Systematic review of functional outcome and quality of life after total pancreatectomy

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Background: Surgeons have traditionally been reluctant to perform total pancreatectomy because of concerns for brittle diabetes and poor quality of life (QoL). Several recent studies have suggested that outcomes following total pancreatectomy have improved, but a systematic review is lacking.

Methods: A systematic review was undertaken of studies reporting on outcomes after total pancreatectomy for all indications, except chronic pancreatitis. PubMed, EMBASE (Ovid), and Cochrane Library were searched (2005–2018). Endpoints included functional outcome and QoL.

Results: A total of 21 studies, including 1536 patients, fulfilled the eligibility criteria. During a median follow-up of 20·8 (range 1·5–96·0) months, 18·6 per cent (45 of 242 patients) were readmitted for endocrine-related morbidity, with associated mortality in 1·6 per cent (6 of 365 patients). No diabetes-related mortality was reported in studies including only patients treated after 2005. Symptoms related to exocrine insufficiency were reported by 43·5 per cent (143 of 329 patients) during a median follow-up of 15·9 (1·5–96·0) months. Overall QoL, reported by 102 patients with a median follow-up of 28·6 (6·0–66·0) months, using the EORTC QLQ-C30 questionnaire, showed a moderately reduced summary score of 76 per cent, compared with a general population score of 86 per cent ($P = 0.004$).

Conclusion: Overall QoL after total pancreatectomy is affected adversely, in particular by the considerable impact of diarrhoea that requires better treatment. There is also room for improvement in the management of diabetes after total pancreatectomy, particularly with regards to prevention of diabetes-related morbidity.

Introduction

The most common indication for total pancreatectomy is pancreatic cancer, but total pancreatectomy is increasingly performed for main-duct/mixed-type intraductal papillary mucinous neoplasm (IPMN)[1−3]. Total pancreatectomy for IPMN requires extensive counselling, as this is prophylactic surgery. Other indications for total pancreatectomy could be multifocal pancreatic disease (such as neuroendocrine tumours and renal cell cancer metastases) and technical difficulties, or patients with a very high risk of having a pancreatic anastomosis (for instance in arterial reconstruction)[4−6].

Most surgeons have traditionally been reluctant to perform total pancreatectomy because of the associated postoperative morbidity and resulting lifelong insulin-

dependent brittle diabetes, with risk of severe hypoglycaemia and substantial impact on quality of life (QoL).

In recent years, several investigators have suggested that the role of total pancreatectomy in IPMN should be expanded as the postoperative management has improved[7]. Of note, a recent international survey[8] showed no consensus on the use of total pancreatectomy in patients with main-duct/mixed-type IPMN. This lack of consensus is likely to be related to concerns regarding total pancreatectomy-related diabetes and exocrine insufficiency. Others[1,4] have questioned whether any indication remains for an upfront total pancreatectomy in the current era of improved imaging.

Knowledge of long-term functional (endocrine and exocrine insufficiency) outcomes and QoL after total

pancreatectomy is therefore essential during preoperative counselling and shared decision-making. This systematic review focuses on short- and long-term functional outcomes after total pancreatectomy, and its impact on QoL.

Methods

This systematic review was registered with PROSPERO (registration number CRD420016051093)[9] and performed in accordance with the PRISMA guidelines[10].

Search strategy

A systematic literature search was conducted in PubMed, EMBASE (Ovid), and the Cochrane Library for studies published from 1 January 2005 to 31 January 2018. This inclusion period was chosen because management of endocrine and exocrine insufficiency seems to have improved in recent years[11]. The main search term was 'total pancreatectomy'. The full search strategy is shown in *Table S1* (supporting information). Restrictions on English language and studies older than 13 years (arbitrary cutoff) were applied. After excluding duplicates, studies were screened by two authors independently, according to the eligibility criteria by title, abstract and full text. The final decision on eligibility was made by consensus.

Eligibility criteria

Studies of at least ten patients reporting on functional outcomes and QoL after total pancreatectomy were considered eligible. Studies or subgroups where more than 10 per cent of patients had undergone total pancreatectomy for chronic pancreatitis were excluded unless results were given separately. Benign indications with no further description were considered as chronic pancreatitis. Conference abstracts and review articles were also excluded. When there were overlapping cohorts, only unique results were used. If there were overlapping outcomes between these cohorts, the largest study was chosen for analysis.

Definitions

Total pancreatectomy was defined as removal of the entire pancreas, with or without splenectomy, performed via either an open or minimally invasive technique. Primary total pancreatectomy was defined as elective total pancreatectomy (planned before surgery as well as decided during the operation), and emergency total pancreatectomy as surgery performed as a result of trauma. Urgent completion total pancreatectomy was defined as emergency total

pancreatectomy for postoperative complications after pancreatoduodenectomy, whereas elective completion total pancreatectomy was performed mostly for recurrence in the remnant pancreas.

Endocrine insufficiency was defined as diabetes after total pancreatectomy, classified by the WHO[12] and the American Diabetes Association[13] as one of the causes of pancreatogenic (type 3c) diabetes. Exocrine insufficiency was defined as inadequate pancreatic enzyme function, with or without related symptoms, that required enzyme substitution.

