



Venous resection during pancreatectomy for pancreatic cancer: a systematic review

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Abstract: Pancreatic cancer is one of the most aggressive and lethal malignancies with a dismal prognosis and survival. The curative effects of venous resection (VR) in pancreatic cancer remain controversial. A systematic literature search was performed in PubMed, Embase and the Cochrane Library. The overall postoperative complications, perioperative mortality, histopathology, and long-term survival were compared between patients undergoing pancreatectomy combined with (VR+ group) or without (VR- group) VR. Forty-one studies were included in the systematic review. Pancreatectomy combined with VR required longer operation time and led to increased perioperative blood loss, whereas postoperative complications were similar. Patients in the VR+ group showed larger tumors and reduced R0 rates. Regarding long-term survival, patients with VR+ seemed to have impaired 1-, 3-, and 5-year survival. Based on our results, VR in pancreatic cancer is a safe and feasible procedure. Given the fact that patients have miserable outcomes and survival in the palliative setting alone, extended resection including VR is required for the purpose of achieving radical resection.

Keywords: Pancreatectomy; pancreatic cancer; systematic review; venous resection (VR)

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Introduction

Pancreatic cancer is one of the most aggressive and lethal malignancies with a dismal prognosis and survival. The overall 5-year survival is still as low as 8% (1). Even after radical resection, the 5-year survival is only up to 25% due to the high rate of recurrence, but however can also raise up to 40% in high-volume pancreatic cancer surgery centres (2,3). Fortunately, owing to improved chemotherapy regimens in combination with radical surgery, the 5-year survival rates in locally advanced cases have become as good as primarily resectable cases (4).

Therefore, surgical resection remains the only potentially

curative option. Unfortunately, by the time of diagnosis, only a small portion (15–20%) of the newly diagnosed patients are suitable for surgical resection (5) due to local or distant metastases. The superior mesenteric/portal vein infiltration is often infiltrated, as the malignant tumor frequently invades into the retroperitoneal space and due to the intimate anatomic location of the uncinate process into the superior mesenteric or portal vein (6). In the past venous infiltration was considered as a contraindication for surgery due to the limitation of tumor dissection at the vessels. Today, with the development of better operation techniques, pancreatectomy combined with venous resection (VR) can be achieved with acceptable morbidity and mortality in experienced centers (7).

Therefore, venous infiltration is no longer considered as a contraindication for pancreatic cancer resection. According to the NCCN Clinical Practice Guidelines in Oncology 2017 (8), the presence of solid tumor encasement of the superior mesenteric vein or portal vein $>180^\circ$ is considered as a criterion for defining the borderline resectable disease. However, the curative effects of VR in pancreatic cancer remain controversial.

In this study, we aimed to investigate the most up-to-date survival data and the perioperative outcome and survival associated with pancreatectomy with superior mesenteric/portal vein resection, and compared it to patients without VR.

Methods

Search strategy

Quality items of the systematic review were reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. A systematic literature search was performed in PubMed, Embase and the Cochrane Library by applying various combinations of the terms related to pancreatic cancer and VR. The search items were “pancreatic cancer”, “pancreatic ductal adenocarcinoma”, “superior mesenteric vein” and “portal vein”. Articles published until May 2018 were included. No language restriction was applied in the search strategy.

Inclusion and exclusion criteria

For inclusion into the present systematic review, a study had to meet the following criteria:

- (I) To compare the results of pancreatectomy with versus without VR in patients with pancreatic cancer;
- (II) To report at least one outcome of interest.

Animal studies, case reports, review articles without original data, letters, comments, abstracts, duplicate reports and studies that contained non-cancer patients were excluded from the systematic review. Studies that contained arterial resection were also excluded, since arterial resection is frequently associated with impaired survival.

