-stimulated dynamic magnetic resonance pancreatography (D-MRP) [14], also applied postoperatively [15–18]. Although pancreatic insufficiency can be satisfactorily treated with enzyme supplementation independent of the etiology, a better understanding of the mechanism of the insufficiency might help in its prevention. The aim of this study was to investigate whether the pancreatic exocrine insufficiency late after pancreatic head resection is due to the obstructed anastomosis or poor parenchymal secretion.

Material and methods

Twenty-six patients who had undergone invaginated end-to-end pancreaticojejunostomy were included in the study. The operation was performed in each case by I.N. or J.S. in Tampere University Hospital. Sixteen long-term survivors participated, with a median follow-up of 55 months after the operation. In order to evaluate the observation time on the anastomosis, the last nine survivors who had fully recovered from the operation, and who were not part of any other studies or receiving any adjuvant therapy and who did not have any known metastasis, were also asked to participate; which they did. The median follow-up of these patients was 4 months.

The study comprised 10 men and 16 women with a mean age of 61 years (range 34–81 years) at the time of the operation. Not unexpectedly, the final histology showed that a majority of the patients had had benign or non-aggressive malignant disease (Table I). Fifteen patients had undergone pylorus-preserving pancreaticoduodenal resection and 6 patients had had pancreaticoduodenal resection with antrectomy. When duodenum-preserving pancreatic head resection had been undertaken (5 patients), the Beger-type of resection with pancreatic transsection was used with pancreatic body–jejunal anastomosis, which was similar to the other types. The pancreaticojejunostomy was always an end-to-end invaginated telescopic two-layer anastomosis with six to eight inner layer stitches going through the entire pancreas and the pancreatic duct wall [19].

Table I. The extent of the gastroduodenal resection during pancreatic head resection in various pathologies.

Chronic pancreatitis	9
Pancreatic ductal adenocarcinoma	6
Bile duct adenocarcinoma	2
Duodenal adenocarcinoma in papilla	3
Pancreatic islet cell carcinoma	1
Mucinous cystadenoma	1
Serous cystadenoma	4
Overall	26

During the operation, the surgeon assessed the pancreatic duct diameter according to one of three categories (small, when below 3 mm, normal, between 3 and 5 mm, and wide when over 5 mm), and the pancreatic parenchyma as one of two categories (normal or hard). Nine patients (35%) had small ducts, 5 patients (19%) had normal ducts and 12 patients large ducts (46%). Twelve patients (46%) had normal pancreatic parenchyma and 14 (54%) a hard pancreas. Because of the retrospective nature of the study the patients did not undergo routine pancreatic function studies prior to the operation.

A complication of the pancreatic head resection occurred because of a leakage from the anastomosis in five patients (19%) overall. The criterion used for leakage was fluid accumulation from the abdominal drain of 50 ml or more with amylase activity of over 1000 U/l (normal serum amylase <300 U/l) on postoperative day 5 or later. In two patients (8%) this leakage was symptomatic: an abscess requiring percutaneous drainage in one patient and acute pancreatitis treated conservatively in the other. After the initial postoperative stay and one visit in the specialist health-care unit, the patients were placed under surveillance in the basic health-care unit.

As part of the study the patients were re-examined 3–76 months (median 52 months) after the pancreatic head resection by M.P. The disease history during the follow-up did not include pancreatitis, bile obstruction or tumor recurrence.

To correlate the D-MRP findings with the current exocrine function, the patients were asked about their experience of the degree of diarrhea using a visual analogue scale, where 0 represented no diarrhea and 10 represented "the worst imaginable diarrhea". According to a test on a few pilot patients, 0–1.0 was considered minimal diarrhea, 1.1–4.0 moderate diarrhea and >4.0 as severe diarrhea. If the patients indicated, for example, a score of 5, they explained that this severely affected their quality of life, although they could imagine an even worse degree of diarrhea. Previous prescription of any enzyme preparations was recorded. Pancreatic function was measured by analyzing the fecal elastase-1 concentration with a commercial ELISA using an

Scand J Gastroenterol Downloaded from informahealthcare.com by University of Tampere on 06/24/10
For personal use only.

RIGHTSLINK

antibody highly specific for human enzyme. A fecal elastase-1 concentration >200 μg/g was considered normal, 100–200 μg/g moderate and <100 μg/g severe exocrine pancreatic insufficiency. Preoperative data of the pancreatic function with fecal elastase-1 measurement was not available.

The pancreatic glandular size was studied from transverse sections obtained with magnetic resonance imaging (MRI). The glandular and ductal responses on secretin stimulation and the ductal morphology were studied with D-MRP. This was done with a 1.5T magnet (Signa Horizon, GE Medical Systems, Milwaukee, Wisc., USA) with a phased-array torso coil. Fat saturated T2-weighted Fast Spin Echo (20 slices 8 mm each with a 2-mm gap, TR 4650 ms, TE 96 ms) and T1-weighted Spin Echo (20 slices 8 mm each with a 2-mm gap, TR 360–440, TE 10 ms) sequences were first obtained in the axial plane to assess the position and morphology of the pancreas, followed by the heavily T2-weighted fat saturated Single Shot Fast Spin Echo (SSFSE) sequence (9 slices 20 mm each with an 0-mm gap, TR 22750 ms, TE 959 ms, acquired during an 23-s breath-hold) radial in the coronal plane, without secretin and repeatedly at a 1-min interval up to 9 min after the injection of 100 IU secretin pentahydrochloride (Secrelux®; Sanochemia Diagnostics, Neuss, Germany).

For interpretation of the results, the previously used dynamic secretin-stimulated D-MRP categories originally developed for the intact pancreas were used (Table II) [14]. An experienced gastrointestinal radiologist (A.P.) interpreted the D-MRP images without knowing the other data. When the size of the remnant pancreas was assessed from the MRI transverse sections, each remnant of pancreas was categorized as small, moderate or large, taking into consideration both the resection line and the atrophy/hypertrophy of the remnant gland. None of the patients demonstrated residual or recurrent tumor growth in the MRI.

In the statistical analysis, the chi-square test, the Fisher exact test and the Mann-Whitney U-test were used for univariate analysis. A logistic regression model (forward stepwise) was used for multivariate analysis. Correlations were evaluated by calculating the correlation coefficient. The study was approved by the Ethics Committee of Tampere University Hospital.

Results

Pancreatic insufficiency

Sixteen patients had fecal elastase-1 concentration below the limit of the sensitivity of the assay (15 μg/g). Eight patients had a fecal elastase-1 concentration below 100 μg/g. Thus 24 patients (92%) overall had severe pancreatic exocrine insufficiency, as assessed by fecal elastase-1 assay. The two remaining patients had moderate pancreatic insufficiency.

The diagnosis of chronic pancreatitis or pancreatic ductal adenocarcinoma was significantly associated with the most decreased fecal elastase-1 concentration, whereas, for example, the postoperative leakage of the anastomosis was not.

The median severity of diarrhea was 2.2 (range 0–9.4) on a scale of 0–10. Eight patients (31%) had minimal diarrhea, 12 patients (46%) had moderate diarrhea and 6 patients (23%) reported severe diarrhea. Seven patients (27%) used enzyme supplementation. One of these seven patients still suffered from severe diarrhea.

According to the univariate analysis, the patients experienced more severe diarrhea if the operation had been performed more than three years earlier, if the primary diagnosis had been chronic pancreatitis, if the gland had been considered hard with a small duct, and if the duodenum was preserved (Table III). It is worth bearing in mind that postoperative leakage in the pancreaticojejunal anastomosis did not affect the degree of diarrhea

Table II. D-MRP grading of the pancreatic secretory function.

Grade	Finding	Interpretation
Grade 0	Impossible to evaluate owing to excessive intestinal fluid	Discharged from analysis
Grade 1	No secretion into the jejunum, pancreatic duct not visible	Glandular malfunction
Grade 2	No secretion into the jejunum, pancreatic duct visible but remains large	Total obstruction in the anastomosis
Grade 3	Secretion into the jejunum detected, pancreatic duct visible but remains large	Partial obstruction in the anastomosis
Grade 4	Secretion into the jejunum detected, pancreatic duct visible, diameter changes with secretin stimulus	Normal glandular function and open anastomosis

Abbreviation: D-MRCP = dynamic magnetic resonance pancreatography.

Scand J Gastroenterol Downloaded from informahealthcare.com by University of Tampere on 06/24/10
For personal use only.

RIGHTSLINK

Table III. Severity of diarrhea and pancreatic exocrine function (assessed by fecal elastase-1 assay) in the patients who have undergone pancreatic head resection.

				Diarrhea[a]			Fecal elastase (μg/g)[b]	
	n	Med (range)	Min.	Mod.	Sev.	Med (range)	Below the limit	Measured value
Men	10	3.7 (1–9.4)	2	3	5	<15 (<15–146)	6	4
Women	16	1.6 (0–9.0)	7	6	3	<15 (<15–234)	10	6
Age								
<60 years	12	2.7 (1.0–9.4)	2	5	5	<15 (<15–234)	8	4
≥60 years	14	1.5 (0–9.0)	7	4	3	<15 (<15–44)	8	6
Resected								
<36 months ago	9	1.0 (1.0–9.0)	6	1	2[c]	<15 (<15–146)	7	2
>36 months ago	17	3.0 (0–9.4)	3	8	6	<15 (<15–234)	9	8
Chronic pancr.	9	4.4 (0–9.4)	1	3	5	<15 (<15–234)	5	4
Ductal adenocacinoma	6	2.5 (1.0–9.0)	3	1	2	<15 (all)	6	0
Other	11	1.2 (0–4.1)[d]	5	5	1	16 (<15–146)[e]	5	6
Small duct	9	1.0 (0–3.0)[f]	5	4	0	21 (<15–146)	4	5
Normal duct	5	3.0 (1–9.4)	2	1	2	<15 (<15–16)	4	1
Large duct	12	4.2 (0–9.0)	2	4	6	<15 (<15–234)	8	4
Normal gland	12	1.0 (0–9.0)[g]	7	3	1[h]	16 (<15–146)	6	6
Hard gland	14	4.1 (1.0–9.4)	2	5	7	<15 (<15–246)	10	4
Pancr. complic.								
None	21	2.0 (0–9.4)	7	8	6	<15 (<15–234)	13	8
Fistula	5	2.4 (1.0–8.0)	2	1	2	<15 (<15–44)	3	2
Pancreatic remnant size								
Small	8	1.3 (0–9.0)	3	2	3	<15 (<15–78)	5	3
Moderate	10	3.0 (1.0–8.2)	2	5	3	<15 (<15–44)	7	3
Large	8	4.0 (1.0–9.0)	3	2	3	23 (<15–234)	4	4

[a]Visual analogue scale 0–10. Median (range); [b]fecal elastase-1 concentration (μg/g) median (range); [c]chi-square $p=0.037$; [d]Mann-Whitney U-test $p=0.043$ chronic pancr. versus other; [e]Mann-Whitney U-test $p=0.034$ ductal adenocarcinoma versus other; [f]Mann-Whitney U-test $p=0.012$ small duct versus large duct; [g]Mann-Whitney U-test $p=0.008$; [h]chi-square $p=0.023$.

Scand J Gastroenterol Downloaded from informahealthcare.com by University of Tampere on 06/24/10
For personal use only.

experienced. In the multivariate analysis the only independent risk factor for developing severe diarrhea was the hard parenchyma ($p=0.02$, odds ratio = 16; 95% CI 1.5–166).

Magnetic resonance imaging of the pancreatic remnant in transverse sections (MRI)

The size of the remnant gland (Figure 1A, 2A) was not significantly associated with the experienced diarrhea or the measured fecal elastase-1 concentration.

Dynamic secretin-stimulated magnetic resonance pancreatography (D-MRP)

The D-MRP results of three patients (12%) were eliminated from further analysis owing to the excessive fluid in the intestine that was already there before the secretin dose, therefore rendering the interpretation impossible (Grade 0). Out of the 23 successful D-MRP examinations, 7 (30%) showed severe glandular malfunction (Grade 1) which did not allow the evaluation of the anastomosis, because not enough fluid accumulated in the duct. The anastomosis could thus be evaluated in 16 patients. Five patients (22%) showed total obstruction of the anastomosis (Grade 2) (Figure 1B–D), 6 (26%) showed partial obstruction (Grade 3) and in 5 patients their anastomoses (22%) were considered fully open (Grade 4) (Figure 2B–D).

