Expanding eligibility and improving patient outcomes for pancreatic surgery

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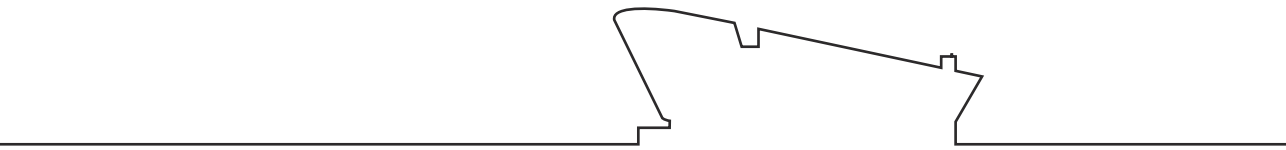

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Systematic review of outcomes after distal pancreatectomy with coeliac axis resection for locally advanced pancreatic cancer

Authors

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ABSTRACT

BACKGROUND: Pancreatic cancer involving the coeliac axis is considered unresectable by most guidelines, with a median survival of 6–11 months. A subgroup of these patients can undergo distal pancreatectomy with coeliac axis resection, but consensus on the value of this procedure is lacking. The evidence for this procedure, including the impact of preoperative hepatic artery embolization and (neo)adjuvant therapy, was evaluated.

METHODS: A systematic review was performed according to the PRISMA guidelines until 27 May 2015. The primary endpoint was overall survival; secondary endpoints included morbidity and radical resection rates.

RESULTS: A total of 19 retrospective studies, involving 240 patients, were included. The methodological quality of the studies ranged from poor to moderate. A radical resection was reported in 75.0 per cent (152 of 204), major morbidity in 27.1 per cent (26 of 96), ischaemic morbidity in 9.0 per cent (21 of 223) and 90-day mortality in 3.5 per cent (4 of 113). Overall, 35.5 per cent of patients (55 of 155) underwent preoperative hepatic artery embolization without an apparent beneficial impact on ischaemic morbidity. Overall, 15.7 per cent (29 of 185) had neoadjuvant and 51.0 per cent (75 of 147) had adjuvant therapy. There was a difference in survival between patient series where less than half of patients had (neo)adjuvant chemotherapy and series where more than half were receiving this treatment: case-weighted median overall survival was 16 (range 9–48) *versus* 18 (10–26) months respectively; $P = 0.002$). Overall median survival for the whole study population was 14.4 (range 9–48) months.

CONCLUSION: Distal pancreatectomy with coeliac axis resection seems a valuable option for selected patients with pancreatic cancer involving the coeliac axis with acceptable morbidity and mortality, and a median survival of 18 months, when combined with (neo) adjuvant therapy. Further studies are needed to assess the benefits of preoperative hepatic artery embolization.

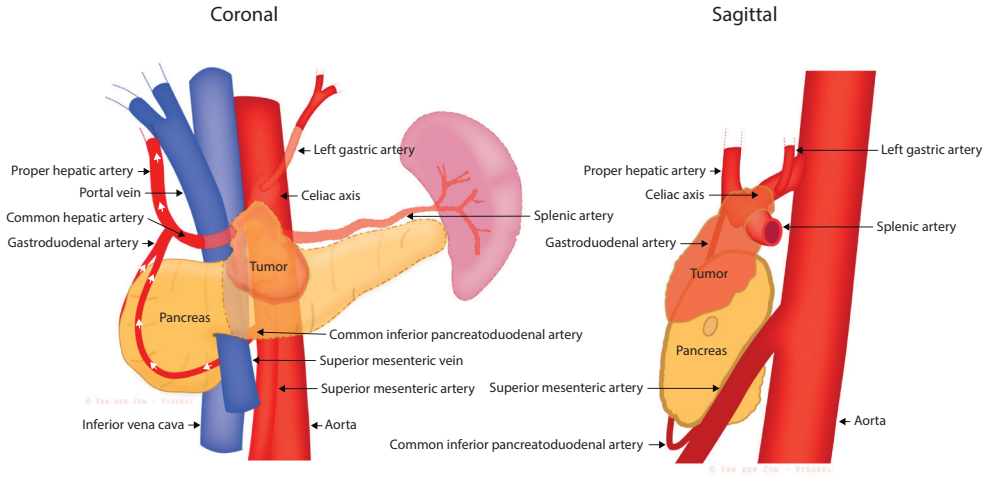

Figure 1. Locally advanced cancer of the pancreatic body with coeliac axis involvement, eligible for distal pancreatectomy with coeliac axis resection (transparent). Resection is feasible only when the gastroduodenal artery, superior mesenteric artery and aorta are not involved. The white arrows represent arterial flow to the liver after resection.