Where only readmissions were reported, these were not defined as complications to avoid underestimation of diabetes-related morbidity. Invasive or malignant IPMNs were grouped under carcinomas as 'invasive IPMN'. When studies did not report the grade of dysplasia, the IPMNs were grouped as 'potentially malignant'. When studies presented only the minimum duration of follow-up, that value was chosen to calculate the pooled weighted median. When studies presented the maximum follow-up or the range, the half of this value was used to calculate the pooled weighted median. The postoperative period was defined as a maximum of 90 days after surgery.

Extracted data

The following data were extracted per study by two authors: first author, country, year of publication, study design, age, sex, diagnosis/indication for surgery, duration of follow-up, number of patients undergoing total pancreatectomy, and outcomes of exocrine and endocrine insufficiency and QoL. Two authors cross-checked all data independently. Corresponding authors of the included studies were contacted where there was missing or insufficient data. The European Organization for Research and Treatment in Cancer Quality of Life Questionnaire Cancer (EORTC QLQ-C30) global health status, functioning and symptom scores were determined, and differences with the general population calculated. Clinically important differences were categorized and defined according to Osoba *et al.* [14]: less than 5 per cent, no change; 5–10 per cent, a little change; 10–20 per cent, moderate change; more than 20 per cent, very much change.

Quality assessment

The methodological quality of the included studies was assessed by two authors independently, using the Newcastle–Ottawa Scale (NOS)[15]. Methodological quality was scored for 'selection of patients', 'comparability' and 'outcome of study participants', and was ranked with a maximum of 5 points. In this systematic review, the parts

Fig. 1 PRISMA diagram for the systematic review
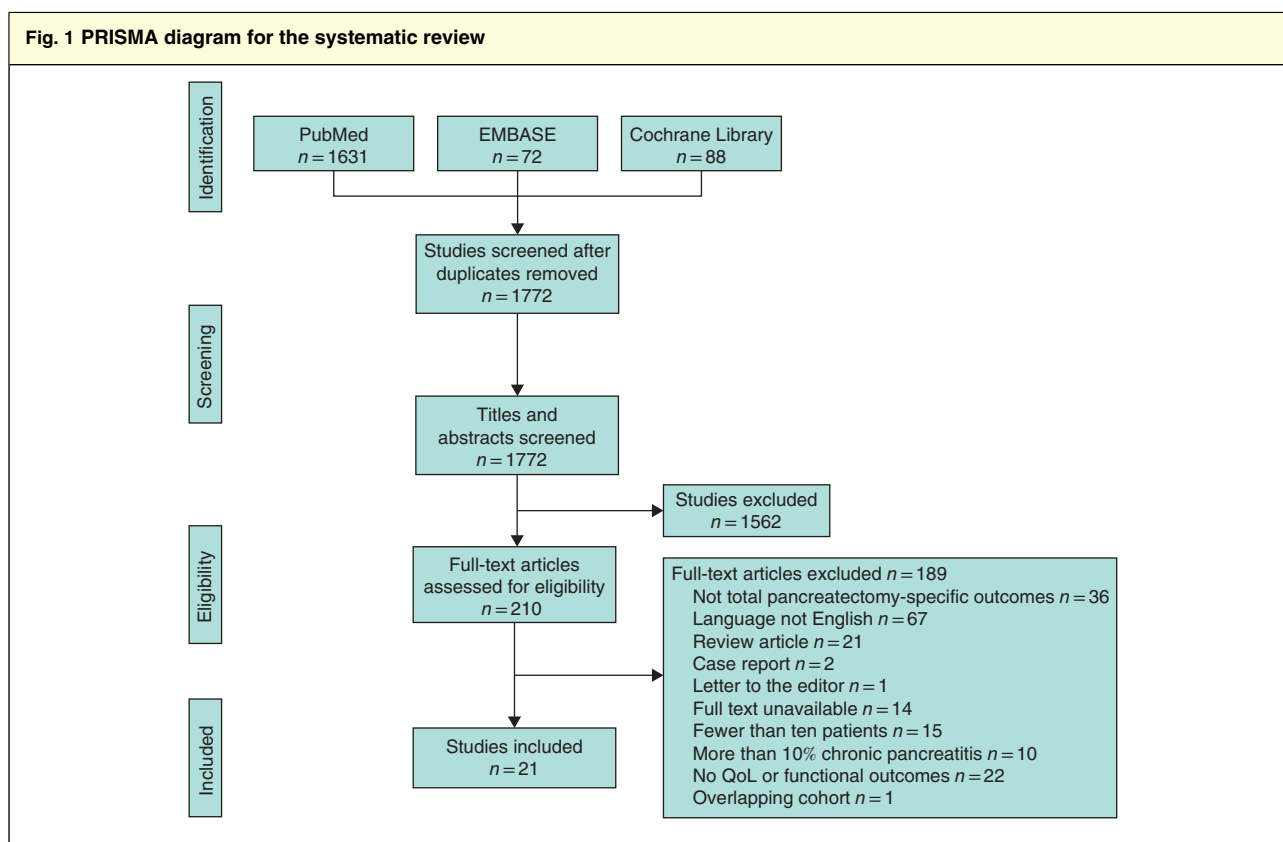
QoL, quality of life.

of the NOS score ('selection of the non-exposed', 'outcome of interest' and 'comparability') were not applicable, because of its descriptive nature. In this study, cohort studies with a NOS score of 5 or higher were considered of high quality.