The 23 patients with informative D-MRP examinations were further analyzed to determine whether diarrhea and fecal elastase-1 activity correlated with the glandular or anastomotic malfunction. The patients with severe glandular malfunction (Grade 1) did not differ significantly in the reported diarrhea or measured fecal elastase-1 compared with patients with ductal malfunction (Grades 2–3), whereas the patients showing normal postoperative pancreatic secretion in the D-MRP (Grade 4) had the highest measured median fecal elastase-1 concentration (68 μg/g).

Finally, factors associated with either glandular or anastomotic malfunction were analyzed (Table IV). The Fisher exact test demonstrated none of the study parameters to be significantly associated with the

RIGHTSLINK

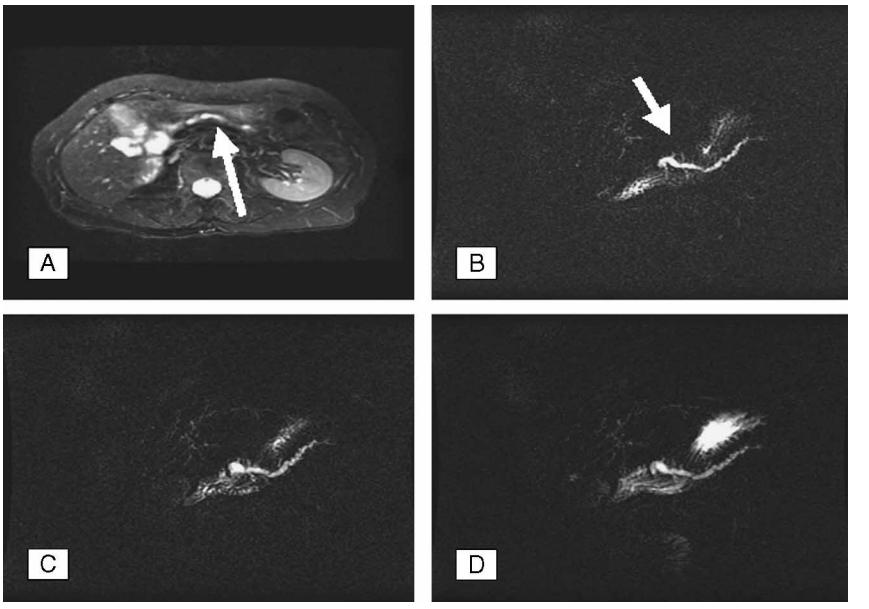

Figure 1. A. T2-weighted fat-saturated axial image of a patient with atrophic pancreatic remnant parenchyma (*arrow*). T2-FSSE dynamic magnetic resonance pancreatography (D-MRP) without (B) as well as at 4 min (C) and at 9 min (D) after i.v. secretin injection shows large duct and side branches (*arrow*) throughout the study with no fluid accumulation into the jejunum, indicating malfunction of the anastomosis (Grade 2).

glandular malfunction in the univariate analysis. Patient age over 60 years at the time of the operation and resection of the duodenum were significantly associated with an increased prevalence of obstructed anastomosis in the univariate analysis. In addition, a trend was found towards an association between small duct size and late anastomotic obstruction. Independent risk factors could not be found by multivariate analysis

Discussion

Although quality of life after pancreatic resection is considered to be good [2,10,20], it may be con-

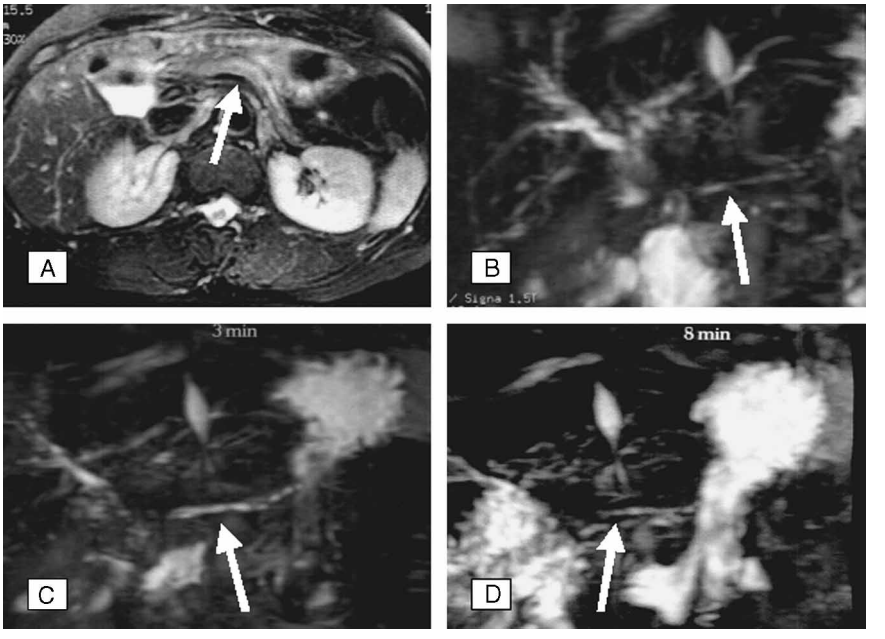

Figure 2. A. T2-weighted fat-saturated axial image of a patient with a large pancreatic remnant parenchyma and pancreatic ductal dilatation (*arrow*). T2-FSSE dynamic magnetic resonance pancreatography (D-MRP) without (B) as well as at 3 min (C) and at 8 min (D) after i.v. secretin injection shows a normal sized pancreatic duct (*arrow*) that initially increases in response to secretin and rapidly narrows to the basic level with fluid accumulation into the intestine, indicating normal glandular function and open anastomosis (Grade 4).

Scand J Gastroenterol Downloaded from informahealthcare.com by University of Tampere on 06/24/10
For personal use only.

RIGHTSLINK

Table IV. Effect of the patient, disease and the extent of operation on the pancreatic exocrine secretion assessed by D-MRCP.

		Grade					
	n	1	2	3	4	Malfunction of remnant gland (Grade 1 versus 2+3+4)	Obstructed anastomosis (Grade 2+3 versus 4)
Men	10	2	2	2	4	NS	NS
Women	13	5	3	4	1		
Age							
<60 years	11	2	2	2	5	NS	0.028
≥60 years	12	5	3	4	0		
Resected							
<36 months ago	9	4	3	1	0	NS	NS
>36 months ago	15	3	2	5	5		
Chronic pancr.	9	2	2	1	4	NS	NS
Ductal adenocarcinoma	5	2	2	1	0		
Other	9	3	1	4	1		
Small/norm. duct	11	4	3	3	1	NS	0.09
Large duct	12	3	2	3	4		
Normal gland	9	3	3	2	1	NS	NS
Hard gland	14	4	2	4	4		
Duodenum							
Preserved	5	0	1	0	4	NS	0.013
Removed	18	7	4	6	1		
Pancreatic complication							
None	19	6	4	5	4	NS	NS
Fistula	4	1	1	1	1		
Pancreatic remnant size							
Small	6	1	2	0	3	NS	NS
Moderate	9	4	2	3	0		
Large	6	2	1	1	2		

Abbreviation: D-MRCP = dynamic magnetic resonance pancreatography.

Scand J Gastroenterol Downloaded from informahealthcare.com by University of Tampere on 06/24/10
For personal use only.

siderably decreased by unsatisfactory bowel function [4]. This is largely caused by pancreatic exocrine insufficiency. According to the current results there are two main determinants for the development of exocrine insufficiency. One is preoperative chronic pancreatitis, either primarily or secondarily from ductal obstruction, and the other is obstructed anastomosis, the role of which has been given little emphasis thus far.

The number of subjects in this study was small (only 26) but the number of long-term survivors is limited in a single center. However, the few previous studies on the function of pancreatic anastomosis after pancreatic resection have also included a small number of patients ($n = 16–34$), perhaps partly because of the expensive method of investigation (D-MRP) [15–18]. In this retrospective study we did not have the preoperative pancreatic function measurements available. Despite these disadvantages, the advantages of the current study include the good standardization of the main study parameter (anastomosis), because all the operations had been performed by the same team and with identical reconstruction techniques [19], and the blind evaluation of all the study parameters.

This cross-sectional study does not answer the question of the timetable of the observed abnormalities in individual patients. However, we also sought to include some patients operated on more recently in order to suggest any difference according to the follow-up time. In fact, diarrhea was more severe when more time had elapsed since surgery, but there was no difference in the status of the anastomosis when comparing those who had been operated on recently with those operated on earlier.

Diarrhea was commonly observed: two-thirds of the patients experienced moderate or severe diarrhea. All patients suffered from pancreatic exocrine insufficiency, and most of them from severe insufficiency. The best-preserved exocrine function was found in patients with a diagnosis other than chronic pancreatitis or ductal adenocarcinoma of the pancreas. Thus chronic pancreatitis, either primarily or secondarily from ductal obstruction, appears to be an important determinant of late exocrine function. We do not know the exact function of exocrine pancreas before

RIGHTSLINK

the surgery, performed a median of more than 4 years earlier, but with these diagnoses the patients probably already had exocrine malfunction at that time.

The best fecal elastase-1 values were observed in the Grade 4 D-MRP examination, which are considered to have both good glandular function and fully open anastomosis. This supports the suggestion that this examination can be used for the evaluation of the pancreatic exocrine function also after the resection. Thirty percent of the patients were suggested to have glandular malfunction according to the D-MRP examination. This, however, did not correlate with the pancreatic exocrine function. This is obvious since, besides for glandular reasons, ductal reasons may also prohibit the pancreatic enzymes from entering the intestine. But when we analyzed only patients with good pancreatic glandular functioning, we were able to demonstrate that two-thirds of these patients had either totally or partially obstructed anastomoses, while only a third of the anastomoses were considered fully open. This is in the same range [13,15,16], or better [17] than previously observed. It thus would seem that the function of the anastomosis is perhaps more important than previously indicated [21]. Dilatation of such obstruction is, however, often impossible because the method of reconstruction does not allow any access using endoscopic techniques.

A small duct size was associated with the increased prevalence of obstruction in the pancreaticojejunal anastomosis. It is understandable that a small size of duct, technically causing a more difficult anastomosis, may be associated with a higher obstruction rate. The pancreaticojejunal stent, either removable [22] or biodegradable [23], has been used to prevent early complications, such as leakage, but the role of such stents in maintaining the good long-term status of the anastomosis remains to be investigated.

Patient age of over 60 years at the time of surgery and the removal of the duodenum were associated with the increased prevalence of obstruction in the pancreaticojejunal anastomosis. Studies of duodenal aspirates suggest that the pancreatic exocrine output decreases with age [24]. Furthermore, the preservation of the duodenum presumably better preserves the pancreatic hormonal stimulus and thus secretion [25]. It could therefore be hypothesized that it is the increased pancreatic stimulus that maintains pancreatic juice flow and prohibits late stenosis. Consequently, it could also be speculated whether secretory stimulants should be used during the convalescent period to promote better late pancreatic function. In fact, instead of pancreatic stimulants, the pancreatic suppressor somatostatin is used in some centers to prevent early pancreatic complications. To our knowledge, there are no data on the long-term effects of postoperative somatostatin treatment on the later pancreatic function – this could be investigated by re-examining patients of the previous randomized trials, so far focusing only on the early complications [26,27]. Currently, the explanation for the association between younger age and a preserved duodenum and the better later status of the pancreaticojejunal anastomosis remains unknown.

In conclusion, most patients who have undergone end-to-end invaginated pancreaticojejunostomy after pancreatic head resection suffer later from diarrhea and pancreatic exocrine insufficiency. This may be explained partly by malfunction of the gland induced by the disease even before the pancreas resection, and partly by obstructed anastomosis. Better late-functional results may require improvements in the surgical techniques.

Acknowledgements

This work was supported by the Research Fund of Pirkanmaa Hospital District (Drs Räty and Sand). We thank Heikki Kolehmainen, MD, for help in the initial phase of the study.