INTRODUCTION

Current guidelines consider American Joint Committee on Cancer stage III pancreatic cancer either unresectable[1–4] or borderline resectable, provided the tumour is confined to the body of the pancreas and coeliac axis involvement is less than 90–180°.[5–8] In selected patients, resection of the stomach, pancreatic tail and coeliac axis might lead to a radical resection (named the Appleby procedure).[9] This procedure was modified by Nimura and colleagues,[10] who omitted the gastric resection for pancreatic cancer. The procedure is now known as the modified Appleby procedure or distal pancreatectomy with coeliac axis resection.

After coeliac axis resection, the arterial perfusion of the liver and stomach runs by retrograde flow via the superior mesenteric artery, pancreatoduodenal arcades in the pancreatic head and the gastroduodenal artery (*Fig. 1*). Preoperative embolization of the common hepatic artery, as first described by Kondo and co-workers[11] in 2000, has been advocated by some authors to mature this collateral pathway formation, aimed at reducing the rate of ischaemic complications.

A meta-analysis[12] of the perioperative and long-term outcomes of patients with arterial resection during pancreatectomy for pancreatic cancer concluded that this combination of resections is associated with poor short- and long-term outcomes. In contrast, a Cochrane review[13] of resection *versus* other therapies in locally advanced pancreatic cancer found a 5-year survival benefit in favour of surgery in two randomized trials of surgical intervention *versus* palliative treatment alone (risk ratio 8.7, 95 per cent c.i. 1.1 to 66.9). However, no

specific analyses were done on distal pancreatectomy with coeliac axis resection in either review; hence a limited amount of evidence exists on the risks, morbidity and oncological efficacy of this procedure. The aim in this systematic review was to evaluate outcomes, including survival, and the added benefit of preoperative hepatic artery embolization and (neo)adjuvant therapy in distal pancreatectomy with coeliac axis resection for locally advanced pancreatic cancer.

METHODS

The study was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[14] Two authors independently performed the literature search, study selection, data extraction and critical appraisal of the selected studies. Disagreement on article eligibility was resolved by discussion and consensus.

Eligibility criteria

Included articles were those reporting on the perioperative and postoperative outcomes after distal pancreatectomy with coeliac axis resection for locally advanced pancreatic cancer, including non-adenocarcinomas. Excluded were articles in languages other than English or German, and articles reporting on fewer than three patients. In case of overlapping cohorts, either the most recent or the most relevant publication was included.

Study selection

A systematic literature search was performed using PubMed, Embase and the Cochrane Library, to identify articles published before 27 May 2015. Search terms were based on organ ('pancreas'), intervention ('surgery'), type of procedure ('pancreatectomy'), additional resection ('celiac', 'vascular', or 'vessel') and possible specific nomenclature ('Appleby'). After removal of duplicates, articles were screened for adherence to the eligibility criteria by title, abstract, and subsequently full text. The reference lists of all included studies were screened manually for missed but relevant studies.

Critical appraisal

The methodological quality of the included studies was assessed using the Cochrane Handbook for Systematic Reviews[15] and the Newcastle–Ottawa Scale.[16] Both tools were customized for the purpose of this systematic review, focusing on assessment of observational studies. Retrospective studies were grouped either as cohort studies, if an absolute risk could be calculated from the presented data, or as case series, if cases were selected based on a certain outcome.[17] Quality of follow-up was assessed only when the

authors reported on long-term outcomes, such as survival. Each study was classified according to the Oxford Centre for Evidence-Based Medicine levels of evidence,[18] ranging from level 1 to level 5.