Statistical analysis

Age, length of follow-up and QoL parameters from the different questionnaires are presented as mean(s.d.) and median (range) values. Categorical data are presented as frequencies and percentages. Overall follow-up values are presented as pooled weighted median. When included studies reported median (range) values, means(s.d.) values were calculated using statistical algorithms according to the method of Wan and colleagues[16] and Hozo and co-workers[17]. $P < 0.050$ was considered statistically significant. Statistical analysis was performed using SPSS version 24 (IBM, Armonk, New York, USA).

Results

The systematic search (Table S1, supporting information) identified 21 eligible studies, all cohort studies, comprising 1536 patients undergoing total pancreatectomy[2,6,18−36]. The PRISMA diagram of studies included in this systematic review is presented in Fig. 1. Most patients were men (52·6 per cent), and the median age was 65 years; the methodological quality was scored as high in 20 of the 21 studies (Table S2, supporting information).

Surgical details

Of 1536 patients, indication for total pancreatectomy was pancreatic ductal adenocarcinoma (PDAC) in 806 patients (52·5 per cent) and IPMN in 454 patients (29·6 per cent); IPMN consisted of 227 patients (14·8 per cent) with non-invasive IPMN and 227 (14·8 per cent) with invasive IPMN (Table 1).

In 1254 patients (81·6 per cent), the type of total pancreatectomy (primary versus completion pancreatectomy) was described. Primary total pancreatectomy was performed in 1120 patients (89·3 per cent), of whom 1117 (99·7 per cent) had elective surgery and three (0·3 per cent) had emergency surgery. Completion total pancreatectomy was performed in 134 patients (10·7 per cent), electively in 110 (82·1 per cent) and as an emergency in 24 (17·9 per cent).

Table 1 Diagnosis in patients who had a total pancreatectomy

| Reference | n | Carcinomas | Non-carcinomas | | CP* | Other |
			Potentially malignant	Benign		
Barbier et al.[18]	56	PDAC (4)	IPMN (20)	–	1 (2)	Renal mets (2)
		Invasive IPMN (22)	NET (6)			
		Acinar cell carcinoma (1)				
Casadei et al.[19]†	20	PDAC (7)	IPMN (2)	–	1 (5)	Renal mets (2)
		Invasive IPMN (6)	NET (2)			
Casadei et al.[20]†	73	PDAC (38)	IPMN (15)	–	2 (3)§	Mets (3)
		Periampullary cancer (3)	NET (6)			
						Other (5)
		Serous cystic tumours (1)				
Crippa et al.[21]†	65	PDAC (19)	IPMN (6)	SCA (1)	1 (2)	Renal mets (6)
		Invasive IPMN (25)	NET (6)			
		Periampullary cancer (1)				
Crippa et al.[22]†‡	29¶	Invasive IPMN (13)	IPMN (16)	–	0 (0)	–
Epelboym et al.[23]	77	PDAC (50)	IPMN (15)	SCA (1)	4 (5)§	Renal mets (1)
		Invasive IPMN (2)	NET (4)			
Fujino et al.[24]	36	PDAC (17)	NET (2)	Acute pancreatitis (1)	1 (3)	Mets (1)
		Invasive IPMN (14)				
Hartwig et al.[6]	434	PDAC (289)	IPMN (44)	SCN (4)	4 (0·9)§	Other (4)
		Invasive IPMN (31)	NET (28)			
		Adenosquamous carcinoma (8)				
		Acinar cell carcinoma (4)				
		Other (18)				
Hata et al.[25]	43	PDAC (21)	IPMN (11)	Solid pseudopapillary neoplasm (1)	1 (2)	Mets (3)
			NET (2)	SCN (1) AVM (3)		
Jamil et al.[26]	14	IPMN (9)	IPMN (5)	–	0 (0)	–
Kitagawa et al.[27]	10	Carcinoma (4)	IPMN (5)	Gastrinoma (1)	0 (0)	–
Müller et al.[2]‡	147	PDAC (78)	IPMN (12)	Cystic tumours (5)	13 (8·8)	Renal mets (9)
		Invasive IPMN (10)	NET (11)			
		Periampullary cancer (7)				
		Cystic tumour (2)				
Nikfarjam et al.[28]	15	Adenocarcinoma (13)	IPMN (1)	Cystadenoma (1)	0 (0)	–
Parsaik et al.[29]‡	97	PDAC (49)	Cystic neoplasm (7)	–	0 (0)	Other (14)
		Invasive IPMN (24)				
		Periampullary adenocarcinoma (3)				
Reddy et al.[30]	100	PDAC (100)	–	–	0 (0)	–
Shi et al.[31]	52	PDAC (43)	–	–	0 (0)	Renal mets (1)
		Invasive IPMN (4)				
		Adenosquamous carcinoma (1)				
		Acinar adenocarcinoma (1)				
		Cystadenocarcinoma (2)				
Stauffer et al.[32]	47	PDAC (10)	IPMN (21)	–	2 (4)	Renal mets (1)
		Invasive IPMN (10)	NET (1)			Trauma (1)
		Cholangiocarcinoma (1)				
Suzuki et al.[33]	41	PDAC (13)	IPMN (5)	–	0 (0)	Renal mets (2)
		Invasive IPMN (20)	Intraductal tubulopapillary neoplasm (1)			