References

[1] Nordback I, Parviainen M, Räty S, Kuivanen H, Sand J. Resection of the head of the pancreas in Finland: effects of hospital and surgeon on short and long-term results. Scand J Gastroenterol 2002;37:1454–60.

[2] Nguyen TC, Sohn TA, Cameron JL, Lillemoe KD, Campbell KA, Coleman JA, et al. Standard vs. radical pancreaticoduodenectomy for periampullary adenocarcinoma: a prospective, randomized trial evaluating quality of life in pancreaticoduodenectomy survivors. J Gastrointest Surg 2003;7:1–11.

[3] Jang JY, Kim SW, Park SJ, Park YH. Comparison of the functional outcome after pylorus preserving pancreaticoduodenectomy: pancreaticogastrostomy and pancreaticojejunostomy. World J Surg 2002;26:366–71.

[4] Armstrong T, Walters E, Varshney S, Johnson CD. Deficiencies of micronutritients, altered bowel function, and quality of life during late follow-up after pancreaticoduodenectomy for malignancy. Pancreatology 2002;2:528–34.

[5] Büchler MW, Friess H, Muller MW, Wheatley AM, Beger HG. Randomized trial of duodenum preserving pancreatic head resection versus pylorus preserving Whipple in chronic pancreatitis. Am J Surg 1995;169:65–9.

[6] Klempa I, Spatney M, Menzel J, Baca I, Nustede R, Stockmann F, et al. Pancreatic function and quality of life after resection of the head of the pancreas in chronic pancreatitis. A prospective randomized comparative study after duodenum preserving resection of the head of the pancreas versus Whipple's operation. Chirurgie 1995;66:350–9.

[7] Izbicki JR, Bloechle C, Broering DC, Knoefel WT, Kuechler T, Broelsch CE. Extended drainage versus resection in surgery for chronic pancreatitis: a prospective randomized trial comparing longitudinal pancreaticojejunostomy combined with local pancreatic head excision with the pylorus preserving PD. Ann Surg 1998;228:771–9.

Scand J Gastroenterol Downloaded from informahealthcare.com by University of Tampere on 06/24/10
For personal use only.

RIGHTSLINK

[8] Witzigmann H, Max D, Uhlmann D, Geissler F, Ludwig S, Schwartz R, et al. Quality of life in chronic pancreatitis: a prospective trial comparing classical Whipple procedure and duodenum-preserving pancreatic head resection. J Gastrointest Surg 2002;6:173–80.

[9] Hall RI, Rhodes M, Isabel-Martinez L, Kelleher J, Venables CW. Pancreatic exocrine function after a sutureless pancreaticojejunostomy following pancreaticoduodenectomy. Br J Surg 1990;77:83–5.

[10] Sato N, Yamaguchi K, Yokohata K, Shimizu S, Morisaki T, Chijiiwa K, et al. Short-term and long-term pancreatic exocrine and endocrine functions after pancreaticoduodenectomy. Dig Dis Sci 1998;43:2616–21.

[11] Dominici R, Franzini C. Fecal elastase-1 as a test for pancreatic function: a review. Clin Chem Lab Med 2002; 40:325–32.

[12] Amano H, Takada T, Ammori BJ, Yasuda H, Yoshida M, Uchida T, et al. Pancreatic duct patency after pancreaticogastrostomy: long-term follow-up study. Hepato-Gastroenterology 1998;45:2382–7.

[13] Arnaud JP, Casa C, Serra-Maudet V, Georgeac C, Ronceray J. Pancreato-gastric anastomosis after cephalic duodenopancreatectomy. A propos of 36 cases. Chirurgie 1994;119: 317–9.

[14] Matos C, Metens T, Devière J, Nicaise N, Braudé P, van Yperen G, et al. Pancreatic duct: morphologic and functional evaluation with dynamic MR pancreatography after secretin stimulation. Radiology 1997;203:435–41.

[15] Sho M, Nakajima Y, Kanehiro H, Hisanaga M, Nishio K, Nagao M, et al. A new evaluation of pancreatic function after pancreatoduodenectomy using secretin magnetic resonance cholangiopancreatography. Am J Surg 1998;176:279–82.

[16] Pessaux P, Aube C, Lebigot J, Tuech J-J, Regenet N, Kapel N, et al. Permeability and functionality of pancreaticogastrostomy after pancreaticoduodenectomy with dynamic magnetic resonance pancreatography after secretin stimulation. J Am Coll Surg 2002;194:454–62.

[17] Tang Y, Yamashita Y, Arakawa A, Namimoto T, Mitsuzaki K, Abe Y, et al. Pancreatobiliary ductal system: value of half-Fourier rapid acquisition with relaxation enhancement MR cholangiopancreatography for post-operative evaluation. Radiology 2000;215:81–8.

[18] Sugiyama M, Abe N, Tokuhara M, Tadahiko M, Mori T, Takahara T, et al. Magnetic resonance cholangiography for post-operative follow-up of intraductal papillary mucinous tumours of the pancreas. Am J Surg 2003;185:251–5.

[19] Cameron JL. Atlas of Surgery. Vol I. Philadelphia: Decker; 1990. pp 386–413.

[20] Peters JH, Carey LC. Historical review of pancreaticoduodenectomy. Am J Surg 1991;161:219–25.

[21] Tanaka T, Ichiba Y, Fujii Y, Kodama O, Dohi K. Clinical and experimental study of pancreatic exocrine function after pancreaticoduodenectomy for periampullary carcinoma. Surg Gyn Obstet 1988;166:200–5.

[22] Lygidakis NJ, van der Heyde MN. Reconstruction of alimentary tract continuity after subtotal duodenopancreatectomy. In: Lygidakis NJ, van der Heyde MN, editors. Hepatobiliary and pancreatic malignancies. Diagnosis, medical and surgical management. New York: Thieme Medical Publishers; 1989. pp 287–94.

[23] Parviainen M, Sand J, Harmoinen A, Kainulainen H, Välimaa T, Törmälä P, et al. A new biodegradable stent for the pancreaticojejunal anastomosis after pancreaticoduodenal resection: in vitro examination and pilot human experiences. Pancreas 2000;21:14–21.

[24] Vellas B, Balas D, Moreau J, Bouisson M, Senegas-Balas F, Guidet M, et al. Exocrine pancreatic secretion in the elderly. Int J Pancreatol 1988;3:497–502.

[25] Beger HG, Schlosser W, Friess HM, Büchler MW. Duodenum-preserving head resection in chronic pancreatitis changes the natural course of the disease: a single-center 26-year experience. Ann Surg 1999;230:512–32.

[26] Büchler M, Friess H, Klempa I, Hermanek P, Sulkowski U, Becker H, et al. Role of octreotide in the prevention of postoperative complications following pancreatic resection. Am J Surg 1992;163:125–31.

[27] Yeo CJ, Cameron JL, Lillemoe KD, Sauter PK, Coleman JA, Sohn TA, et al. Does prophylactic octreotide decrease the rates of pancreatic fistula and other complications after pancreaticoduodenectomy? Results of a prospective randomized placebo-controlled trial. Ann Surg 2000;232:419–29.

Scand J Gastroenterol Downloaded from informahealthcare.com by University of Tampere on 06/24/10
For personal use only.

RIGHTSLINK

Original Paper

Late Postoperative Quality of Life Following Pancreatic Head Resections

M Parviainen MD[1], S Räty MD[1], I Nordback MD[1], H Sintonen PhD[2]
P Vehkalahti MD[3], J Sand MD[1]
[1]Departments of Gastroenterology and Alimentary Tract Surgery, and [3]Radiology
Tampere University Hospital, Tampere, Finland, [2]Department of Public Health
University of Helsinki, Finland
Corresponding Author: Juhani Sand, MD, Department of Gastroenterology and Alimentary Tract Surgery
Tampere University Hospital, P.O.BOX 2000, FIN-33521 Tampere, Finland
Tel: +358 3 31166375, Fax: +358 3 31164358, E-mail: juhani.sand@pshp.fi

ABSTRACT

Background/Aims: To evaluate health-related quality of life (HRQoL) in patients that have undergone pancreatic resection and compare the results with representative population samples in early and late stage evaluations. Also, this study aims to observe possible associations with postoperative complications.

Methodology: Twenty-seven single-institute patients operated on during a 3-year period due to a benign or malignant process of the periampullary region. HRQoL was measured by the 15D instrument. Data were compared with those obtained from representative Finnish general population samples.

Results: Twenty-five patients were interviewed in the early stage (24 months postoperatively). Fifteen had a benign and 12 a malignant disease. No differences were found in the postoperative HRQoL when the nature of the disease or the postoperative complications were considered. When compared with the general population in the early stage, HRQoL was lower in the study group in whole, and also when sleep, elimination (bladder or bowel function) and sexual activity were considered separately. In the late stage evaluation (110 months postoperatively) the study group consisted of 15 surviving patients. There were no differences in comparison to the general population. Also when comparing the same patients in 2 evaluation points (24 and 110 months), we did not find any difference in any of the 15D parameters.

Conclusions: Postoperative HRQoL deteriorated in comparison to general population in the early stage but there were no differences in the late stage. This study encourages us to continue the use of the 15D at least as a part of HRQoL evaluation, because it allows comparisons between different diseases and the general population.

KEY WORDS: Postoperative quality of life; Pancreatic resection; Complications

ABBREVIATIONS: Health-related Quality of Life (HRQoL); Pylorus Preserving Pancreaticoduodenectomy (PPPD); Gastrointestinal Quality of Life Index (GIQLI)

INTRODUCTION

Health-related quality of life (HRQoL), with all different ways it is measured, has gained increased attention during the last decade. Improved cancer treatment and supportive care have lead to extended length of survival in many diseases (1). HRQoL has different cultural influences (1,2), but the 2 fundamental components of HRQoL are subjectivity and multidimensionality (3,4). In the field of pancreas surgery, classical pancreaticoduodenectomy with antrectomy has been associated with unsatisfactory postoperative HRQoL in patients operated on for chronic pancreatitis (5), whereas various surgical therapies in complicated chronic pancreatitis may result in improved HRQoL (6). In pancreatic cancer patients, postoperative HRQoL has generally been thought to be poor after extended pancreatic resections (7,8), whereas HRQoL results have been better after less aggressive resections (9,10).

Until now, there have been few studies of HRQoL in patients who have undergone pancreatic resection, where comparison with healthy controls has been performed (11,12). Moreover, little is known about the long term trends in HRQoL after pancreatic head resections. Early postoperative mortality has fallen to a level well below 2-5% in experienced centers, and an increasing number of operations are performed for benign diseases (13). Therefore, the number of patients surviving even long-term after such a major operation has increased, which makes HRQoL an even more important issue.

Symptom-related questions derived from Gastrointestinal Quality of Life Index (GIQLI) have been used in follow-up studies, considering such subjects as esophageal (14), colorectal (15,16), hepatic (17), gastric (18) and pancreatic surgery (19,20,21). While this index contains questions for many unfavourable symptoms which are often noticed after pancreatic resection, these questionnaires ignore many important more general aspects affecting HRQoL, such as sexual activity and sleeping. A more general instrument to measure HRQoL has been recently developed. The 15D is a generic, 15-dimensional instrument to measure HRQoL. It can be used both as a

Hepato-Gastroenterology 2008; 55:711-716
© H.G.E. Update Medical Publishing S.A., Athens-Stuttgart

profile and as a single index score measure (22) and it is therefore suitable for comparing HRQoL between patients after pancreatic head resection and general population. The 15D has been used in a wide range of diseases (www.15D-instrument.net), including gastrointestinal diseases (23), but not to our knowledge in pancreatic surgery.

This study's aim was to perform a pilot evaluation of the use of the 15D in patients who had undergone pancreatic resection and to compare their HRQoL with that of general population. Furthermore, we also wanted to study whether the HRQoL of these patients changed during the long-term follow-up and whether the initial postoperative complications had any association with the observed HRQoL.