Data collection

Predefined data extraction forms were used to collect data on variables comprising demographics (sex, age), perioperative parameters (preoperative artery embolization, estimated blood loss, duration of surgery, resected arteries, (neo)adjuvant therapy and resection margins), postoperative parameters (major morbidity (defined as Clavien–Dindo[19] grade IIIa or higher), ischaemia-related morbidity, pancreatic ductal adenocarcinoma rate and survival). If the Clavien–Dindo classification was not mentioned in reports, grades were assigned based on the provided information. Ischaemia-related morbidity was defined as ischaemic complications to the liver, gallbladder, omentum, small intestine (if an anastomosis was made) or stomach. Radical resection margin was defined as R0 (microscopically tumour-free). Corresponding authors were contacted and requested to submit additional information on preoperative hepatic artery embolization and (neo)adjuvant treatment, if this was not reported primarily.

Data synthesis and statistical analysis

All statistical analyses were performed using SPSS® for Windows® v22 (IBM, Armonk, New York, USA). Outcomes were either displayed as reported originally, or calculated from the published raw data if possible. Mean (s.d.) values were converted to median (i.q.r.), in compliance with the Cochrane Handbook[15]. Outcomes were summed and weighted averages of the medians were determined. In cases of proportional data, the overall proportion was determined, censoring studies that did not report on the variable of interest. If survival analysis was not performed, Kaplan–Meier analysis was performed based on the published data, provided sufficient reliable raw data were presented. All tests were two-tailed and $P < 0.050$ was considered statistically significant.

RESULTS

A systematic search yielded 19 retrospective studies fulfilling the eligibility criteria (*Fig. 2*), comprising 240 patients included between 1975 and 2015, with a case-weighted median age of 63 years (*Table 1*).[20,21,30–38,22–29] The majority of patients for whom pathology was reported had pancreatic ductal adenocarcinoma (188 of 194, 96.9 per cent). Other diagnoses were mucinous carcinoma (3 patients), intraductal papillary mucinous neoplasm with high-grade dysplasia (1), anaplastic carcinoma (1) and acinar cell carcinoma (1). Formal meta-analysis

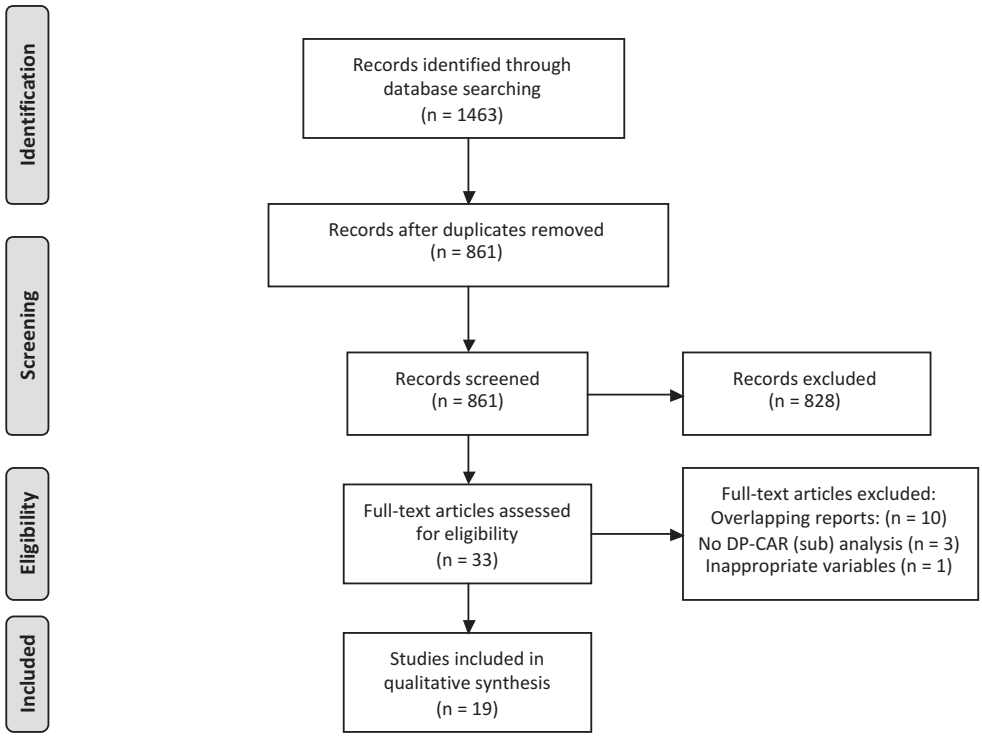

Figure 2. PRISMA flow diagram of articles included in the systematic review

was not performed because of obvious clinical heterogeneity between studies and the lack of comparative analyses.

