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Pancreatectomy Combined with Superior Mesenteric Vein–Portal Vein Resection for Pancreatic Cancer: A Meta-analysis

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Abstract

Background Pancreatectomy combined with superior mesenteric vein–portal vein resection (VR) for pancreatic cancer remains a matter of debate. The present study is a meta-analysis of the available evidence.

Methods Articles published until end of March 2011, comparing the results of pancreatic resections with VR versus without VR, were searched. Pooled odds ratios (OR) and weighted mean differences (WMD; with 95% Confidence Intervals [95% CI]) were calculated using either the fixed effects model or the random effects model.

Results Nineteen nonrandomized studies met the inclusion criteria, comprising 2,247 patients. There was no difference in perioperative morbidity (OR: 0.95; 95% CI: 0.74–1.21; $P = 0.67$), mortality (OR: 1.19; 95% CI: 0.73–1.96; $P = 0.48$), or 5-year overall survival (OR: 0.57; 95% CI: 0.32–1.02; $P = 0.06$) between patients with VR and those without VR.

Conclusions Pancreatectomy combined with VR resection for pancreatic cancer is justified because it can result in good perioperative outcome and long-term survival comparable to that obtained with standard resection. Owing to the selection bias and low level of clinical evidence available so far, the results should be interpreted with caution.

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Introduction

Pancreatic cancer is one of the most aggressive malignancies in the gastrointestinal system. Surgery may provide the only chance for long-term survival. Unfortunately, because of the presence of distant metastases or locally advanced disease in the form of vascular involvement, only 15%–20% of patients are suitable candidates for surgery [1]. Pancreatic tumor frequently extends directly into the retroperitoneal spaces and involves the superior mesenteric vein–portal vein (SMV-PV). In a further effort to improve life expectancy, in many centres a more aggressive approach involving SMV-PV resection (VR) has been performed to increase the curability of pancreatic cancer [2–11]. However, these reports have shown contradictory results. For example, Allema et al. [3] and Roder et al. [4] observed VR resection did not offer survival benefit for patients undergoing pancreaticoduodenectomy for carcinoma of the pancreas. By contrast, Takahashi et al. [5] found this procedure is associated with an improved long-term survival for patients with pancreatic cancer. In the light of this controversy, the present study used meta-analytical techniques to provide an evidence-based evaluation regarding the perioperative outcomes and long-term survival of patients undergoing VR in pancreatectomy for pancreatic cancer, compared with outcomes and survival of patients without VR.

Materials and methods

Study selection

A computerized search was made of Medline and PubMed from the time of inception to July 2011. The following

Mesh search headings were used: "pancreatic cancer," "portal vein," and "superior mesenteric vein." Only studies on humans and in the English language were considered for inclusion. Reference lists of all retrieved articles were manually searched for additional studies.

Data extraction

Two reviewers (B.L. and Y.Z.) independently extracted the following parameters from each study: first author, year of publication, study population characteristics, study design, inclusion and exclusion criteria, number of subjects operated on with each procedure, procedure-related morbidity and mortality, and overall survival. All relevant text, tables, and figures were reviewed for data extraction.

Criteria for inclusion and exclusion

For inclusion in the meta-analysis, a study had to fulfil the following criteria: (1) compare the results of pancreatic resections with VR versus without VR for pancreatic cancer; (2) report on at least one of the outcome measures mentioned below, noting whether the standard deviation of the mean for continuous outcomes of interest was reported or could be calculated; (3) when dual (or multiple) studies were reported by the same institution and/or authors, either the one of higher quality or the most recent publication was included in the analysis.

Abstracts, letters, editorials and expert opinions, reviews without original data, case reports, and studies lacking control groups were excluded.

Outcomes of interest

Perioperative outcomes included operative time, operative blood loss, number of patients requiring blood transfusion, morbidity, and mortality. Long-term outcomes included 1-, 3-, and 5-year overall survival.