METHODOLOGY

Twenty seven patients were included, 13 male, 14 female, median age 66 yr (range 34–85) who had undergone resection of the pancreatic head in Tampere University Hospital between April 94 and June 97. Of the operations performed, 19 (70%) were pylorus preserving pancreaticoduodenectomies (PPPD), 2 (7%) were classic Whipple's resections with antrectomy and 6 (22%) were duodenum preserving pancreatic head resections (Beger's operations). Twelve (44%) had a malignant disease and 15 (56%) had a benign disease. Of the malignancies, 5 (42%) were ductal adenocarcinomas of the head of the pancreas, 5 (42%) adenocarcinomas of the ampulla of Vater, 1 (8%) adenocarcinoma of the distal bile duct and 1 (8%) carcinoid tumour of the pancreatic head. Four of the 12 patients (33%) with malignant disease were treated with extended lymphadenectomy and the rest with standard local lymphadenectomy. Eleven of the benign diseases were chronic pancreatitis. Two others of the benign diseases were serous cystadenomas, 1 retention cyst and 1 ulcerative inflammation of the common bile duct. In addition to the disease indicating surgery, 18 patients had also other diseases. One of the patients had had a gastrectomy 11 years ago due to gastric cancer. One had been operated on for breast cancer, and 2 had been operated on for peptic ulcers in the past. Other significant preoperative diseases were coronary artery disease with or without cardiac failure in 5 patients, arterial hypertension in 5 patients, diabetes in 4 patients, and aortic reconstruction due to arteriosclerosis, rheumatoid arthritis, hypothyreosis and chronic atrial fibrillation in 1 patient.

TABLE 1 Comparison of HRQoL between Patients and a General Population Sample (median 24 mo postoperatively, National Health Survey 1995/96)

	HRQoL according to 15D				
	Study group n=25		Population sample n=2768		
15D dimensions	x	±SEM	x	±SEM	p^*
D15 score	**0.8284**	**0.1286**	**0.8784**	**0.1166**	**0.03**
Mobility	0.8774	0.1776	0.8869	0.1850	0.80
Vision	0.9278	0.1306	0.9138	0.1179	0.70
Hearing	0.8668	0.1709	0.9234	0.1491	0.06
Breathing	0.8019	0.2244	0.8637	0.2201	0.16
Sleeping	**0.7042**	**0.2186**	**0.8501**	**0.1932**	**<0.01**
Eating	0.9717	0.0980	0.9891	0.6731	0.20
Speech	0.9763	0.0822	0.9731	0.0942	0.89
Elimination	**0.7299**	**0.2523**	**0.8772**	**0.1946**	**<0.01**
Usual activities	0.7699	0.2384	0.8367	0.2266	0.14
Mental function	0.8466	0.1986	0.8726	0.1851	0.49
Discomfort and symptoms	0.7418	0.1860	0.7622	0.2301	0.66
Depression	0.8384	0.1659	0.8893	0.1654	0.11
Distress	0.8385	0.1875	0.8828	0.1635	0.18
Vitality	0.7742	0.2013	0.8294	0.1770	0.12
Sexual activity	**0.6999**	**0.3041**	**0.8160**	**0.2785**	**0.04**

*Independent samples *t*-test

Pancreatin 150mg responding 10000 Eur U of lipase (Pankreon^R, Solvay Pharmaceuticals GmbH, Hannover, Germany) was used as digestive enzyme supplementation in a dosage of 1-2 capsules 3 times a day. This has no effect on fecal elastase 1 (FE1) (24).

The patients were interviewed in the late 1990s at median 24 (range 3-43) mo after the operation (early stage evaluation). During the interview a normal clinical examination was performed and blood tests were taken: white blood cell count, haemoglobin concentration, glucose concentration, alkaline phosphatase (ALP) activity, albumin concentration and CA 19-9 level. In addition, FE1 activity was measured. Chest x-ray and upper abdominal ultrasound were performed to exclude tumour recurrence or metastasis of a malignant tumour.

The interview was performed by using a questionnaire with a specific part (age, sex, character of disease, time of operation, early and late complications) and a general part, which included the 15D questionnaire. It produces a 15-dimensional profile of level values on a 0-1 scale (0=being dead, 1=no problems on the dimension) and an overall HRQoL score (15D score) on a 0-1 scale (0=being dead, 1=no problems on any dimension). The HRQoL of the patients was compared to that of a sample representative of the over 15-year-old Finnish non-institutionalized population from the National Health Survey in 1995/96 (25).

To evaluate the possible late changes of HRQoL, those 17 patients who were still alive in September 2004 were invited to a new 15D interview for late stage evaluation. The median follow-up time from surgery was 110 (range 87-126) mo. Two of the patients did not attend the second interview, so the possible change in HRQoL during the long-term follow-up could be assessed in 15 patients. The HRQoL of the patients was compared to that of a sample representative of the over 30-year-old Finnish population from the National Health 2000 Health Examination Survey (26).

Before testing whether there were statistically significant differences between the patients and general population samples in the total 15D scores and on different dimensions (level values), the population samples were made compatible with the age and gen-

der distribution of the patients with appropriate weighting.

As separate additional objectives, we examined the effect of early complications on HRQoL in 2 time points (median 24 and 110 mo postoperatively). We also compared the effect of the nature of the disease (benign *vs.* malignant) and the possible abnormal results in the laboratory or imaging tests in the first step evaluation.

Ethics

The study was approved by the Ethical Committee of Tampere University Hospital.

Statistics

Independent samples *t*-test was used to compare the means of patients and population samples and paired t-test was used to compare the means of study groups in different point of time. Correlations of different study parameters were calculated by Pearson correlation coefficient test. *p*-value <0.05 was considered statistically significant.

RESULTS

Of the 25 patients who responded to the first interview, 3 had abnormal findings in the clinical examination. One of these had slight jaundice and 2 had small incisional hernias. All but one of the patients had very low FE1 activity (<15ig/g) suggesting severe pancreatic exocrine insufficiency. Furthermore, 7 patients had elevated ALP activity and 2 patients had elevated CA 19-9 level, one with chronic pancreatitis and biliary obstruction and another with a recurrent pancreatic carcinoma. Carcinoma of the head of the pancreas had been the primary diagnosis in this patient, and she had also had infiltration to the portal vein in the operation. Other patients had no signs of recurrence of cancer. One patient had pulmonary congestion in the x-ray of the chest but the others had no abnormal findings. Eight had normal abdominal ultrasound. Three had dilated intrahepatic biliary ducts. These patients had been operated on for chronic pancreatitis. In the remaining 14 patients, the findings included adipose degeneration and cirrhosis of the liver, cysts and haemangioma of the liver, renal cysts, seriously calcified aorta and signs of chronic pancreatitis, i.e. calcified parenchyma, wide pancreatic duct or a pseudocyst.

In the first interview no differences were found in HRQoL when the patients were divided into groups according to the nature of the disease (benign or malignant) (data not shown). Neither FE1 activity nor ALP activity correlated with 15D scores. The patient with recurrent pancreatic carcinoma had low scores in 15D, but otherwise the findings in chest x-ray or abdominal ultrasound did not correlate with 15D scores (data not shown). HRQoL was significantly lower in the study group than in the general population sample (0.8284 *vs.* 0.8784, p=0.03) **(Table 1)**. The patients were statistically significantly worse off than general population on the dimensions of sleeping (0.7042 *vs.* 0.8501, p<0.01), elimination (i.e. bladder and bowel function) (0.7299 *vs.* 0.8772, p<0.01) and sexual activity (0.6999 *vs.* 0.8160, p=0.04) **(Table 1)**.

Nine of the 25 patients (36%) had early postoperative complications. Of these, 7 had postoperative pancreatic fistula, of which one had needed a reoperation. Two more patients needed a reoperation due to postoperative haemorrhage of the wound. One had a postoperative peptic ulcer. At the first step evaluation (24 mo), however, the overall surgical complication rate was not associated with difference in the HRQoL compared to patients with uneventful recovery or with the population sample.

At the second measurement (110 mo) the HRQoL

TABLE 2 Comparison of HRQoL between the 15 Surviving Patients and the General Population Sample (median 110 mo postoperatively, National Health 2000 Health Examination Survey)

	HRQoL according to 15D				
	Study group n=15		Population sample n=4602		
15D dimensions	x	±SEM	x	±SEM	p^*
D15 score	0.86854	0.11797	0.8747	0.11360	0.83
Mobility	0.8883	0.17328	0.8893	0.18545	0.98
Vision	0.9424	0.09887	0.9177	0.17138	0.58
Hearing	0.8990	0.21037	0.9239	0.15402	0.53
Breathing	0.8754	0.23508	0.8604	0.21532	0.79
Sleeping	0.7670	0.25608	0.8295	0.19085	0.21
Speech	0.9802	0.07661	0.9688	0.10602	0.68
Elimination	0.7968	0.27256	0.8584	0.20745	0.25
Usual activities	0.9051	0.17781	0.8517	0.22150	0.35
Mental function	0.9049	0.16323	0.8475	0.20376	0.28
Discomfort and symptoms	0.7278	0.24857	0.7546	0.20717	0.62
Depression	0.8424	0.14739	0.8968	0.15109	0.16
Distress	0.8370	0.16947	0.8970	0.15456	0.13
Vitality	0.8134	0.16171	0.8335	0.17091	0.65
Sexual activity	0.7596	0.30780	0.8152	0.26899	0.42

* Independent samples *t*-test

TABLE 3 Comparison of HRQoL in the Early (24 mo) and Late (110 mo) Stage Evaluation of the 15 Surviving Patients

	HRQoL according to 15D				
	24 mo		110 mo		
15D dimensions	x	±SEM	x	±SEM	p^*
D15 score	0.8716	0.13847	0.8685	0.11797	0.86
Mobility	0.9234	0.13142	0.8883	0.17328	0.36
Vision	0.9568	0.08943	0.9424	0.09887	0.58
Hearing	0.9140	0.16201	0.8990	0.21037	0.61
Breathing	0.8551	0.22172	0.8754	0.23508	0.73
Sleeping	0.7306	0.23306	0.7670	0.25608	0.65
Speech	1.0000	0.00000	0.9802	0.07661	0.33
Elimination	0.7950	0.24830	0.7968	0.27256	0.97
Usual activities	0.8455	0.24350	0.9051	0.17781	0.18
Mental function	0.8811	0.17400	0.9049	0.16323	0.58
Discomfort and symptoms	0.7885	0.21784	0.7278	0.24857	0.27
Depression	0.8570	0.17729	0.8424	0.14739	0.70
Distress	0.8611	0.23178	0.8370	0.16947	0.65
Vitality	0.8274	0.22812	0.8134	0.16171	0.80
Sexual activity	0.8110	0.22906	0.7596	0.30780	0.31

*Paired *t*-test

TABLE 4 Summary of Different Studies Measuring HRQoL in Pancreatic Diseases and Surgery

Author	Year	Instrument of measuring QOL	Clinical application	Study	n
McLeod (31)	1995	TTOT*, DQO**, GIQLI, SIP***, PGA****, Visick Scale	Whipple (malignant)	Retrospective	42
Luman (32)	1997	EORTC*****, QLQ-30 with suppl	Inoperable, stented patients	Retrospective	47
McLeod (19)	1999	SIP, GIQLI	PD (unselected)	Retrospective	25
Izbicki (33)	1999	No specific, QLQ-30 and GIQLI mentioned	Chronic pancreatitis		
Sohn (34)	2000	Visual analogue scale	PD in chronic pancreatitis	Retrospective	255, (96 PD:s)
Huang (11)	2000	Visual analogue scale to LCC and healthy controls	PD, compared	Retrospective	192
Kelemen (35)	2002	GIQLI	Chronic pancreatitis, 3 different operations	Retrospective	33 Beger, 13 Frey, 21 PPPD
Ohtsuka (36)	2001	Modified Kurihara's Questionnaire	PPPD (malignant, benign)	Prospective	20
Jang (37)	2002	DQO, Visick Scale, PGA	PPPD (malignant)	Retrospective	67

* Time Trade-off Technique; ** Direct Questioning of Objective Technique; *** Sickness Impact Profile; **** Physician Global Assessment
***** European Organization for Research and Treatment of Cancer, Quality of Life Questionnaire

of the 15 study patients did not differ from that of the population sample **(Table 2)**. Also whether the patient had experienced an early postoperative complication or not did not correlate with HRQoL at the second evaluation (data not shown). When HRQoL was compared between the 2 evaluations (median 24 and 110 mo) in the 15 survived patients, there were no differences in any parameters of HRQoL **(Table 3)**.