Critical appraisal

Critical appraisal resulted in 18 studies with evidence level 4 and one study with evidence level 2b, with zero to high risk of bias (*Table S1*, supporting information). One study[28] was performed prospectively, but it lacked a control group and the study design was insufficiently solid; it was therefore graded as level 4. Two studies[27,36] had an appropriate control cohort (unresectable locally advanced pancreatic adenocarcinoma), but only one[37] adequately reported on the control group and this article was therefore considered to have the highest level of evidence available for observational studies (2b). Two studies[28,37] were assessed as having a high risk of bias, due to lacking information on follow-up procedures.

Preoperative hepatic artery embolization

Preoperative hepatic artery embolization was reported in 55 of 155 patients (35.5 per cent), with no reported serious adverse events related to this procedure (*Table 2*). Okada and colleagues[31] referred to earlier publications in which they had described this treatment

Table 1. Study and patient characteristics

Reference	Country	Inclusion period	No. of patients	Sex ratio (M : F)	Median age (years)
Baumgartner *et al.*[20]	USA	2007–2010	11	5 : 6	61
Denecke *et al.*[21]	Germany	2007–2009	6	4 : 2	63
Gagandeep *et al.*[22]	USA	2002–2004	3	3 : 0	60
Hishinuma *et al.*[23]	Japan	1997–2003	7	4 : 3	62
Jing *et al.*[24]	China	2005–2010	24	18 : 6	55[a]
Kimura *et al.*[25]	Japan	2010–2011	3	1 : 2	66
Konishi *et al.*[26]	Japan	1992–1998	4	0 : 4	57
Mayumi *et al.*[27]	Japan	1975–1994	6	4 : 2	62
Mittal *et al.*[28]	Australia	2007–2014	7	4 : 3	64
Miura *et al.*[29]	Japan	1998–2008	50	26 : 24	64
Okada *et al.*[30]	Japan	2004–2012	37	22 : 15	66*
Shimura *et al.*[31]	Japan	1992–2011	14	10 : 4	69
Sperti *et al.*[32]	Italy	1989–2007	5	3 : 2	70
Takahashi *et al.*[33]	Japan	1993–2010	16	8 : 8	65*
Wang *et al.*[34]	China	2003–2012	15	7 : 8	61
Yamaguchi *et al.*[35]	Japan	n.r.	3	2 : 1	60
Yamamoto *et al.*[36]	Japan	1991–2009	13	10 : 3	64*
Zhou *et al.*[37]	China	2006–2013	12	8 : 4	52
Zureikat *et al.*[38]	USA	2008–2012	4	n.r.	n.r.
Overall		1975–2014	240	139 : 97	63†

*Data originally reported as mean(s.d.); †weighted average of medians.

addition as the standard of operation, as later confirmed by formal correspondence. In three studies (93 patients) more than 50 per cent underwent preoperative hepatic artery embolization. The ischaemic morbidity rate in these patients was 10 of 93 (10.8 per cent), compared with one of 99 patients (1.0 per cent) in the 12 studies in which less than 50 per cent of patients had preoperative hepatic artery embolization (*Table 2*).

Surgical outcomes

The overall major morbidity rate was 26 of 96 patients (27.1 per cent), of which at least eight patients had Clavien–Dindo grade IIIb or higher. Reported ischaemia-related complications varied from ischaemic gastropathy (14 patients) to more severe events, such as gastric ulceration or necrosis (4), liver or gallbladder necrosis (4). The overall radical (R0) resection rate was 152 of 204 (75.0 per cent) (*Table 2*). The case-weighted median length of hospital stay was 32 (range 9–76) days. This comprised a case-weighted median of 20 (9–43) days in studies from non-Asian countries (36 patients) *versus* 35 (16–76) days in studies from Asian countries (204 patients) ($P < 0.001$). The overall 90-day mortality rate was 3.5 per cent (4 of 113) (*Table 3*).