Statistical analysis

The meta-analysis was performed using the Review Manager (RevMan) software, version 4.2.7. We analyzed dichotomous variables with estimation of odds ratios (OR) together with a 95% CI, and we analyzed continuous variables with weighted mean difference (WMD) and a 95% CI. Pooled effect was calculated using either the fixed effects model or the random effects model. Statistical heterogeneity between trials was evaluated by χ^2 and I^2, with significance being set at $p < 0.10$. In the absence of statistically significant heterogeneity, the fixed-effect method was used to combine the results. When heterogeneity was confirmed ($p \leq 0.10$), the random-effect method was used. Publication bias was assessed visually with a funnel plot.

Results

Eligible studies

The literature search identified 21 comparable studies that met the selection criteria. In three of the 21 studies, the VR cases and arterial resection cases were analyzed in aggregate, so no conclusions can be drawn about the outcomes for those patients undergoing VR [11–13]. Finally, a total of 19 nonrandomized studies were included for analysis [1, 3, 6–10, 14–25]. Demographics information (sex and age) was available in 17 studies [1, 3, 7, 9, 10, 14–25], and all had matched patients in the two groups. The two reviewers had 100% agreement in their reviews of the data extraction.

The 19 studies included a total of 2,247 patients: 661 with VR and 1,586 without VR. Five studies were conducted in the United States [1, 6, 7, 16, 22], three in France [8, 9, 19], five in Japan [10, 15, 17, 21, 23], two in Germany [14, 20], one in Hong Kong [18], one in the Netherlands [3], one in Taiwan [24], and one in Belgium [25].The sample size of each study varied from 45 to 158 patients. The rate of VR varied from 11.7 to 65.1%. Information on the histopathology of resected vessels was available in 15 studies [3, 7–10, 14–22, 25]. Tumor invasion was found microscopically in 279 of the 490 patients who underwent VR (56.9%; range 21–100%), while 211 had inflammatory adhesions without cancer invasion (43.1%).The characteristics of the included studies are shown in Table 1.

Meta-analysis of perioperative outcomes

Results from overall meta-analysis are outlined in Table 2. Pooled analysis of studies furnishing data found VR was associated with longer operative time (six trials reported this data, WMD: 78.77; 95% CI: 56.6–100.95; $p < 0.001$) and higher blood loss (four trials reported this data, WMD: 483.33; 95% CI: 142.98–823.68; $P = 0.005$). Concerning transfusion requirements, despite there being a trend toward a greater number in the VR group, this difference failed to reach statistical significance (four trials reported these data, OR: 1.96; 95% CI: 0.87–4.43; $P = 0.11$).

Meta-analysis of the 13 that reported overall morbidity showed no difference between the two groups (OR: 0.95; 95% CI: 0.74–1.21; $P = 0.67$) (Fig. 1). Subanalysis showed that the occurrence of pancreatic fistula was significantly lower in the patients with VR resection (OR: 0.53; 95% CI: 0.35–0.79; $P = 0.002$). In contrast,