DISCUSSION

Instruments used in clinical trials to measure HRQoL can be divided into 3 types: generic, disease-specific and symptom-specific. Disease-specific instruments are likely to be more responsive to any change during the course of the disease, but they can not be used to compare different diseases or normal subjects. Symptom-specific instruments focus solely on the symptoms produced by a given disease process (27). Generic instruments allow comparisons across conditions and interventions, but they may fail to capture aspects of patients' experience that are of clinical interest in specific clinical settings. Examples of generic instruments are the Short Form 36-item Health Survey, the Nottingham Health Profile (28) and the 15D (22). Examples of disease-specific are Rotterdam Symptom Check List and QL Index (29). An example of symptom severity instruments is the McGill Pain Questionnaire (30). However, there does not seem to be a consensus of the best instrument to measure HRQoL. When considering pancreatic diseases and therapeutic interventions, some publications and their instruments are listed in **Table 4**. Until now, there have not been disease-specific instruments for measuring HRQoL in chronic pancreatitis (33,38). EORTC-QLQ, which originally was designed for patients with malignant diseases (39,40) has also been applied in HRQoL in patients with chronic pancreatitis (33). EORTC-QLQ-PAN26 has been specifically designed for use in pancreatic cancer (41,42).

In this study a pilot evaluation was made of the use of the generic 15D in comparing patients who had undergone the resection of pancreatic head for both malignant tumours and benign conditions, mostly chronic pancreatitis, with age- and gender-standardised Finnish general population. The 15D was chosen also to evaluate the effects of this kind of major surgery and severe diseases on non-pancreas-specific aspects of HRQoL, such as sexual activity, elimination (ability to defecate and urinate), sleeping, and so on, which may be important determinants of HRQoL and easily ignored in disease-orientated evaluations.

Decreased overall HRQoL at 24 months was found in patients who had undergone pancreatic surgery. Previously Huang and others did not find this kind of difference at 6 months after pancreaticoduodenectomy when compared to healthy controls or patients after laparoscopic cholecystectomy (11). This difference may be due to the different tool to measure the HRQoL or the small number of pancreaticoduodenectomy patients in this study and small number of controls in Huang's study. According to a prospective study of 98 patients, HRQoL was impaired in comparison to normal population in almost every domain of the tool used (SF-36). Follow-up time was, however, short (15 mo) (43).

Unfortunately it was not possible to evaluate the preoperative HRQoL in our patients. In patients operated on for chronic pancreatitis the general HRQoL has been observed to improve from preoperative results in a 2 year follow-up in both after Whipple operation and duodenum preserving head resection (12). When comparing results obtained from a Dutch study, no differences were noticed in HRQoL between pancreaticoduodenectomy and double-bypass. Both showed a temporary decrease in physical and gastrointestinal functioning (44). In patients who were only palliated for malignant biliary obstruction increased HRQoL was found 1 mo after the stenting (32).

This was a unique opportunity to re-evaluate a small number of patients over 9 years later (median 110 mo after the surgery) and no HRQoL difference was found any more, when compared to the general population. This phenomenon may be explained by

the fact that the patients with the lowest HRQoL scores at short-term follow-up studies are usually those with chronic pancreatitis and pancreatic adenocarcinoma (11) and in our second evaluation all of the patients with pancreatic adenocarcinoma had already died. One may also speculate that some of the patients in the first evaluation had recurrent malignancy and so decreased HRQoL. In the first evaluation we had one patient with a known recurrence, but leaving that particular patient out of the calculation did not change the 15D result. The late evaluation consisted of patients operated on for non-malignant tumours and chronic pancreatitis. In this subgroup of patients there were no differences in 15D scores between the 2 evaluations points or when compared to the general population. To our knowledge this kind of long-term evaluation has not been done previously.

When looking at the specific dimensions at the first evaluation median 24 months postoperatively, there were decreased scores for sleeping, elimination (ability to defecate or urinate), ability to hear, and for sexual activity when comparing to the general population. At the second evaluation median 110 months later there was no statistically significant difference on any of these dimensions from the scores of general population giving an impression of improved HRQoL. However, when looking at those scores as paired observations in the same patients there are slightly improved scores for sleeping, but impaired rather than improved scores for ability to hear and for sexual activity, although without statistical significance. The possible trend for lower sexual activity or ability to hear might be explained by the effect of aging, which must be kept in mind when comparing the total 15D scores in different time points.

Postoperative morbidity is, in general thinking, associated with reduced HRQoL. The role of early postoperative complications, such as haemorrhage, abscess, anastomotic fistula or early delayed gastric emptying, has been discussed as causes of deterioration in HRQoL, also the methods to avoid these complications have been emphasised (45). The effect of these complications on HRQoL, in more long-term, however, has not been measured. Surprisingly, in our study the overall early postoperative complication rate did not affect the long-term HRQoL either at 24 months or at 110 months. This may be partly explained by the use of a generic HRQoL instrument and partly due to small number of patients in our study.

In conclusion, this pilot study encourages us to continue the use of the 15D at least as a part of HRQoL evaluation, because it gives a good opportunity to comparisons between different disease groups and population samples. This study also emphasis the importance of relevant control population and the effect of selection bias during the long-term follow-up.

ACKNOWLEDGEMENTS

Medical Research Fund of Tampere University Hospital, Pirkanmaa Hospital District.

REFERENCES

1 **Ferrell BR, Hassey Dow K, Grant M:** Measurement of the quality of life in cancer survivors. Qual Life Res 1995; 4:523-531.
2 **Stiefel F:** Cancer and Quality of life. Support Care Cancer 1995; 3:327-328.
3 **Cella DF:** Quality of life: the concept. J Palliat Care 1992; 8:8-13.
4 **Schmier J, Elixhauser A, Halpern MT:** Health-related quality of life evaluations of gastric and pancreatic cancer. Hepatogastroenterology 1999; 46:1998-2004.
5 **Büchler MW, Berberat P, Reber PU, Friess H:** Surgical therapy in chronic pancreatitis. Ther Umsch. 1996; 53:365-376.
6 **Evans JD, Wilson PG, Carver C, Bramhall SR, Buckels JA, Mayer A, et al:** Outcome of surgery for chronic pancreatitis. Br J Surg 1997; 84:624-629.
7 **Nagakawa T, Nagamori M, Futakami F, Tsukioka Y, Kayahara M, Ohta T, et al:** Results of extensive surgery for pancreatic carcinoma. Cancer 1996; 77:640-645.
8 **Henne-Bruns D, Vogel I, Luttges J, Kloeppel G, Kremer B:** Ductal adenocarcinoma of the pancreas head: survival after regional versus extended lymphadenectomy. Hepatogastroenterology 1998; 45:855-866.
9 **Kawarada Y, Yokoi H, Isaji S, Naganuma T, Tabata M, Machishi H, et al:** Modified standard pancreaticoduodenectomy for the treatment of pancreatic head cancer. Digestion 1999; 60:120-125.
10 **Nguyen TC, Sohn TA, Cameron JL, Lillemoe KD, Campbell KA, Coleman J, et al:** Standard *vs.* radical pancreaticoduodenectomy for periampullary adenocarcinoma: a prospective, randomised trial evaluating quality of life in pancreaticoduodenectomy survivors. J Gastroenterol Surg 2003; 7:1-11.
11 **Huang JJ, Yeo CJ, Sohn TA, Lillemoe KD, Sauter PK, Coleman JA, et al:** Quality of life and outcomes after pancreaticoduodenectomy. Ann Surg 2000; 231:890-898.
12 **Witzigmann H, Max D, Uhlmann D, Geissler F, Schwartz R, Ludwig S, et al:** Outcome after duodenum-preserving pancreatic head resection is improved compared with classic Whipple procedure in the treatment of chronic pancreatitis. Surgery 2003; 134:53-62.
13 **Yeo CJ, Cameron JL, Sohn TA, Lillemoe KD, Pitt HA, Talamini MA, et al:** Six hundred fifty consecutive pancreaticoduodenectomies in the 1990s: pathology, complications, and outcomes. Ann Surg 1997; 226:248-257.
14 **Stein HJ, Feith M, Mueller J, Werner M, Siewert JR:** Limited resection for early adenocarcinoma in Barrett's esophagus. Ann Surg 2000; 232:733-742.
15 **Sailer M, Fuchs KH, Fein M, Thiede A:** Randomized clinical trial comparing quality of life afer straight and pouch coloanal reconstruction. Br J Surg 2002; 89:1108-1117.
16 **Thaler K, Dinnewitzer A, Oberwalder M, Weiss EG, Nogueras JJ, Wexner SD:** Assessment of long-term quality of life after laparoscopic and open surgery for Crohn's disease. Colorectal Dis 2005; 7:735-781.
17 **Chen L, Liu Y, Li GG, Tao SF, Xu Y, Tian H:** Quality of life in patients with liver cancer after operation: a 2-year follow-up study. Hepatobiliary Pancreat Dis Int 2004; 3:530-533.
18 **Jentschura D, Strohmeier N, Winkler M, Sturm J:** Comparative study of the quality of life after stomach resection. Langenbecks Arch Chir Suppl Kongressbd 1996; 113:247-248.
19 **McLeod RS:** Quality of life, nutritional status and gastrointestinal hormone profile following the Whipple procedure. Ann Oncol 1999; 10:281-284.
20 **Olah A, Kelemen D, Horvath OP, Belagyi T:** Long-term