Table 2. Perioperative variables in 263 patients undergoing distal pancreatectomy with coeliac axis resection

Reference	PHAE (%)	Median duration of surgery (min)	Median blood loss (ml)	PV resection (%)	AR (%)	Radical resection (%)	Major morbidity (%)	Ischemic morbidity (%)
Baumgartner *et al.*[20]	0	494	700	64	9	91	9	0
Denecke *et al.*[21]	67	267	n.r.	33	n.r.	33	33	33
Gagandeep *et al.*[22]	33	558	1700	0	33	67	33	0
Hishinuma *et al.*[23]	0	n.r.	n.r.	100	0	57§	0	0
Jing *et al.*[24]	n.r.	200*	1779*	n.r.	n.r.	100§	54¶	25
Kimura *et al.*[25]	0	427	185 g#	0	33	100§	100¶	n.r.
Konishi *et al.*[26]	n.r.	357	3669	75	50	75§	33	0
Mayumi *et al.*[27]	n.r.	321*	1777*	17	n.r.	n.r.	33	17
Mittal *et al.*[28]	0	240	340	14	29	86	0	0
Miura *et al.*[29]	100	454	940	64	6	92	54¶	12
Okada *et al.*[30]	> 50	365	1349	22	0	57	n.r.	5
Shimura *et al.*[31]	n.r.	n.r.	n.r.	36	7	n.r.	35	21
Sperti *et al.*[32]	0	233	n.r.	20	20	60	80¶	0
Takahashi *et al.*[33]	0	237*	702 g*#	25	6	56	56	0
Wang *et al.*[34]	0	295	1000	20	27	100	7	0
Yamaguchi *et al.*[35]	0	n.r.	n.r.	0	33	0§	0	0
Yamamoto *et al.*[36]	0	620	1300	23	n.r.	31	92¶	8
Zhou *et al.*[37]	0	330	1200	n.r.	n.r.	n.r.	75¶	0
Zureikat *et al.*[38]	0	371*	200	n.r.	n.r.	n.r.	100	n.r.
Overall	35.5 (55 of 155)‡	365†	1222†	38.5 (77 of 200)‡	10.3 (18 of 175)‡	75.0 (152 of 204)‡	27.1 (26 of 96)‡	9.0 (21 of 233)‡

*Data originally reported as mean(s.d.); †weighted average of medians; ‡overall proportions in studies reporting on the outcome; §R1/R0 margin definition not reported; ¶overall morbidity; #blood loss reported in grams. PHAE, preoperative hepatic artery embolization; PV, portal vein; AR, additional arterial resection; g, grams; n.r., not reported.

Survival

The weighted median postoperative survival was 14.4 months (Table 3). The 1-year overall cumulative survival rate varied substantially between 33 and 100 per cent, the 3-year survival rate varied between 0 and 67 per cent, and the 5-year survival rate varied between 0 and 14 per cent.

Neoadjuvant and adjuvant therapy

In total, 29 (15.7 per cent) of 185 patients reportedly received neoadjuvant therapy, and 75 of 147 (51.0 per cent) received adjuvant chemotherapy or radiotherapy (*Table 3*). A crude comparative survival analysis was performed, based on the (neo)adjuvant therapy regimen

Table 3. Mortality and survival in 263 patients undergoing distal pancreatectomy with celiac axis resection