Table 1 Study population characteristics of included trials

Author	Year	Country	Group	No. of patients	M/F	Mean age, years	Type of procedure	Histologic VI *n* (%)
Allema et al. [3]	1994	Netherlands	With VR	20	11/9	61*	st-PD: 11; t-PD: 9	10 (50)
			Without VR	156	107/49	60*	st-PD: 135; t-PD: 21	
Fuhrman et al. [6]	1996	USA	With VR	23	–	–	all PD	–
			Without VR	26	–	–	all PD	
Harrison et al. [1]	1996	USA	With VR	58	29/29	63 (35–78)*	PD: 42; t-P: 8; dst-P: 8	–
			Without VR	274	142/132	66 (34–84)*	PD: 231; t-P: 18; dst-P: 25	
Leach et al. [7]	1998	USA	With VR	31	19/12	66*	all PD	13/18 (72.2)
			Without VR	44	23/21	64*	all PD	
Launois et al. [8]	1999	France	With VR	14	–	–	–	3 (21)
			Without VR	74	–	–	–	
Bachellier et al. [9]	2001	France	With VR	21	10/11	60.4 ± 2.5	PD: 11; t-P: 10	14 (66.6)
			Without VR	66	39/27	62.7 ± 1.3	PD: 54; t-P: 12	
Shibata et al. [10]	2001	Japan	With VR	28	21/7	56 (30–81)	PD: 23; t-P: 3; d-P: 2	7/12 (58.3)
			Without VR	46	32/14	64 (40–82)	PD: 38; t-P: 3; d-P: 10	
Hartel et al. [14]	2002	Germany	With VR	68	39/29	64 (36–77)*	PD: 56; t-P: 12	56 (82%)
			Without VR	203	132/71	61 (24–87)*	PD: 186; t-P: 16	
Kawada et al. [15]	2002	Japan	With VR	28	17/11	60.9 (31–78)	t-P: 5; PD: 23	21 (75)
			Without VR	15	10/5	65.0 (38–78)	all PD	
Howard et al. [16]	2003	USA	With VR	13	7/6	68 ± 13	all PD	13 (100)
			Without VR	23	14/9	67 ± 8.6	all PD	
Nakagohri et al. [17]	2003	Japan	With VR	33	13/20	58	PD: 27; d-P: 6	16 (48.4)
			Without VR	48	34/14	65	PD: 34; d-P: 14	
Poon et al. [18]	2004	Hong Kong	With VR	12	7/5	61.5 (38–73)	all PD	6 (50)
			Without VR	38	24/14	62.5 (41–83)	all PD	
Carrère et al. [19]	2006	France	With VR	45	32/13	58.8 ± 1.7	all PD	29 (64)
			Without VR	88	59/29	61.5 ± 1.1	all PD	
Riediger et al. [20]	2006	Germany	With VR	53	31/22	64 (37–83)*	PD: 51; t-P: 4	25/42 (60)
			Without VR	169	91/78	64 (16–79)*	PD: 167; t-P: 2	
Shimada et al. [21]	2006	Japan	With VR	86	49/37	< 62 ($n = 38$)	PD: 81; t-P: 5	28 (33)
			Without VR	63	39/24	< 62 ($n = 36$)	PD: 62; t-P: 1	
Al-Haddad et al. [22]	2007	USA	With VR	22	11/11	70 (48–82)*	PD: 19;t-P: 2; d-P: 1	14/19 (73.6)
			Without VR	54	31/23	71 (39–89)*	PD: 38; t-P: 6; d-P: 10	
Kurosaki et al. [23]	2008	Japan	With VR	35	16/19	66.2 ± 9.2	all PD	–
			Without VR	42	18/24	64.1 ± 8.8	all PD	
Chakravarty et al. [24]	2010	Taiwan	With VR	12	7/5	62.9 ± 11.0	all PD	–
			Without VR	75	50/25	62.9 ± 9.8	all PD	
Ouaissi et al. [25]	2010	Belgium	With VR	59	30/29	64 (40–82)*	PD: 52; t-P: 7	24 (40.6)
			Without VR	82	42/40	63 (36–85)*	PD: 76; t-P: 6	

VR vein resection; *PD* pancreaticoduodenectomy; *st-PD* subtotal pancreatoduodenectomy; *t-PD* total pancreatoduodenectomy; *t-P* total pancreatectomy; *dst-P* distal subtotal pancreatectomy; *d-P* distal pancreatectomy

*Median

reoperation (with VR, 9.1%; without VR, 10.0%; $P = 0.92$), wound infection (with VR, 4.5%; without VR, 8.0%; $P = 0.09$), bleeding (with VR, 7.1%; without VR, 6.4%; $P = 0.42$), intestinal occlusion (with VR, 1.0%; without VR, 1.1%; $P = 0.94$), delayed gastric emptying (with VR, 18.8%; without VR, 16.4%; $P = 0.57$), intra-abdominal abscess (with VR, 3.4%; without VR, 6.3%; $P = 0.13$), biliary complications (with VR, 4.6%; without VR, 4.1%; $P = 0.59$), sepsis (with VR, 9.0%; without VR, 2.8%; $P = 0.08$), and gastric ulcer (with VR, 2.9%; without VR, 2.2%; $P = 0.93$) were similar between the two groups.