follow-up results of surgery for chronic pancreatitis. Hepatogastroenterology 2004; 51:1179-1182.
21 **Witzigmann H, Max D, Uhlmann D, Gessler F, Ludwig S, Schwartz R, et al:** Quality of life in chronic pancreatitis: a prospective trial comparing classical Whipple procedure and duodenum-preserving pancreatic head resection. J Gastrointest Surg 2002; 6:173-179.
22 **Sintonen H:** The 15D instrument of health-related quality of life: properties and applications. Ann Med 2001; 33:328-336.
23 **Räsänen JV, Niskanen MM, Miettinen P, Sintonen H, Alhava E:** Health-related quality of life before and after gastrointestinal surgery. Eur J Surg 2001; 167:419-425.
24 **Farkas G, Leindler L, Mihalovits G:** Dose-dependent effect of pancreatin replacement upon the pancreatic function in the period after pancreatic surgery. Magy Seb 2001; 54:247-250.
25 **Arinen S, Häkkinen U, Klaukka T, Klavus J, Lehtonen R, Aro S:** Sampling design. In: Health and the use of health services in Finland. Main findings of the Finnish Health Care Survey 1995/96 and changes from 1987. Official Statistics of Finland, Health Care 1998; 5. Helsinki: National Research and Development for Welfare and Health 1998. pp.12. (in Finnish with English abstract)
26 **Aromaa A, Koskinen S (Eds):** Health and functional capacity in Finland. Baseline results of the Health 2000 health examination survey. Helsinki, 2004.
27 **Langenhoff BS, Krabbe PFM, Wobbes T, Ruers TJM:** Quality of life as an outcome measure in surgical oncology. Br J Surg 2001; 88:643-652.
28 **Essink-Bot ML, Krabbe PFM, Bonsel GJ, Aaronson NK:** An empirical comparison of four generic health status measures. The Nottingham Health Profile, the Medical Outcomes Study 36-item Short-Form Health Survey, the COOP/WONCA charts and the EuroCol instrument. Med Care 1997; 35:522-537.
29 **Batel-Copel LM, Kornblith AB, Batel PC, Holland JC:** Do oncologists have an increasing interest in the quality of life of their patients? A literature review of the last 15 years. Eur J Cancer 1997; 33:29-32.
30 **Melzack R:** The McGill Pain Questionnaire: major properties and scoring methods. Pain 1975; 1:277-299.
31 **McLeod RS, Taylor BR, O'Connor BI, Greenberg GR, Jeejeebhoy KN, Royall D, et al:** Quality of life, nutritional status, and gastrointestinal hormone profile following the Whipple procedure. Am J Surg 1995; 169:179-185.
32 **Luman W, Cull A, Palmer KR:** Quality of life in patients stented for malignant biliary obstructions. Eur J Gastroenterol Hepatol 1997; 9:481-484.
33 **Izbicki JR, Bloechle C, Knoefel WT, Rogiers X, Kuechler T:** Surgical treatment of chronic pancreatitis and quality of life after operation. Surg Clin North Am 1999; 79:913-944.
34 **Sohn TA, Campbell KA, Pitt HA, Sauter PK, Coleman JA, Lillemoe KD, et al:** Quality of life and long-term survival after surgery for chronic pancreatitis. J Gastrointest Surg 2000; 4:355-364.
35 **Kelemen D, Horváth ÖP:** Clinical experience with different techniques of pancreatic head resection for chronic pancreatitis. Dig Surg 2002; 19:28-35.
36 **Ohtsuka T, Yamaguchi K, Chijiiwa K, Kinukawa N, Tanaka M:** Quality of life after pylorus-preserving pancreatoduodenectomy. Am J Surg 2001; 182:230-236.
37 **Jang JY, Kim SW, Park SJ, Park YH:** Comparison of the functional outcome after pylorus-preserving pancreatoduodenectomy: pancreatogastrostomy and pancreatojejunostomy. World J Surg 2002; 26:366-371.
38 **Talamini G, Bassi C, Butturini G, Falconi M, Casetti L, Gumbus A, et al:** Outcome and quality of life in chronic pancreatitis. JOP 2001; 2:117-123.
39 **McLachlan SA, Devins GM, Goodwin PJ:** Validation of the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (QLQ-C30) as a measure of psychosocial function in breast cancer patients. Eur J Cancer 1998; 34:510-517.
40 **Billingham LJ, Abrams KR:** Simultaneous analysis of quality of life and survival data. Stat Methods Med Res 2002; 11:25-48.
41 **Fitzsimmons D, Johnson CD:** Quality of life after treatment of pancreatic cancer. Langenbeck's Arch Surg 1998; 383:145-151.
42 **Fitzsimmons D, Johnson CD, George S, Payne S, Andrén Sandberg A, Bassi C, et al on behalf of the EORTC study group on quality of life:** Development of a disease specific quality of life (QoL) questionnaire module to supplement the EORTC core cancer QoL questionnaire, the QLQ-C30 in patients with pancreatic cancer. Eur J Cancer 1999; 35:939-941.
43 **Scheingraber S, Scheingraber T, Brauckhoff M, Dralle H:** Comparison between a general and a disease-specific health-related quality-of-life questionnaire in patients after pancreatic surgery. J Hepatobiliary Pancreat Surg 2005; 12:290-297.
44 **Nieveen van Dijkum EJM, Kuhlmann KFD, Terwee CB, Obertop H, de Haes JCJM, et al:** Quality of life after curative or palliative surgical treatment of pancreatic and periampullary carcinoma. Br J Surg 2005; 92:471-477.
45 **Spanknebel K, Conlon KCP:** Advances in the surgical management of pancreatic cancer. Cancer J 2001; 7:312-323.

Pancreas
Vol. 21, No. 1, pp. 14–21
© 2000 Lippincott Williams & Wilkins, Inc., Philadelphia

A New Biodegradable Stent for the Pancreaticojejunal Anastomosis After Pancreaticoduodenal Resection: In Vitro Examination and Pilot Experiences in Humans

Mickael Parviainen, Juhani Sand, *Aimo Harmoinen, †Heikki Kainulainen, ‡Tero Välimaa, ‡Pertti Törmälä, and Isto Nordback

*Departments of Surgery and *Clinical Chemistry, Tampere University Hospital and Medical School, University of Tampere, and †Institute of Medical Technology, and ‡Institute of Biomaterials, University of Technology, Tampere, Finland*

Summary: We sought to develop a biodegradable pancreatic stent that could be easily placed at operation into the human pancreatic duct and the degradation of which could be easily followed up. Spiral-shaped, gamma-sterilized stents were manufactured of 0.4-mm polylactide wire in which there was added 23 weight-% barium sulfate. The biodegradability of the stents was studied in vitro at two different pH values, the first resembling that of pancreatic juice and the other that of bile. The effects of enzymoactivity in the test solution and the composition of the stents (with or without barium addition) also were tested. These kinds of stents have been experimented with in two pilot patients. Degradation of the stents occurred from 24 to 52 weeks of incubation. Alkaline milieu together with the presence of pancreatic enzyme made the stents degrade twice as fast as when either alkaline milieu or enzyme was present. In the milieu resembling pancreatic juice, barium sulfate had no effect on the degradation time. Neither of the pilot patients had any postoperative complications. Biodegradable, x-ray–positive stents degrade faster in pancreatic than in biliary milieu. Their safety and efficacy in human pancreaticojejunal anastomoses need further study. **Key Words:** Pancreas—Resection—Anastomosis—Biodegradable—Stent.

The most important complication after pancreaticoduodenal resection is the anastomotic leakage, which occurs in ~13% of the patients, ranging from none (1–3) to 28% (4). The criteria for leakage are amylase activity in the drainage (>3 times the respective serum level) and the amount of the secretion (>50 ml/day on postoperative day 7). The patient may have clinical or laboratory signs of intraabdominal infection and may develop an abscess (4). One important cause of these leakages may be postoperative pancreatitis, resulting in partial dehiscence of anastomosis (5). Another possible complication of the pancreaticojejunal anastomosis is a stricture formation that can seldom be shown directly. Impairment of the exocrine function of the pancreas may, however, partly be explained by such a stricture (6).

Manuscript received August 2, 1999; revised manuscript accepted December 4, 1999.

Address correspondence and reprint requests to Dr. J. Sand, Department of Surgery, Tampere University Hospital, P.O.B. 2000, FIN-33521 Tampere, Finland. E-mail: juhani.sand@tays.fi

There have been efforts to solve these problems by using different kinds of drainage methods. For example, with a percutaneous T drain, the risk of a pancreaticojejunal anastomotic leakage has been lowered to 3%, but this method has not been protected from the impairment of the exocrine function of the pancreas (7). There have been similar figures when using a silicone drain externally (8). Internal polytetrafluoroethylene stents have been experimentally used in animals, and they seemed to prevent anastomotic leakages and strictures, although the results were not statistically significant (3).

Biodegradable implants have been used in orthopaedics for >10 years (9–15) as intraosseal pins and screws. One of the used materials is polylactide (PLA), the degradation of which is considerably slower than the degradation of polyglycolide (PGA) and polydioxanone (PDS) (16–18). These materials have been used in resorbable sutures (e.g., Vicryl, Dexon) since 1970 (19–21).

In urology, biodegradable, self-expanding stents have been tested clinically in the treatment of benign prostatic hyperplasia, and they have been considered superior to

suprapubic catheters in preventing urinary retention after laser resection of the prostate (9,10). Moreover, according to an experimental study, there have been promising results in prevention of restenosis of urethral strictures (22).

In gastroenterology, a biodegradable stent has been tested in the treatment of benign esophageal stricture associated with radical radiotherapy (23). In that case report, the poly-L-lactide stent began to collapse 6 weeks after it had been inserted. Until now, to our knowledge, biodegradable stents have not been developed for pancreatobiliary operations.

Our aim was to develop a biodegradable pancreatic stent that could be easily placed at operation into the human pancreatic duct and the degradation of which could easily be followed up. We also wanted to examine its mechanical properties in vitro, evaluating the effect of pH, amylase/lipase activity, and barium (to visualize stents in plain radiographs) on its biodegradability. Finally, we report our experiences with the first pilot patients.

MATERIALS AND METHODS

Originally, our idea was to have a stent manufactured of a poly-L,D-lactide (PLA 96, L/D ratio, 96:4) spiral covered by a polyglycolide (PGA) membrane, the latter being meant to protect the anastomosis from a leakage, and the former, from a stricture. There were different sizes of stents to fit the pancreatic ducts with use of a metal guide. We soon noticed that this two-part stent was too stiff and almost impossible to insert into the human pancreatic duct. Thus, the PGA cover was abandoned.

How to follow the degradation in vivo

Follow-up of the degradation of the stents in vivo was tried with magnetic resonance imaging (MRI). This was based on our initial observation that the stent could be seen in vitro as a signal-free zone when using 5-mm axial segments in T_1 and T_2 examinations. Unfortunately the stents could not be detected in vivo with MRI in our three pilot patients, probably because of artefactual movements of breathing and vascular pulse. Nor could they be followed up with a gastroscope, as the anastomosis could not always be reached with the scope.

Use of an x-ray–positive compound as a part of the stents was first tested with zirconium oxide by placing the volunteer supine and taking a radiograph so that the stents were under the back (body mask). The stents could be detected well enough, but the possible tissue toxicity of zirconium oxide (24–26) made us abandon that compound. We also tested similarly calcium sulfate incorporated stents but found these invisible in the body-masked radiographs. The best results were achieved when barium sulfate, a common contrast medium, was incorporated into the stents. The biodegradability of this kind of stent was investigated in vitro.

Final stent composition

The spiral-shaped and gamma-sterilized stents were manufactured of 0.4-mm polylactide (PLA 96) wire in which there was added 23 weight % barium sulfate during the manufacturing process. The PLA96 (L/D ratio, 96:4) was obtained from Purac Biochem b.v., The Netherlands, and barium sulfate ($BaSO_4$) from Fluka Chemie AG, Switzerland. The self-reinforcing (SR) wire of the stent was made by solid-state drawing. The draw ratio of the self-reinforced wire was 6. The diameter of the wire was 0.4 ± 0.05 mm, and the outside diameters of the stents were 3 ± 0.2 mm (Fig. 1). The lengths of the stents in compression tests were 15 mm.

In vitro studies

The in vitro biodegradability of the stents was studied at two different pH values, the first resembling that of pancreatic juice (normal range, 7.0–8.4) (27), and the other, that of bile (normal range, 6.5–7.7) (28,29). The effects of enzymoactivity in the test solution and the composition with or without barium addition to the stents also were tested. The temperature of the solutions was 37°C. Thus there were four different study groups. The characteristics of the groups were

Study group A: pH 6.8, PLA 96 stents with barium sulfate in an enzyme-substituted solution;
Study group B: as in study group A, except that pH was 8.4;

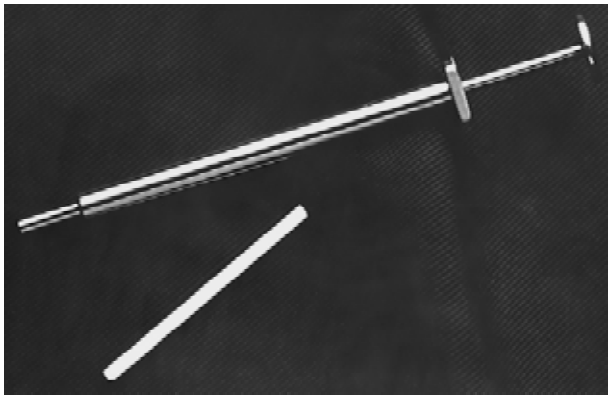

FIG. 1. A biodegradable, x-ray–positive pancreatic stent with an applicator.

Study group C: as in study group B, except that the stents were without barium sulfate; and

Study group D: as in study group B, except that the solution was without enzyme.

The pH values tended to change between the changes of the incubation medium. The values tended to decrease in solutions A (2.5%), B, and C (12%) and increase in solution D (0.3%). They still remained within the physiologic limits.

In vitro enzyme substitution constituted distilled water mixed with crushed granules of Pankreon, 300 mg (Kali-Chemie GmbH, Hannover, Germany) enterocapsules, which contain lipase, amylase, and protease.

Salts were added to simulate body fluids: sodium chloride concentrate [Addex-Natriumklorid infusion concentrate (Na, 4 mmol/ml; Cl, 4 mmol/ml), Pharmacia AB, Stockholm, Sweden], potassium chloride concentrate [Kalisteril, 150 mg/ml infusion concentrate (K, 2 mmol/ml; Cl, 2 mmol/ml), Medipolar (Orion Company), Oulu, Finland], and sodium bicarbonate [Natr.bicarb., 75 mg/ml infusion solution (Na, 90 mmol/100 ml; HCO_3, 90 mmol/100 ml), Pharmacia AB, Stockholm, Sweden].