Table 1 Continued

| Reference | n | Carcinomas | Non-carcinomas | | | Other |
			Potentially malignant	Benign	CP*	
Takami et al.[34]‡	33	PDAC (25)	IPMN (7)	–	1 (3)§	–
Watanabe et al.[35]	44	PDAC (20)	IPMN (2)	–	1 (2)§	Renal mets (1)
		Invasive IPMN (18)	NET (1)			
		Distal cholangiocarcinoma (1)				
Zakaria et al.[36]	103	PDAC (23)	IPMN (40)	Ampullary adenoma with IPMN (1)	8 (7·8)	Renal mets (1)
		Invasive IPMN (19)	NET (7)			
		Ampullary adenocarcinoma (1)				Trauma (1)
		Cholangiocarcinoma (1)				
		Sarcoma (1)				
Overall*	1536	1106 (72·0)	312 (20·3)	20 (1·3)	40 (2·6)	58 (3·8)

*Values in parentheses are percentages. †No overlapping cohorts; used unique results and the biggest group in case of non-unique results; ‡subgroup used; §benign tumours (possible chronic pancreatitis (CP)); ¶after contacting author. PDAC, pancreatic ductal adenocarcinoma; IPMN, intraductal papillary mucinous neoplasm; NET, neuroendocrine tumour; mets, metastases; SCA, serous cystadenoma; SCN, serous cystic neoplasm; AVM, arteriovenous malformation.

Endocrine insufficiency

Outcomes related to endocrine insufficiency after total pancreatectomy were reported in 19 studies[2,6,18−24,26−33,35,36], including 809 patients, after a median follow-up of 20·8 (range 1·5−96·0) months. The endocrine-related morbidity rate was 25·9 per cent (112 of 432 patients). Ten studies[18−24,32,33,35], including 299 patients, reported the number of prescribed insulin units per day (mean 27 units/day). Mean(s.d.) HbA1c levels at 6 and 12 months after surgery were 7·5(0·5) and 7·2(0·7) per cent respectively[24,26,31−33]. Two studies[31,33] found an increase in HbA1c concentration during the first 3 months after surgery, although stabilization was seen afterwards. During the first year after surgery, HbA1c levels were increased in both benign and malignant diseases, after which the levels remained stable at acceptable levels[6]. For endocrine-related reasons, 45 of 242 patients (18·6 per cent) were admitted to hospital[2,18,19,21,23,26,27,32,35].

Two studies[21,29] reported on long-term diabetes-related complications. Crippa and colleagues[21] reported long-term diabetes-related complications in six of 45 patients after total pancreatectomy (follow-up at least 60 months), including peripheral vascular disease (4 patients), stroke (1) and retinopathy (1). During a median follow-up of 2 years, Parsaik et al[29]. found development of target organ complications in seven of 26 patients.

Nine studies[2,18,19,21,22,24,31,32,35] described diabetes-related mortality, which occurred in six of 365 patients (1·6 per cent). Three patients died from hypoglycaemia, two after 8 and 22 months, and one patient at an unknown time during a median follow-up of 35 (range 4−168) months. Two patients died from ketoacidosis, one patient after 5 months and the other at an unknown time during a median follow-up of 21 (2−222) months. Hyperglycaemia was the cause of death in one patient 17 days after surgery. In addition, diabetes-related mortality was 0 per cent (0 of 94 patients) in the most recent series, comprising the studies that included patients treated after 2005[19,22,31] (*Table 2*).

Exocrine insufficiency

Outcomes related to exocrine insufficiency were reported in 15 studies[2,6,18,19,21,24−27,29,31−35], including 495 patients, during a median follow-up of 19·6 (range 1·5−96·0) months (*Table 3*). Exocrine insufficiency-related symptoms were reported by 43·5 per cent (143 of 329 patients) during a median follow-up of 15·9 (1·5−96·0) months. Among 136 patients receiving pancreatic enzyme substitution, 32 (23·5 per cent) still reported symptoms[18,21,33,35]. In general, the most common symptom was diarrhoea, which occurred in 0−64 per cent of the patients[2,18,21,33−35]. Steatorrhoea was described by two studies[21,26], varying between 14 and 27 per cent of patients. Ten studies[18,19,21,24,27,29,32−35] reported on loss of bodyweight after surgery, with an occurrence of 44−85 per cent of the patients and a median loss of 6·7 (range 3·1−15) kg. Shi and co-workers[31] observed stabilization of