Table 2 Results of a meta-analysis comparing pancreatectomy with or without VR for pancreatic cancer

Outcome of interest	No. of studies	No. of patients	Results with VR, without VR	OR/ WMD	95% CI	*p* Value	HG *p* value
Perioperative outcomes							
Operative time, min	6 [9, 10, 16, 19, 21, 24]	566	497.3, 427.6	78.77	56.6, 100.95	< 0.001	< 0.001
Blood loss, ml	4 [10, 16, 19, 21]	392	1,412, 896	483.33	142.98, 823.68	0.005	< 0.001
Blood Transfusions requirement	4 [18, 19, 21, 25]	473	40.1, 26.9%	1.96	0.87, 4.43	0.11	0.02
Overall morbidity	13 [3, 6, 9, 10, 14–20, 23–25]	1,446	41.9, 44.0%	0.95	0.74, 1.21	0.67	0.92
Pancreatic Fistula	11 [9, 10, 14, 16, 18–25]	1,327	9.0, 13.1%	0.53	0.35, 0.79	0.002	0.65
Reoperation	9 [1, 9, 14, 15, 19–21, 23, 25]	1,448	9.1, 10.0%	1.02	0.68, 1.52	0.92	0.77
Wound infection	7 [9, 16, 18–21, 24]	764	4.5, 8.0%	0.54	0.27, 1.10	0.09	0.83
Bleeding	9 [9, 14, 15, 18, 19, 21, 24, 25]	1,038	7.1, 6.4%	1.24	0.74, 2.10	0.42	0.79
Intestinal occlusion	4 [9, 19, 21, 23]	446	1.0, 1.1%	1.06	0.21, 5.32	0.94	0.92
Delayed gastric emptying	8 [9, 10, 16, 18, 19, 21, 24, 25]	757	18.8, 16.4%	0.89	0.59, 1.33	0.57	0.88
Intra-abdominal abscess	9 [9, 10, 14, 16, 18, 19, 21, 23, 24]	964	3.4, 6.3%	0.61	0.32, 1.16	0.13	0.41
Biliary complications	7 [9, 10, 15, 19, 21, 24, 25]	714	4.6, 4.1%	1.22	0.59, 2.53	0.59	0.76
Pulmonary complications	6 [9, 15, 18, 19, 21, 23]	539	5.7, 6.0%	1.28	0.61, 2.68	0.51	0.83
Sepsis	2 [9, 24]	174	9.0, 2.8%	3.79	0.84, 17.1	0.08	0.19
Gastric ulcer	3 [9, 10, 21]	310	2.9, 2.2%	1.07	0.22, 5.15	0.93	0.72
Mortality	19 [1, 3, 6–10, 14–25]	2,247	3.3, 3.7%	1.19	0.73, 1.96	0.48	0.99
Long-term outcomes							
1-year overall survival	17 [1, 3, 7–10, 15–25]	1,815	61.3, 61.8%	0.92	0.66, 1.28	0.62	0.01
3-year overall survival	14 [1, 3, 7, 15, 17–25]	1,604	19.4, 26.6%	0.71	0.47, 1.06	0.09	0.03
5-year overall survival	11 [1, 8, 10, 14, 17, 19–23, 25]	1,532	12.3, 17.0%	0.61	0.37, 1.02	0.06	0.02

OR odds ratio; *WMD* weighted mean difference; *CI* confidence interval; *HG* heterogeneity