The pH values of the new solutions were measured and titrated to the desired level by using 2–6 *M* NaOH and HCl solutions and electrolyte concentrations. These were Na^+, 120 (normal range in pancreatic juice, 115–180) mEq/ml; K^+, 5 (normal range, 3–8) mEq/ml; Cl–, 55 (normal range, 55–95) mEq/ml; and HCO_3^-, 70 (normal range, 60–110) mEq/ml (16).

The solutions were changed twice a week. Crushed Pankreon granules were daily added into the solutions (study groups A–C) to maintain the enzyme activity of the solution within the normal range of human pancreatic juice, amylase being 100,000–800,000 U/L (30,31). Our initial observation showed that the amylase activity of the solution decreased to 13% of the original activity in 1 day. Other pancreatic enzymes were not measured. We noticed that the concentration of HCO_3^- in the solutions decreased below the lower range after 4 days of incubation. The pH was also measured daily and titrated by using the previously mentioned acids and bases to maintain the pH corresponding to the pancreatic juice in study groups B–D and bile in study group A.

The 15-mm-long stents with barium sulfate (study groups A, B, and D) and those without it (study group C) were incubated, the number of stents per volume unit being determined by the FDA Guidance Document for Testing Biodegradable Polymer Implant Devices (32).

After a certain period of weeks (Figs. 2 and 3) three stents were randomly chosen. The compression stability of each stent was tested. The compression test was performed by using Lloyd LR30K Materials Testing Machine (Lloyd Instruments PLC, Faremham, U.K.), and the stents being measured were put horizontally between two parallel planes. The measured buckling force was the maximal force before the stent collapsed. Compression modulus is a variable that characterizes the rigidity of the spiral (33). The experiment was continued until all stents were degraded. Mean of the three stents at each time point is given.

Bonferroni Multiple Comparisons Test was used to test the statistical significance of the results between the groups.

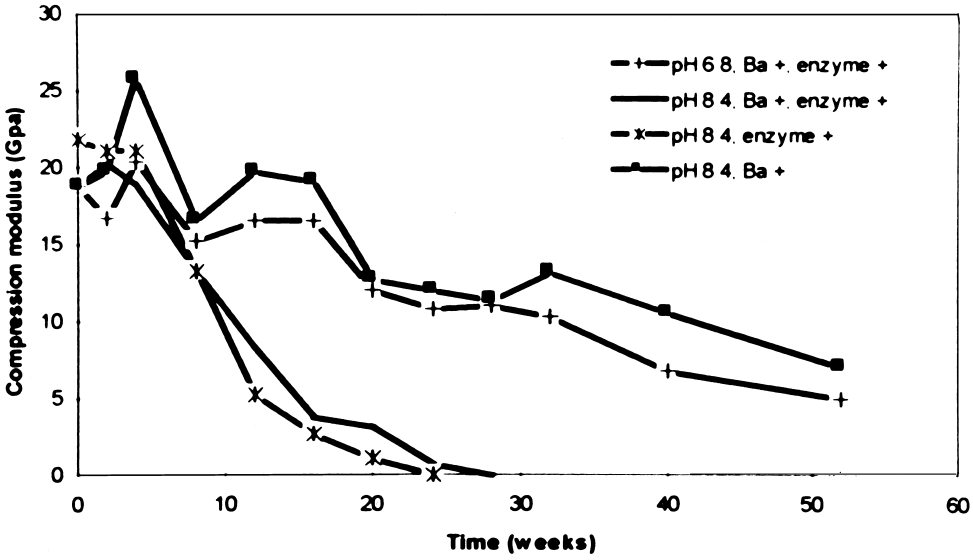

FIG. 2. Effect of pancreatic enzyme and pH on the compression modulus of the stents.

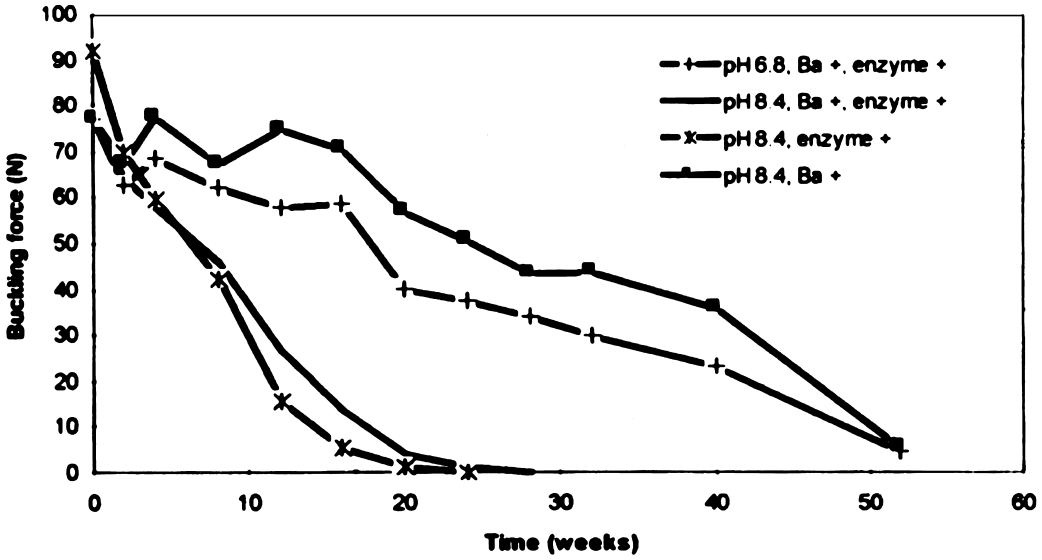

FIG. 3. Effect of pancreatic enzyme and pH on the buckling force of the stents.

RESULTS

In vitro

Complete degradation of the stents occurred between 24 and 52 weeks of incubation, depending on the milieu (Figs. 2 and 3). Alkaline milieu and the presence of enzyme accelerated degradation of the stents and made them degrade twice as fast as when either alkaline milieu or amylase was present. In alkaline milieu and in the presence of enzyme, there was no significant difference in the degradation time when presence of barium sulfate was considered (Figs. 2 and 3). Results of the statistical analysis are shown in Tables 1 and 2.

In vivo

Two patients, a 66-year-old woman and a 67-year-old man, underwent pylorus-preserving pancreaticoduodenectomy for periampullary carcinoma, and the woman also an extended retroperitoneal lymphadenectomy with the extension of the pancreas resection 5 cm left to the superior mesenteric vein. They gave written consent for the stent experiment, which was approved by the Ethical Committee of Tampere University Hospital. Both patients had fibrosis in the resection lines of the pancreas. After the resection, the diameter of the duct in the pancreatic body was measured by probing, and was 3.0–3.5 mm. The invaginated pancreaticojejunal anastomosis was sutured in two layers with interrupted 4-0 Surgilon (Davis Geck, Wayne, NJ, U.S.A.) stitches (34). Before completion of the anterior part of the anastomosis, a 5-cm-long barium sulfate-PLA 96 spiral stent with an outer diameter of 3 mm (inner diameter, 2.2 mm) was placed into the pancreaticojejunal anastomosis with a

TABLE 1. *Statistical difference (*p *values) of the effect of pH (study groups 1 and 2), barium sulfate (study groups 2 and 3), and enzymes (study groups 2 and 4) when compression modulus is considered*

Weeks	pH	Barium sulfate	Enzymes
0	NS	NS	NS
2	NS	NS	NS
4	NS	NS	NS
8	NS	NS	NS
12	<0.05	NS	<0.01
16	<0.001	NS	<0.001
20	<0.01	NS	<0.01
24	<0.001	NS	<0.001
28	<0.001	NS	<0.001
32	<0.001	NS	<0.001
40	<0.001	NS	<0.001
52	<0.001	NS	<0.001

TABLE 2. *Statistical difference (*p *values) of the effect of pH (study groups 1 and 2), barium sulfate (study groups 2 and 3), and enzymes (study groups 2 and 4) when buckling force is considered*

Weeks	pH	Barium sulfate	Enzymes
0	NS	<0.01	NS
2	NS	NS	NS
4	NS	NS	<0.05
8	NS	NS	<0.05
12	<0.01	NS	<0.001
16	<0.001	NS	<0.001
20	<0.001	NS	<0.001
24	<0.001	NS	<0.001
28	<0.001	NS	<0.001
32	<0.001	NS	<0.001
40	<0.001	NS	<0.001
52	<0.001	NS	<0.001

tailor-made applicator (Fig. 1), so that 1.0 cm of the stent was within the pancreatic duct. Neither of the patients had any postoperative complications during hospitalization. Early postoperative plain radiographs confirmed the stents in place (Figs. 4 and 5). At 8 weeks the man was symptomless, and the female complained of some diarrhea. Plain radiograph controls showed that the stent had disappeared in the man (Fig. 6). In the woman, a piece of the stent could be seen in a radiograph photo 12 (Fig. 7) and 16 (Fig. 8) weeks postoperatively. Both patients had normal liver chemistry. At 8 weeks, fecal elastase in both patients was <15 μg/g, indicating pancreatic exocrine insufficiency. Both used enzyme substitution.

DISCUSSION

Numerous efforts have been made to reduce the incidence of postoperative complications of the pancreaticojejunal anastomosis after pancreaticoduodenal resections. Results of using metal and plastic stents have been controversial (3). Biodegradable stents in these anastomoses have not been experimented with until now, as they are quite new in gastroenterology.

FIG. 4. In the male patient, the stent can be distinguished in the early postoperative radiograph photo on the right side of the first lumbar vertebra.

FIG. 5. In the female patient, the stent can be distinguished in the early postoperative radiograph photo on the left side of the body of the first lumbar vertebra.

We have developed a new, biodegradable, radioopaque stent to be used to protect pancreaticojejunal anastomosis after pancreaticojejunal resection and investigated its properties in vitro.

When developing a biodegradable stent, it is absolutely necessary to know how long it takes to dissolve. That means one must be able to follow the degradation in vivo. Our attempts to follow the degradation of the stents with MRI or gastroscope did not succeed, even though the stent could be localized with MRI in an ex vivo experiment. Finally, we decided to use barium sulfate mixed with PLA, and after that were able to follow the degradation with plain radiograph. In orthopaedics the degradation of biodegradable pins and screws has been followed up with MRI (35). Biodegradable urethral stents have been followed up with cystoscopy (36), and the esophagus stent, with gastroscopy (23).

Our hope was to diminish both problems associated with pancreaticojejunal anastomoses: early leakage and late obstruction. So we made a stent with an inner slowly degradable spiral to keep the anastomosis open as previously used in urology (10). The spiral was then covered

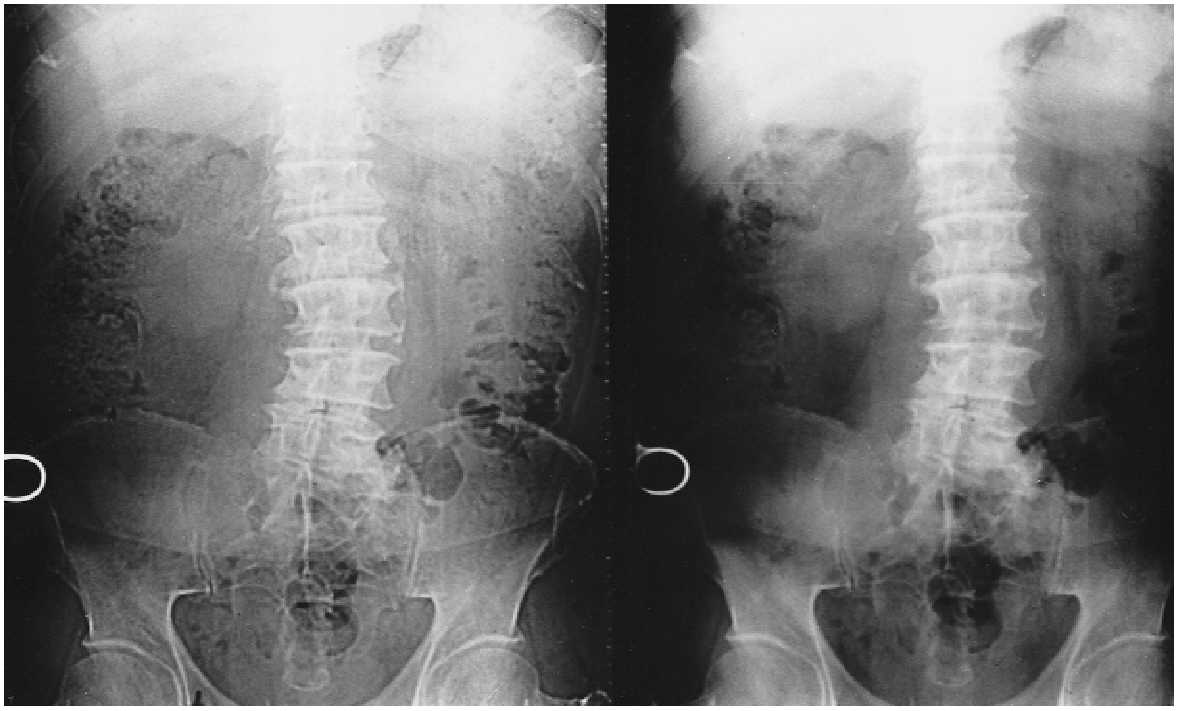

FIG. 6. The stent has disappeared in the male patient 8 weeks postoperatively.