Reference	PDAC (%)	Neoadjuvant therapy (%)	Adjuvant therapy (%)	90-day mortality (%)	Median survival (months)
Baumgartner *et al.*[20]	100	100 RT\100 CT	45 CT	18	26
Denecke *et al.*[21]	100	0	83 CT	17	12.4
Gagandeep *et al.*[22]	100	66 UN	100 RT/100 CT	0	n.r.
Hishinuma *et al.*[23]	100	0	86 RT/17 CT	0	19
Jing *et al.*[24]	100	0	0	n.r.	9.3
Kimura *et al.*[25]	100	0	33	0	48
Konishi *et al.*[26]	100	n.r.	n.r.	0	10
Mayumi *et al.*[27]	83	n.r.	n.r.	0	9
Mittal *et al.*[28]	86	14 UN	86 UN	0	n.r.
Miura *et al.*[29]	100	0	72 CT	n.r.	24.7§
Okada *et al.*[30]	92	41 UN	> 50	n.r.	n.r.
Shimura *et al.*[31]	n.r.	n.r.	n.r.	0	10
Sperti *et al.*[32]	100	0	60 UN	0	10
Takahashi *et al.*[33]	n.r.	0	n.r.	6‡	9.7
Wang *et al.*[34]	100	n.r.	30 CT	7	19
Yamaguchi *et al.*[35]	67	0	66 RT	0	10
Yamamoto *et al.*[36]	100	0	31 CT/0 RT	0	20.8
Zhou *et al.*[37]	n.r.	n.r.	n.r.	0	10
Zureikat *et al.*[38]	n.r.	> 50	> 50	0	n.r.
Overall	96.9 (188 of 194)*	15.7 (29 of 185)*	51.0 (75 of 147)*	3.5 (4 of 113)*	14.4†

*Overall proportions in studies reporting on the outcome; †weighted average of medians; ‡30-d Mortality; § Disease-specific survival. PDAC, pancreatic ductal adenocarcinoma; RT, radiotherapy; CT, chemotherapy; UN, unknown adjuvant therapy; n.r., not reported.

within study populations. There was a difference in survival seen between three studies (40 patients) in which less than 50 per cent of patients received any form of (neo)adjuvant chemoradiotherapy and ten studies (133 patients) in which more than 50 per cent of patients received any form of (neo)adjuvant therapy (median overall survival 16 (range 9-48) *versus* 18 (range 10-26) months; $P = 0.002$) (*Fig. 3*).

DISCUSSION

This systematic review of distal pancreatectomy with coeliac axis resection for pancreatic cancer involving the coeliac axis found a radical (R0) resection rate of 75.0 per cent, a major morbidity rate of 27.1 per cent, 90-day mortality rate of 3.5 per cent, and a weighted median overall survival of 14.4 months, with a median of 18 months in series where more than 50 per cent of patients received (neo)adjuvant therapy. These findings suggest that this procedure can be a valuable treatment option in selected patients, if combined with neoadjuvant or adjuvant treatment. Available data did not suggest that preoperative hepatic artery embolization reduces the rate of postoperative ischaemic complications.

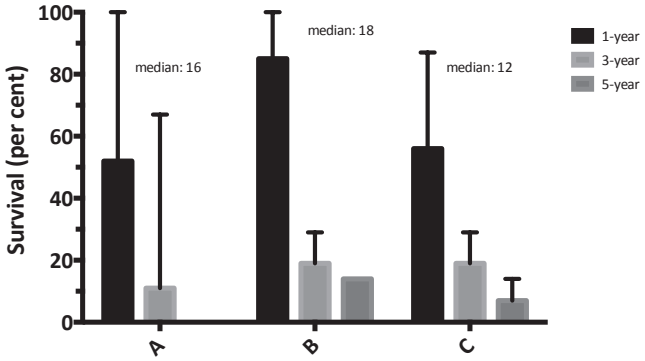

Figure 3. Overall survival in studies reporting on any form of (neo)adjuvant therapy. In group A (40 patients), comprising three studies (Jing et al, Yamamoto et al, Kimura et al), less than 50 per cent of patients received (neo)adjuvant therapy. In group B (133 patients), comprising ten studies[19–21,23,28–30,32,35,38], more than 50 per cent of patients received (neo)adjuvant therapy. In group C (67 patients), comprising six studies[26,27,31,33,34,37], the (neo) adjuvant regimen was unknown. Proportions were censored for missing data; ranges are denoted by error bars. Weighted median survival times in groups A, B and C were 16, 18 and 12 months respectively.