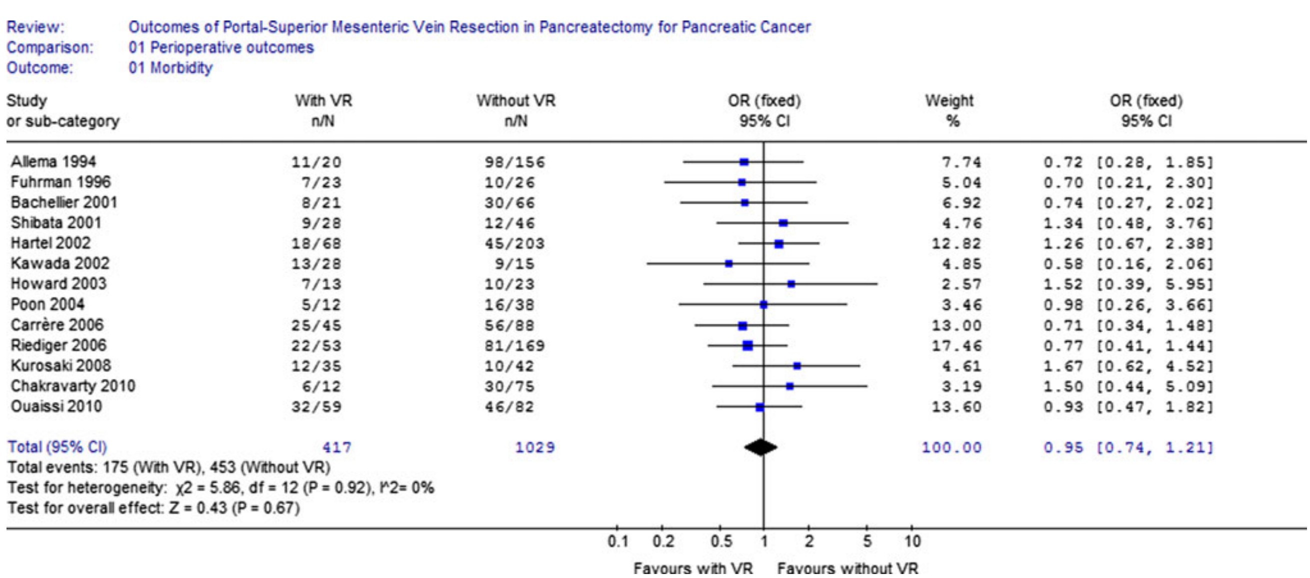

Fig. 1 Results of the meta-analysis on overall morbidity

All 19 studies reported on mortality. There were 22 deaths reported in the patients with VR, and 60 in the group without VR, giving a mean mortality rate of 3.3 and 3.7%, respectively ($P = 0.48$) (Fig. 2).

Meta-analysis of survival

There was no significant difference in overall survival between the two groups at 1 year (17 trials reported these