FIG. 7. A piece of the stent can be distinguished in the female patient on the left side of the body of the second lumbar vertebra in the radiograph photo taken 12 weeks postoperatively.

FIG. 8. A piece of the stent can still be distinguished in the female patient on the left side of the intervertebral space of the first and second lumbar vertebrae in the radiograph photo taken 16 weeks postoperatively. This photo was taken supine.

with a faster degradable polyglycolide sheet to lead the pancreatic juice away from the anastomosis, thus perhaps ameliorating the effects of anastomotic dehiscence. However, there were too many technical problems to insert such a double-layer prosthesis into the anastomosis, and we decided to continue with the spiral only.

Before in vivo experiments, it is essential to know how long it takes until the stents collapse. So we tested the mechanical properties of stents in milieux resembling that of pancreatic juice and bile. In enzyme-rich alkaline solution, as in pancreatic juice, the stents lost their rigidity in ~6 months. That is the same time as reported for an esophageal stent in vivo (23). In the milieu resembling that of bile, the stents did not collapse until after a year of incubation. In the milieu resembling pancreatic juice, barium sulfate had no effect on the degradation time. The alkaline milieu or enzymes did not have effect separately on the degradation time of barium sulfate stents. When the milieu was alkaline and enzymes were present, the degradation rate was twice as fast compared with a milieu where only one of these components was present.

In light of our pilot patients, these stents seem to be safe, although the pancreatic duct tissue reaction to the PLA stent needs further study. In addition to the previously mentioned two patients, we had three others, in whom degradation of the stents could not be followed up. One of the two pilot patients was asymptomatic, but both had low fecal elastase values. We do not know if the stents protected the pancreaticojejunal anastomosis of these patients after all, or if they had too little functional pancreatic tissue left. A method to follow up the patency of the anastomosis is needed to distinguish these conditions. Nor do we know if the degradation time is suitable (i.e., if the composition of the stents is optimal). When using plastic stents for biliary strictures, it is known that occlusion of the stents occurs in a median of 14 weeks (37). The stents should probably degrade faster, as there could still be seen particles of the stent in the plain radiograph photo of one patient 16 weeks postoperatively, and ex vivo, the time to collapse was about 24 weeks. Risk of pancreatitis may increase if the stent degrades too slowly, allowing clothing to occur. Conversely, maturing of the scar tissue in the anastomosis may take ~6 months (38) and to ensure the patency of the anastomoses, the stent should stay in its place long enough. The degradation time also may vary from patient to patient according to the exocrine function of the remaining pancreas.

In conclusion, it is possible to make biodegradable stents, the degradation of which can easily be followed up with simple plain radiographs, for human pancreatic anastomoses. Alkaline- and enzyme-rich milieux, as around pancreatic anastomoses, accelerate the degradation of the stents when compared with biliary-type milieu. Further studies are needed to confirm the safety and efficacy of such stents in human pancreaticojejunal anastomoses.

Acknowledgment: We thank Miss Hannele Kuivanen, M.B., from University of Tampere, and Mrs. Maiju Kylmäkoski, Mrs. Raija Reinikainen, and Mrs. Tuija Virta from Tampere University of Technology for technical assistance during the in vitro study. We also thank Mr. Olavi Hartman from Tampere University Hospital for photo processing.

This study was financially supported by the Medical Research Fund of Tampere University Hospital.

REFERENCES

1. Kingsnorth AN. Duct to mucosa isolated roux loop pancreaticojejunostomy as an improved anastomosis after resection of the pancreas. *Surg Gynecol Obstet* 1989;169:451–3.
2. Maki HS, Kolts RL, Kuehner ME. Prevention of pancreatic fistula by modified pancreaticojejunal anastomosis. *Am J Surg* 1990;160: 533–4.
3. Biehl T, Traverso LW. Is stenting necessary for a successful pancreatic anastomosis? *Am J Surg* 1992;163:530–2.
4. Büchler M, Friess H, Klempa I, et al. Role of octreotide on the prevention of postoperative complications following pancreatic resection. *Am J Surg* 1992;163:125–31.
5. Parviainen MC, Sand JA, Nordback IH. Coincidence of pancreatic and biliary leakages after pancreaticoduodenal resections. *Hepatogastroenterology* 1996;43:1246–9.
6. Tanaka T, Ichiba Y, Fujii Y, Kodama O, Dohi K. Clinical and experimental study of pancreatic exocrine function after pancreaticoduodenectomy for periampullary carcinoma. *Surg Gynecol Obstet* 1988;166:200–5.
7. Hall RI, Rhodes M, Isabel-Martinez L, Kelleher J, Venables CW. Pancreatic exocrine function after a sutureless pancreaticojejunostomy following pancreaticoduodenectomy. *Br J Surg* 1990;77: 83–5.
8. Keck H, Steffen R, Waluja W, Neuhaus P. Anastomosenprotektion durch ein spezielles Drainageverfahren bei der Kausch-Whipple-Operation. *Chirurgie* 1991;62:561–5.
9. Pétas A, Talja M, Tammela T, et al. A randomized study to compare biodegradable self-reinforced polyglycolic acid spiral stents to suprapubic and indwelling catheters after visual laser ablation of the prostate. *J Urol* 1997;157:173–6.
10. Talja M, Tammela T, PJtas A, et al. Biodegradable self-reinforced polyglycolic acid spiral stent in prevention of postoperative urinary retention after visual laser ablation of the prostate: laser prostatectomy. *J Urol* 1995;154:2089–92.
11. Rokkanen P, Böstman O, Hirvensalo E, et al. The use of absorbable internal fracture fixation devices. *Adv Biomater* 1992;10:447.
12. Böstman O, Vainionpää S, Hirvensalo E, et al. Biodegradable internal fixation for malleolar fractures: a prospective randomised trial. *J Bone Joint Surg Br* 1987;69:615–94.
13. Rokkanen P. Absorbable implants in the fixation of fractures. *Ann Chir Gynaecol* 1990;79:117–22.
14. Rokkanen P, Böstman O, Vainionpää S, et al. Biodegradable implants in fracture fixation: early results of treatment of fractures of the ankle. *Lancet* 1985;1:1422–4.
15. Wüstner MC, Partecke BD, Buck-Gramcko D. Resorbierbare PDS-splinte zur frakturstabilisierung und fhr arthrodesen an der hand. *Handchir Mikrochir Plast Chir* 1986;18:298–301.
16. Päivärinta U, Böstman O, Majola A, Toivonen T, Törmälä P, Rokkanen P. Intraosseous cellular response to biodegradable frac-

ture fixation screws made of polyglycolide or polylactide. *Arch Orthop Trauma Surg* 1993;112:71–4.
17. Böstman OM. Absorbable implants for the fixation of fractures. *J Bone Joint Surg Am* 1991;73:148–53.
18. Miller RA, Brady JM, Cutright DE. Degradation rates of oral resorbable implants (polylactates and polyglycolates): rate modification with changes in PLA/PGA copolymer ratios. *J Biomed Mater Res* 1977;11:711–9.
19. Chu CC. A Comparison of the effect of pH on the biodegradation of two synthetic absorbable sutures. *Ann Surg* 1982;1:55–9.
20. Chu CC. The effect of gamma irradiation on the enzymatic degradation of polyglycolic acid absorbable sutures. *J Biomed Mater Res* 1983;17:1029–40.
21. Mäkelä EA, Böstman O, Kekomäki M, et al. Biodegradable fixation of distal humeral physeal fractures. *Clin Orthop* 1992;283: 237–43.
22. Kemppainen E, Talja M, Riihelä M, Pohjonen T, Törmälä P, Alfthan O. A bioresorbable urethral stent: an experimental study. *Urol Res* 1993;21:235–8.
23. Fry SW, Fleischer DE. Management of a refractory benign esophageal stricture with a new biodegradable stent. *Gastrointest Endosc* 1997;45:179–82.
24. Ghosh S, Sharma A, Talukder G. Cytotoxic effects of zirconium oxychloride on bone marrow cells of mice. *Mutat Res* 1990;243: 29–33.
25. Takamura K, Hayashi K, Ishnishi N, Yamada T, Sugioka Y. Evaluation of carcinogenicity and chronic toxicity associated with orthopaedic implants in mice. *J Biomed Mater Res* 1994;28:583–9.
26. Ghosh S, Sharma A, Talukder G. Zirconium: an abnormal trace element in biology. *Biol Trace Elem Res* 1992;35:247–1.
27. Reber HA, Way LW. Pancreas. In: Way LW, ed. *Current surgical diagnosis and treatment*. 6th ed. Los Altos, CA: Lange Medical Publications, 1988:536–57.
28. Mayes PA. Digestion/absorption in the gastrointestinal tract. In: Martin DW, Mayes PA, Rodwell VW, eds. *Harper's review of biochemistry*. 18th ed. Los Altos, CA: Lange, 1981:527–39.
29. Ewe K, Karbach U. Functions of the alimentary canal: liver and biliary system. In: Schmidt Robert F, Thews Gerhard, eds. *Human physiology*. 2nd ed. Berlin: Springer-Verlag, 1989:717–21.
30. Humphreys MH. Fluid and electrolyte management. In: Way LW, ed. *Current surgical diagnosis and treatment*. 8th ed. Los Altos, CA: Appleton & Lange, 1988:128–40.
31. Demetriou JP, Drewes PA, Gin JB. Enzymes. In: Henry RJ, Cannon DC, Winkelman JW, eds. *Clinical chemistry, principles and technics*. 2nd ed. Hagerstown, MD: Harper & Row, 1974:815–1001.
32. McDermott K. Guidance document for testing biodegradable polymer implant devices (draft): division of general and restorative devices center for devices and radiological health. U.S. Food and Drug Administration, 1996.
33. Andersen TL, Lystrup A. Room temperature filament winding of thermoplastic composites. *Plast Rubber Composites Processing Appl* 1993;19:143–9.
34. Cameron JL. Pancreaticoduodenectomy (pylorus-preserving Whipple procedure). In: Cameron JL, ed. *Atlas of surgery*. Vol I. Toronto: BC Decker, 1990:386–413.
35. Pihlajamäki HK, Karjalainen PT, Aronen HJ, Böstman OM. MR imaging of biodegradable polylevolactide osteosynthesis devices in the ankle. *J Orthop Trauma* 1997;11:559–64.
36. Pétas A, Talja M, Tammela TL, Taari K, Välimaa T, Törmälä P. The biodegradable self-reinforced poly-D-L-lactic acid spiral stent compared with a suprapubic catheter in the treatment of postoperative urinary retention after visual laser ablation of the prostate. *Br J Urol* 1997;80:439–43.
37. Pitt HA, Kaufman SL, Coleman J, White RI, Cameron JL. Benign postoperative biliary strictures: operate or dilate? *Ann Surg* 1989; 210:417–27.
38. Lillemoe KD, Pitt HA, Cameron JL. Current management of benign bile duct strictures. *Adv Surg* 1992;25:119–74.