Table 2 Endocrine insufficiency in patients who had a total pancreatectomy							
Reference	***n***	**Follow-up (months)***	**Insulin (units/day)***	**Glycaemic events/week***	**Complications**	**Hospitalization**	**Mortality**
Barbier et al.[18]	52	35 (4–168)	R: 21 (7–70)	n.r.	n.r.	Hypoglycaemic coma (6)	Ketoacidosis (1)
			L: 16 (7–48)				Hypoglycaemia (1)
			Insulin pump (*n* = 1)				
Subgroup	25	66 (7–168)	n.r.	10 (1–36)/month	Loss of consciousness due to hypoglycaemia (10)	Diabetes equilibration (14)	n.r.
Casadei et al.[19]	13	23 (6–60)	R: 18 (0–18)	4 (1–10) hypoglycaemia and hyperglycaemia	n.r.	Poor glycaemic control (3)	Severe hypoglycaemia (0)
			L: 7 (4–20)				
Casadei et al.[20]	35	> 1 year	R: 7 (0–18)	n.r.	n.r.	n.r.	n.r.
			I: 3 (0–19)				
			L: 19 (4–40)				
Crippa et al.[21]	45	2–14 years	32 (18–52)	2 (0–5)	PVD (4)	Hyperglycaemia (3)	Hypoglycaemia (0)
					Stroke (1)	Hypoglycaemia (7)	
					Retinopathy (1)		
Crippa et al.[22]	29	62 (6–91)	n.r.	n.r.	n.r.	n.r.	Insulin-related coma (0)
Subgroup	15	63 (30–91)	R: 25 (19–38)	n.r.	Severe hypoglycaemia (7)	n.r.	n.r.
			L: 4 (0–14)				
Epelboym et al.[23]	17	40·3 (i.q.r. 32·8)	29·8(18·6)†	2 (i.q.r. 2)	Hypoglycaemic episodes (16)	Hypoglycaemic episodes (4)	n.r.
Fujino et al.[24]	36	n.r.	22(6)†	n.r.	n.r.	n.r.	Severe hypoglycaemia (2)
Hartwig et al.[6]	83	≥ 1 year	n.r.	n.r.	n.r.	n.r.	n.r.
Jamil et al.[26]	14	Up to 24	Insulin pump (*n* = 3)	n.r.	Hypoglycaemic episodes (7)	Hypoglycaemia (1)	n.r.
						Hyperglycaemia (0)	
Kitagawa et al.[27]	10	7·9 (2·1–28·6)	0·45(0·13) units/kg/day‡ at discharge†	n.r.	n.r.	Hypoglycaemia (1)	n.r.
Müller et al.[2]	47	> 6 after surgery	n.r.	n.r.	n.r.	Hyperglycaemia (4)	Mortality (0)
						Hypoglycaemia (3)	
Nikfarjam et al.[28]	15	Postoperative period	n.r.	n.r.	Hypoglycaemia (4)	n.r.	n.r.
Parsaik et al.[29]	26	2 (i.q.r. 0·6–5·3) years	n.r.	n.r.	Mild hypoglycaemic episodes (19)	n.r.	n.r.
					Severe hypoglycaemic episodes (7)		
					Target organ complications (7)		
Reddy et al.[30]	100	Postoperative period	n.r.	n.r.	Glycaemic control: CD I (20), CD IV (1)	n.r.	n.r.
Shi et al.[31]	52	To 12 months after surgery	0·56(0·12) units/kg/day‡ at 12 months†	n.r.	n.r.	n.r.	Hypoglycaemia or diabetic complications (0)

Table 2 Continued

Reference	n	Follow-up (months)*	Insulin (units/day)*	Glycaemic events/week*	Complications	Hospitalization	Mortality
Stauffer et al.[32]	47	Postoperative period	L: 10 (0–80) at discharge	n.r.	Major glycaemic events (2)	n.r.	Hyperglycaemia (1)
Subgroup	46	To 12 months after surgery	n.r.	n.r.	n.r.	Glycaemic events (5)	n.r.
Suzuki et al.[33]	41	To 12 months after surgery	30 (12–50)	n.r.	n.r.	n.r.	n.r.
			0·56 (0·16) units/kg/day at 12 months†				
Watanabe et al.[35]	44	21 (2–222)	n.r.	n.r.	n.r.	n.r.	Ketoacidosis (1)
Subgroup	25	22 (2–73)	R: 17 (10–28)	2 (1–4) (12 patients)	Loss of consciousness (0)	Hyperglycaemia or hypoglycaemia (0)	n.r.
			L: 6 (0–16)				
Zakaria et al.[36]	103	Postoperative period	n.r.	n.r.	Major glycaemic event (6)	n.r.	n.r.
Overall¶	809	20·8 months§	26†§	2·3 (2–4) (125 patients)§	112 of 432 (25·9)	45 of 242 (18·6)	6 of 365 (1·6)
			R: 16				
			L: 12				

Values are *median (range) and †mean(s.d.). ‡Not used in the analysis. §Weighted average of medians. ¶Values in parentheses are percentages unless indicated otherwise. R, rapid-acting insulin; n.r., not reported; L, long-acting insulin; I, intermediate-acting insulin; PVD, peripheral vascular disease; CD, Clavien–Dindo co-morbidity grade.

postoperative weight loss after 6–12 months of follow-up. One study[33] reported the dosages of pancreatic enzymes during the first year after operation and revealed that patients needed higher dosages as time progressed. In that study, pancreatic enzyme dosage was based on patients' stool consistency, BMI, serum albumin and signs of liver steatosis on CT, achieving a stabile BMI and no diarrhoea.

Several studies[6,18,24,25,31,33,34] investigated laboratory tests to assess patients' nutritional status. Serum nutritional markers decreased in the first 1–6 months after total pancreatectomy, but had stabilized or normalized by 12 months after surgery[6,24,31,33,34]. Barbier and colleagues[18] showed that, also in the long term, prealbumin and albumin levels remained stable within normal ranges.