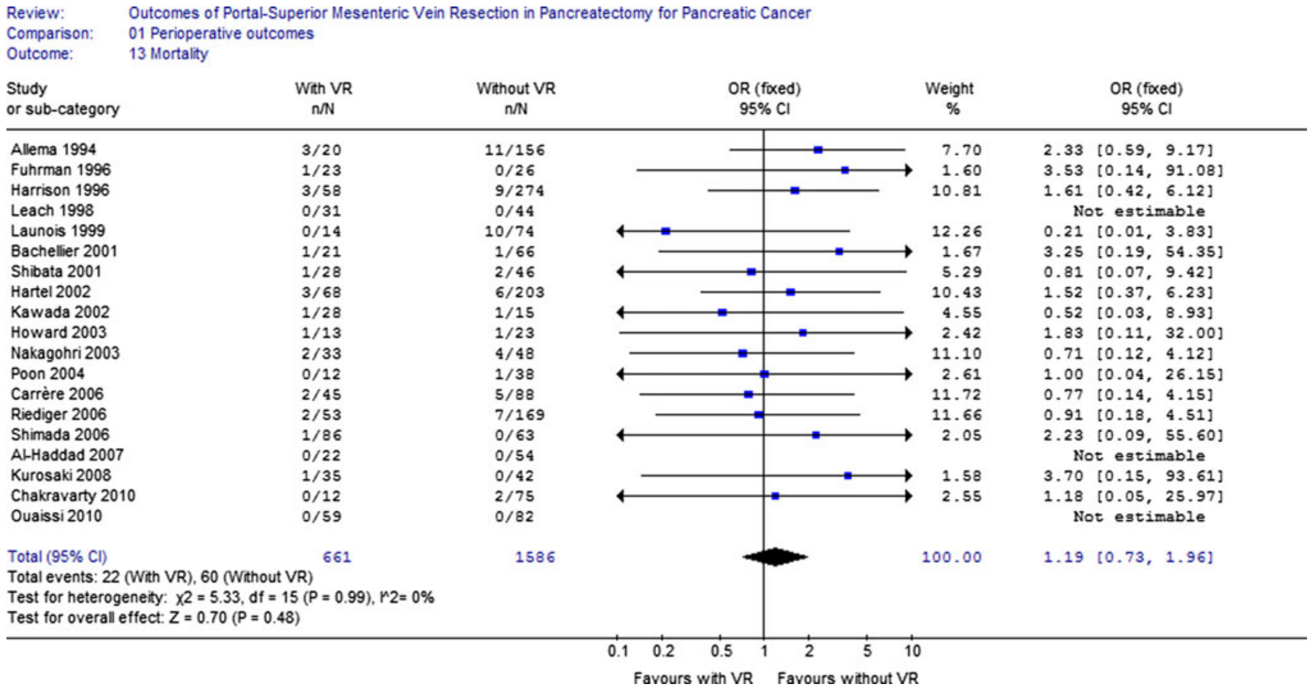

Fig. 2 Results of the meta-analysis on mortality

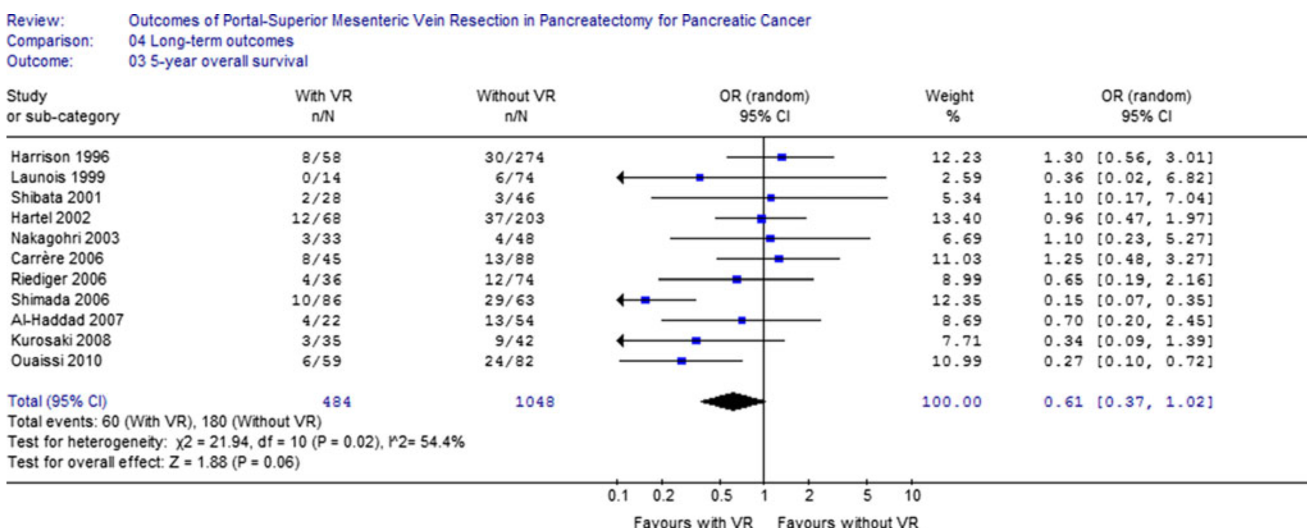

Fig. 3 Results of the meta-analysis on 5-year overall survival rate

data, OR: 0.92, 95% CI: 0.66–1.28; $P = 0.62$), at 3 years (14 trials reported these data, OR: 0.71, 95% CI: 0.47–1.06; $P = 0.09$), and at 5 years (11 trials reported these data, OR: 0.61, 95% CI: 0.37–1.02; $P = 0.06$) (Fig. 3).

The estimated 1-, 3-, and 5-year overall survival rates for the patients with VR and without VR were 61.3, 19.4, 12.3 and 61.8, 26.6, 17.0%, respectively.

Publication bias