A recent meta-analysis[39] of case-matched studies of distal pancreatectomy for pancreatic cancer found similar outcomes, with a radical resection rate of 86 per cent (69 of 80), an overall morbidity rate of 35–40 per cent and a 30-day mortality rate of 0–1 per cent. A recent study[40] of distal pancreatectomy with coeliac axis resection in 16 American College of Surgeons National Surgical Quality Improvement Program® centres reported a 10 per cent mortality rate (2 of 20 patients) in centres that performed between one and three procedures over a 14-month period. Additionally, two small studies[41,42] identified after completion of this review had comparable rates of major morbidity, 90-day mortality, radical resection and overall survival.

Only one study[36] compared overall survival in patients who underwent distal pancreatectomy with coeliac axis resection *versus* observation for pancreatic cancer involving the coeliac axis. The authors reported a median survival of 20.8 months in the resection group, compared with 9.8 months in the unresected control group, despite use of less chemotherapy in the resected group (31 *versus* 96 per cent respectively)[36]. The weighted overall median survival in the present analysis was 14.4 (range 9–48) months, somewhat lower than the reported overall median survival rates of 16–19 months for conventional distal pancreatectomy for pancreatic cancer.[43–47]

Some authors claim that preoperative hepatic artery embolization is required to reduce the rate of ischaemic complications after distal pancreatectomy with coeliac axis resection, by increasing hepatic arterial inflow via the pancreatic arcade before resection. Preoperative hepatic artery embolization was performed routinely at four centres, covering nearly half of the study population, with no major embolization-related complications reported. However, none of the studies compared outcomes between embolization and immediate resection, hampering an adequate subgroup analysis on its efficacy.

Various patient characteristics have been associated with survival in the included studies, in favour of patients under the age of 60 years[34] and those who had a microscopically radical tumour resection.[33] Miura and colleagues[30] even proposed a risk model to predict which patients would benefit most from a distal pancreatectomy with coeliac axis resection. Three significant preoperative predictors for worse survival were found, comprising low platelet count (less than 150×10^9/l), raised C-reactive protein level (0.4 mg/dl or higher) and increased carbohydrate antigen 19-9 level (300 units/ml or above), as median survival was significantly lower in patients with all three predictors present (7.7 months *versus* 50.6 months in patients with none of the three predictors).[29] Despite these internally validated risk models and survival predictors, adequate reporting on patient selection for distal pancreatectomy with coeliac axis resection remains an important issue affecting the quality of assessment of this procedure.

The major limitation of this review is the lack of high-quality studies. All studies reported on highly selected patients, and only one study[36] reported survival outcomes of an adequate control group, posing a substantial risk of bias. Owing to these limitations, meta-analysis was considered inappropriate. This also made it impossible to assess the effect of preoperative staging and margin status on survival. The majority of patients were reported from Asian countries (85 per cent), but, except for differences in length of hospital stay, a sensitivity analysis revealed largely similar surgical outcomes after excluding Asian studies.

Although distal pancreatectomy with coeliac axis resection appears to provide a meaningful treatment option in patients with pancreatic cancer involving the coeliac axis, prospective studies are needed to assess the added benefits of preoperative hepatic artery embolization and to optimize (neo)adjuvant treatment. Given the low incidence of both procedures, such studies would probably involve multicentre (international) registries.[48]

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EDITOR'S COMMENTS

This collective series highlights a procedure that is rarely performed even in high-volume centres. As the authors point out, the accumulated data is heterogeneous and influenced by a few centres performing a majority of the procedures. The collective median overall survival of 14.4 months reported in this series, with an occasional long-term survivor, was improved only slightly (median 18 months) in patients who had either neoadjuvant or adjuvant therapy. Notably, the GEST study[1] and the SCALOP study[2] achieved a median overall survival of 15.9 and 15.2 months respectively in patients with locally advanced pancreatic cancer. It is thus timely to paraphrase a two-decade old analogy on the kingdom of cancer made by Blake Cady MD[3]: 'Biology is King; selection of cases is Queen, and the technical details of surgical procedures are princes and princesses of the realm who frequently try to overthrow the powerful forces of the King and Queen, usually to no long-term avail, although with some temporary apparent victories.' Both surgical and medical strategies behove a highly selective approach in order to achieve reasonable outcomes in patients with pancreas cancer. Thus, to battle this disease, we need to overthrow the King – which remains the biology at the very heart of this disease.

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