Hata et al.[25] investigated long-term consequences by describing development of hepatic steatosis in 16 of 43 patients, which was associated with poor nutritional status early after surgery. None of these patients developed liver cirrhosis or liver failure during long-term follow-up. Suzuki and co-workers[33] suggested that all patients tended to develop hepatic steatosis at 1 year after surgery, but signs of steatosis decreased by enhancing the dose of pancreatic enzymes. Liver function also remained normal in the long term (median follow-up 66 months), according to Barbier et al.[18].

Quality of life

QoL after total pancreatectomy for all indications was reported in seven studies[2,6,18−20,23,35], including 243 patients, using various validated questionnaires. The median weighted follow-up in these studies was 28·6 (range 6·0–66·0) months. The following questionnaires were used: EORTC QLQ-C30 (5 studies[2,6,18,19,23]), EORTC QLQ after pancreatic resection (EORTC QLQ-PAN26) (3 studies)[6,18,23], Audit of Diabetes Dependent Quality of Life (ADD-QoL) (1 study[23]), Short Form 36 (SF-36) (1 study[35]), Problem Areas in Diabetes scale (PAID20) (1 study[20]) and EQ-5D-5L (1 study[20]).

The EORTC QLQ-C30 questionnaire, designed to measure overall health status in patients with cancer[37], was used in four studies[2,18,19,23], including 102 patients. One study[6] with 81 patients was excluded for this analysis, because EORTC QLQ-C30 scores were shown only in figures and no exact data were available. The mean global health status score was 64 per cent, a small clinically important difference (58–69 per cent) compared with the general population score of 71 per cent (*Table 4*). Mean scores in the functioning scales varied from 67 to 78 per cent and, compared with the general population scores, they varied from 9 per cent (little change) to 14 per cent (moderate change). Global health status and all

Table 3 Exocrine insufficiency in patients who had a total pancreatectomy

Reference	n	Follow-up (months)*	Pancreatic lipase (units/day)*	Symptoms and related readmissions	Weight loss	
					No. of patients	kg*
Barbier *et al.*[18]	25	66 (7–168)	150 000 (75 000–450 000)	Diarrhoea (6)	15	9 (2–14)
			6 (3–18 capsules)			
Casadei *et al.*[19]	13	23 (6–60)	8 (6–11) capsules	n.r.	11	15 (1–32)
Crippa *et al.*[21]	45	2–14 years	80 000 (30 000–160 000)	Steatorrhoea (12)	20	5 (1–18)
				Diarrhoea (6)		
Fujino *et al.*[24]	n.r.	> 12	n.r.	n.r.	n.r.	8·8(10·4)%
Hartwig *et al.*[6]	75	≥ 1 year	n.r.	n.r.	n.r.	n.r.
Hata *et al.*[25]	43	> 6	18 patients: high dose (1800 mg/day)	Hepatic steatosis (16)	n.r.	n.r.
			Pancrelipase within 2 weeks of TP			
Jamil *et al.*[26]	14	≥ 24	n.r.	Steatorrhoea because of intolerance to medication (1)	n.r.	n.r.
				Inadequate dosing (1)		
Kitagawa *et al.*[27]	10	7·9 (2·1–28·6)	n.r.	Readmission because of diarrhoea (1)	n.r.	4·1†
				Use of antidiarrhoeal drugs (4)		
Müller *et al.*[2]	47	> 6	n.r.	Flatulence (28)	n.r.	n.r.
				Diarrhoea (30)		
Parsaik *et al.*[29]	26	2 (i.q.r. 0·6–5·3) years	n.r.	n.r.	n.r.	3·1(0·54)†
Shi *et al.*[31]	52	To 12 months after surgery	n.r.	n.r.	n.r.	n.r.
Stauffer *et al.*[32]	46	To 12 months after surgery	n.r.	Readmission because of malnutrition, failure to thrive, nausea, vomiting, diarrhoea or weakness (20)	n.r.	8·8 (1·2–39·5)
Suzuki *et al.*[33]	41	To 12 months after surgery	125 145(97 487) at 12 months†	Diarrhoea (0)	18	4·23
Takami *et al.*[34]	33	Early postoperative period	n.r.	Severe diarrhoea (10)	n.r.	> 10% at 6 months
				Dumping syndrome (0)		
Watanabe *et al.*[35]	25	22 (2–73)	150 000 (0–225 000)	Diarrhoea (8)	17	4·5 (1–15)
Overall‡	495	19·6‡		143 of 329 (43·5)	81 of 149 (54·4)	6·7 (3·1–15)‡

Values are *median (range) and †mean(s.d.); ‡values in parentheses are percentages. ‡Weighted average of medians. n.r., Not reported; TP, total pancreatectomy.

functioning domains differed significantly in comparison with those for the general population. Mean scores in the symptom scales varied from 6 to 38 per cent, with fatigue, dyspnoea and especially diarrhoea as the main symptoms.