A funnel plot of the studies used in the meta-analysis reporting on mortality is shown in Figure 4. This is a scatter plot of the treatment effects estimated from individual studies plotted on the horizontal axis (OR) against the standard error of the estimate shown on the vertical axis (SE). Only one study lies outside of the 95% CI limits.

Discussion

The first case of pancreatectomy with VR was reported by Moore et al. [26] in 1951. In 1973, Fortner [27] proposed the concept of “regional pancreatectomy,” which included venous (type I) and arterial (type II) resection, in an effort

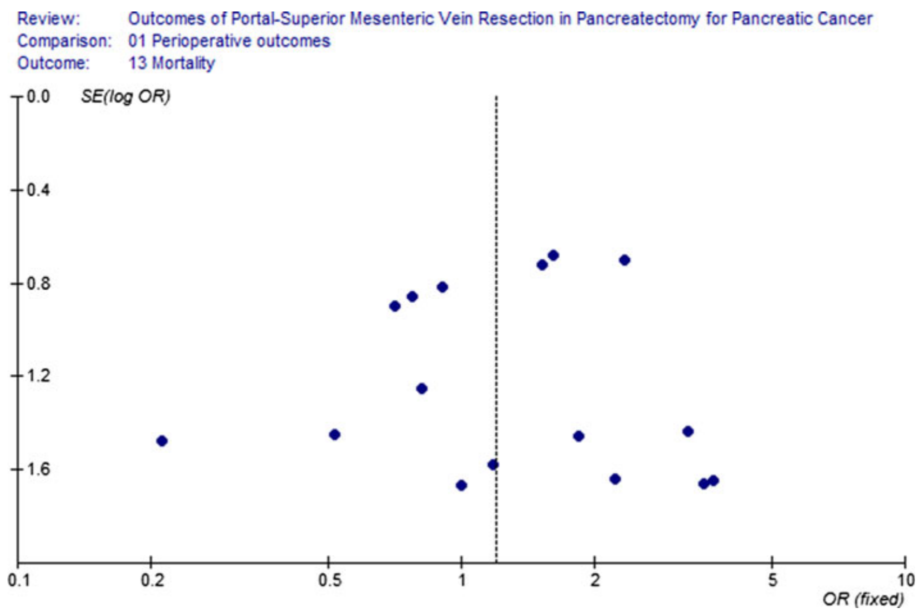

Fig. 4 Funnel plot for the results from all studies comparing mortality in the pancreatectomy combined with and without venous resection groups