Long-term QoL was evaluated in 81 patients by Hartwig and colleagues[6], using the EORTC QLQ-C30. After matching data with an age- and sex-matched healthy control population, no differences in global health status were found. During the first year after surgery, global health status was significantly lower in patients with benign disease, but no differences between benign and malignant disease were seen after this time. Patients with malignant disease suffered significantly more from diarrhoea than those with benign disease, compared with the control population.

The EORTC QLQ-PAN26 questionnaire, designed to evaluate disease symptoms, treatment side-effects and emotional issues specific to pancreatic cancer, was used in three studies[6,18,23] (67 patients). The most frequently described symptom was altered bowel habit.

One study[35] with 25 patients used the SF-36, a questionnaire that evaluates eight domains of physical and mental well-being. The physical aspects of QoL were significantly lower than those in the national population (which included many young people) ($P < 0.050$). In addition,

Table 4 Quality of life assessed with the EORTC QLQ-C30 questionnaire								
	Barbier et al.[18] (n = 25)¶	Casadei et al.[19] (n = 13)	Epelboym et al.[23] (n = 17)	Müller et al.[2] (n = 47)	Total (n = 102)	General population[38] (n = 7802)	P#	Clinically relevant difference (%)[14]
Global health status*	64(4)	58(21)	69(n.r.)	n.r.	64(13)	71(22)	0·019	7 (low)
Functioning scales†	n.r.	n.r.	79(n.r.)	n.r.	79	n.r.		
Physical	84(3)	65(25)	n.r.	n.r.	78(17)	90(16)	<0·001	12 (moderate)
Role	75(2)	67(25)	n.r.	n.r.	72(15)	85(25)	0·001	13 (moderate)
Emotional	76(3)	67(21)	n.r.	63(24)	67(11)	76(23)	<0·001	9 (low)
Cognitive	76(2)	75(25)	n.r.	n.r.	76(15)	86(20)	0·002	10 (moderate)
Social	73(2)	75(25)	n.r.	n.r.	74(15)	88(23)	<0·001	14 (moderate)
Symptom scales‡	n.r.	n.r.	18(n.r.)	n.r.	18	n.r.		
Fatigue	38(3)	39(22)	n.r.	n.r.	38(13)	24(24)	<0·001	14 (moderate)
Nausea and vomiting	15(2)	17(17)	n.r.	n.r.	16(10)	4(12)	<0·001	12 (moderate)
Pain	26(2)	21(21)	n.r.	n.r.	24(13)	21(28)	0·509	3 (none)
Dyspnoea	19(1)	42(25)	n.r.	n.r.	27(18)	12(23)	<0·001	15 (moderate)
Insomnia	20(1)	42(25)	n.r.	n.r.	28(18)	22(30)	0·218	6 (low)
Appetite loss	13(1)	25(25)	n.r.	n.r.	17(16)	7(18)	<0·001	10 (moderate)
Constipation	9(1)	8(8)	n.r.	4·2(17)	6(13)	7(18)	0·646	1 (none)
Diarrhoea	25(1)	33(17)	n.r.	n.r.	28(11)	7(18)	<0·001	21 (high)
Financial difficulties	16(1)	0(0)	n.r.	n.r.	11(8)	10(23)	0·789	1 (none)
EORTC QLQ-C30 summary score§	78	71	n.a.	n.a.	76	86	0·004	11 (moderate)

Values are mean(s.d.). n.r., Not reported; n.a., not applicable. *The higher the score, the better the global health status; †the higher the score, the better the functioning; ‡the higher the score, the greater the symptoms. §(Physical functioning + Role functioning + Social functioning + Emotional functioning + Cognitive functioning + (100 − Fatigue) + (100 − Pain) + (100 − Nausea and Vomiting) + (100 − Dyspnoea) + (100 − Insomnia) + (100 − Appetite loss) + (100 − Constipation) + (100 − Diarrhoea))/13. ¶Data received from corresponding author. #Student's *t* test.

scores of vitality and mental well-being were significantly worse in patients with diarrhoea-related complaints. However, QoL was comparable with that in age-matched controls. These authors concluded that QoL after total pancreatectomy is acceptable if the patient is capable of self-management.

Diabetes-specific quality of life

Epelboym and colleagues[23] assessed the impact of diabetes on the QoL in 17 patients after total pancreatectomy and in eight patients following pancreatoduodenectomy. Insulin was used in all patients in the total pancreatectomy group *versus* half of those in the pancreatoduodenectomy group. All average weighted scores, measured by the ADD-QoL questionnaire, did not differ significantly between the groups. However, leisure time and physical activity were lower in patients after total pancreatectomy. These authors concluded that total pancreatectomy-induced diabetes has a negative impact on functioning and activities, and that overall QoL is comparable with that in patients who have had a pancreatoduodenectomy.

One study[20] used the PAID20 questionnaire in 35 patients after total pancreatectomy and in 43 after pancreatoduodenectomy, and did not find any significant differences, except for the question about feelings of guilt or anxiety about their diabetes management when glucose values were off-track. These authors concluded that diabetes after total pancreatectomy is manageable, with acceptable QoL.