to improve the resectability rates and curability rates for patients with pancreatic cancer. These regional pancreatectomy procedures were gradually abandoned because the results were poor. In recent years, advances in surgical techniques and postoperative care have improved the safety of pancreatic surgery. However, arterial resection in pancreatectomy remains a challenging procedure with significantly high morbidity and mortality rates [28]. In contrast, VR can be safely performed. As demonstrated in the present study, although duration of operation was longer and operative blood loss was greater in patients undergoing VR than in patients not undergoing VR, mortality and overall morbidity rates were comparable between the two groups. The present results showed acceptable rates of mortality (3.3%) and morbidity (41.9%). It is reasonable to assume that as a surgeon's experience increases, operative time and blood loss will likely decrease [6]. In the present study, the incidence of pancreatic fistula was significantly lower in the VR group, a difference due mainly to the results reported by Carrère et al. [19] in whose series there were more patients with fibrotic texture of the pancreatic remnant in the VR group. Concerning complications specific to VR, in this review, no study reported any case of bleeding in relation to venous resection. Three studies observed a total of four patients developed mesenterico-portal vein thrombosis [9, 19, 25]. In one study, Leach et al. [7] reported that the venous occlusion after VR occurred in 22% (7) of 31 patients: five were asymptomatic and the remaining two died of the condition.

In treatment for pancreatic tumors with SMV-PV involvement, results from two prospective randomized studies showed that the surgery group had significantly better survival than the palliative gastrobiliary bypass group or radiochemotherapy group [29, 30]. Our study demonstrates that this patient subset can benefit from aggressive *en bloc* VR, with an estimated 5-year survival rate of 12.3%. Therefore, it is clear that acceptable benefits in terms of long-term survival were achieved with this procedure. Furthermore, the overall survival did not differ between operation with VR and without. This is consistent with the hypothesis that tumor with portal vein adherence or invasion may represent a function of tumor location, and possibly tumor size, rather than an indicator of aggressive tumor biology [6]. In addition, tumor extension to the SMV-PV does not necessarily indicate tumor invasion. In the present study, histopathology evaluations revealed that a considerable percentage of patients (43.1%) who underwent VR for pancreatic cancer were found to have inflammatory adhesions without cancer invasion.

There is still no consensus on the specific indications for vascular resection of the SMV-PV. Tumor involvement of the proximal SMA or celiac axis, in contrast to involvement of the SMV-PV, usually includes extensive involvement of the lymphatic tissue as well as the nerve plexus. As a consequence, oncologic curability is limited by retroperitoneal margin positivity. Thus, some authors advocate that venous resection should not be performed when pretreatment imaging demonstrates tumor extension to the SMA or celiac axis [6, 10, 22]. However, recently, a case-matched control study found that pancreatic resections with arterial resection for adenocarcinoma were associated with a 3-year survival rate similar to that of a group of patients not requiring arterial resection [31]. In contrast, the depth of SMV-PV wall invasion is an indicator of poor outcome after curative pancreatic resection combined with VR [10, 32, 33]. However, occasional long-term survival could be observed after curative resection in patients with deep venous wall invasion [33]. In addition, before or during surgery, it is difficult to differentiate malignant from inflammatory adherence of the SMV-PV. Detecting the precise site of tumor infiltration is only possible by histopathological analysis [15].

The present study has several limitations, and therefor conclusions should be drawn with caution. First, to maintain a homogeneous group of patients, three studies were not included in the meta-analysis because data of patients with venous resections were not separable from data of patients with arterial resections [11–13]. This could have caused a selection bias. Second, all of the data in the present study come from nonrandomized studies, and the overall level of clinical evidence is low. Although randomized controlled trials represent the preferred study design for evaluating the safety and efficacy of a surgical procedure, randomized evaluation of VR during pancreatectomy is difficult due to a lack of patient compliance and some ethically unsustainable positions. Third, considering these reports over a 16-year period, it is important to realize that the results were influenced by differences in the treatment protocols, patient selection, and perioperative care. As a consequence, a test for heterogeneity was significant for some of the outcomes analyzed. We applied a random-effect model that takes possible heterogeneity into consideration.

In conclusion, pancreatectomy combined with VR resection for pancreatic cancer is justified because it can result in a positive perioperative outcome and long-term survival comparable to that obtained with standard resection. Owing to the selection bias and the low level of clinical evidence available so far, the results should be interpreted with caution.

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