Quality of life after pancreatoduodenectomy versus total pancreatectomy

Two studies[20,23] compared QoL after total pancreatectomy with that following pancreatoduodenectomy. Epelboym et al.[23] performed a matched-paired analysis of age, postoperative pathology, and preoperative and postoperative presence of diabetes. After a median follow-up of 45 months, patients in both groups had similar functional and symptom scales and global health status. Overall QoL after total pancreatectomy was good, and showed no significant difference from that in patients who had a pancreatoduodenectomy, according to Casadei and colleagues[20]. Diabetes impacted poorly on QoL in both groups, but the overall PAID20 score tended to favour pancreatoduodenectomy (P = 0·081). Nevertheless, Casadei et al.[20] concluded that overall QoL and the impact of diabetes after total pancreatectomy were acceptable, and comparable with those following pancreatoduodenectomy.

Discussion

This systematic review of 1536 patients after total pancreatectomy has shown that, over a follow-up period of 20·8 months, endocrine-related readmission was fairly common (18·6 per cent) and should be improved. Diabetes-related mortality (1·6 per cent) did occur, but only in patients treated before 2005. The burden of diarrhoea seems to be significant, with a negative impact on QoL, requiring accurate personalized management. Although overall QoL appears acceptably reduced after total pancreatectomy, data are sparse as few studies have reported on long-term endocrine and exocrine insufficiency and QoL.

Most surgeons favour partial over total pancreatectomy in order to prevent the consequences of insulin-dependent diabetes and its effects on QoL. Based on this information, new-onset diabetes after total pancreatectomy seems similar to type 1 diabetes mellitus[26,39,40]. Multiple studies[2,20,26,35,39,41] concluded that diabetes after total pancreatectomy could be managed well, whereas others[18,19] still emphasized its complexity. The present review revealed a substantial rate of diabetes-related morbidity, but nevertheless acceptable and stabilized levels of HbA1c in the first year after surgery, indicating reasonable management. All diabetes-related mortality occurred in studies that included patients between 1990 and 2013. More recent studies, which included patients treated only after 2005, did not report any diabetes-related mortality at all. Hence, brittle diabetes may no longer be a correct term in current practice of total pancreatectomy, owing to improved diabetes management.

Diarrhoea was the most frequently reported symptom after total pancreatectomy; 23·5 per cent of patients still had symptoms despite pancreatic enzyme substitution. The wide range of incidence of diarrhoea (0–64 per cent) suggests that management is difficult, but achievable. In the literature[6,18,25], the extent of resection is mentioned as a contributing cause of diarrhoea. Extended resection could lead to autonomic denervation and therefore impaired bowel control, explaining the difference in severity of diarrhoea between benign and malignant indications[2,6]. Nevertheless, the potential for sufficient stool management and improvement of nutritional status over time suggests a crucial role for extensive patient education and follow-up to optimize pancreatic enzyme replacement therapy[18,33,42]. Moreover, optimal nutritional status seems to be important to reduce the risk of hepatic steatosis[25,33]. In 1991, Dresler *et al.*[43] found that three of 49 patients died as consequence of liver cirrhosis, but cirrhosis was no longer seen in recent literature.

In this review, QoL was reduced significantly in 11 of 15 domains in comparison with that in the general population. Decreases in global health status and functioning were classified as small and moderate, indicating a reasonable reduction. Specifically, two studies[6,35] compared QoL with age- and/or sex-matched healthy individuals and found no significant differences during a median follow-up of 22 (range 2–73) months and up to 5 years respectively. Other studies, including some not in the present systematic review, described impaired but still acceptable QoL, and even comparability with other types of diabetes and partial pancreatectomy[2,18,20,23,40,41,44,45]. Whereas the impact of diabetes on QoL is suggested to be comparable with that of partial pancreatoduodenectomy[20,23], several articles[2,6,18,35] mentioned the major impact of diarrhoea.

The current state of knowledge about functional outcomes after total pancreatectomy and its impact on QoL seems to be limited, and a variety of opinions exist concerning the acceptability of outcomes. Nevertheless, recent studies[1,18,36] have shown an increase in total pancreatectomy performed over time, especially in patients with IPMN. In the present review, however, the majority of patients (52·5 per cent) underwent total pancreatectomy for PDAC and 29·6 per cent for IPMN. Despite the potential benefits of total pancreatectomy as radical treatment for IPMN, international consensus regarding the role of total pancreatectomy is lacking, possibly as result of limited data on functional outcomes, QoL and long-term survival rates compared with those for partial pancreatectomy[8].

This review should be interpreted in the light of some shortcomings. First, the heterogeneity between studies was substantial, mainly because of different indications for total pancreatectomy. Second, follow-up periods varied (from 1 month to several years). Long-term follow-up was limited, and therefore data on long-term consequences of total pancreatectomy are sparse. In addition, one-third of all included studies made no distinction between elective and emergency total pancreatectomy. Potentially, outcomes of (completion) total pancreatectomy in emergency settings may have influenced outcomes negatively. A strength of this review is that studies with relative small cohorts and dated series were excluded.

Several further studies are needed in this field. First, few studies of long-term outcomes on endocrine and exocrine insufficiency and QoL have been published, and this needs to be investigated in large prospective series, evaluating clinicophysiological parameters and their courses over time. Second, such studies should compare outcomes with those following partial pancreatectomy, especially for IPMN. Third, evidence-based guidelines

are needed for optimal management of endocrine and exocrine insufficiency.

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Supporting information

Additional supporting information can be found online in the Supporting Information section at the end of the article.