Data extraction

The following data were extracted from the full texts and supplemental materials: first author, year of publication, period of patient inclusion, title, study design, mean age,

perioperative outcomes, inclusion criteria and exclusion criteria, patient characteristics, median survival and 1-, 2-, 3-, and 5-year survival. The perioperative outcomes included: overall postoperative complications (due to inconsistency in the definition of morbidity or even missing definitions, postoperative complications in general was provided instead), mortality, re-operation rate, sample size, hospital stay, duration of operation, blood loss and histopathology finding.

Statistical analysis

The Review Manager (RevMan, the Cochrane Collaboration) software version 5.3 was used for the data pooling. Dichotomous variables with the estimation of risk ratio (RR) or odds risk (OR) together with a 95% CI and continuous variables with weighted mean difference (WMD) and a 95% CI were analyzed. Pooled effect was calculated using either the fixed effects model or the random-effects model based on data features. Statistical heterogeneity between trials was evaluated by I^2 and P value. If I^2 was less than 50%, the fixed effects model was used as the absence of heterogeneity. Otherwise, the random effects model was applied if I^2 exceeded 50%. P value <0.05 was considered significant. Publication bias was assessed visually with a funnel plot.

Results

Included studies

A total of 1,087 articles were retrieved by the primary search. After screening the titles, abstracts, and full text, 1,046 studies were excluded and 41 studies (9-30) were eligible for inclusion in the review (*Figure 1*) (31-49). There were no randomized clinical trials on the subject. The 41 studies involved 7,567 patients in total; among these, 1,921 underwent pancreatectomy with and 5,646 without VR.

Characteristics of the studied patients

The characteristics of all the included studies and the baseline demographic data of the enrolled patients were summarized in *Table 1*. The studies were published between the years 1996 and 2018, with the sample size varying from a minimum of 34 to a maximum of 1,070. The VR rate ranged from 6.1% to 65.1%. The mean age of the patients was 64.5 years.

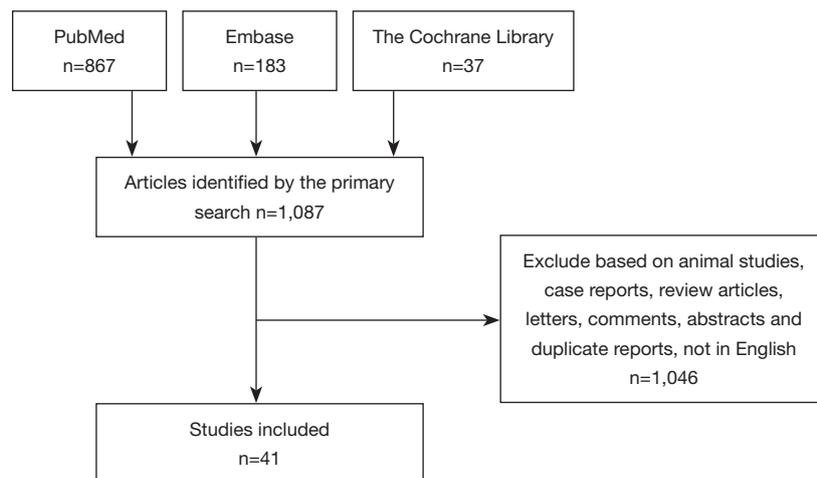


Figure 1 Flowchart of search history.

Perioperative outcomes

Data on duration of surgery were available in 11 (13,17,21,23,28,30,37,43,44,46,47) of 41 studies which demonstrated a prolonged operating time in patients with VR. The mean operating time was 491 minutes (ranging from 342 to 667) for patients undergoing pancreatectomy with VR, compared to 399 minutes (ranging from 306 to 568) for patients without VR ($P < 0.00001$). Meanwhile, data on blood loss during operation was available only in 8 studies (17,21,23,28,34,37,44,46). The average blood loss in the VR+ group was 929 mL (ranging from 343 to 1,686) and in the VR- group 581 mL (ranging from 353 to 866), indicating VR with increased blood loss ($P = 0.0001$).

Data on postoperative mortality (refers to death within 30 days after surgery) was reported in 28 studies, involving 5,773 patients. Compared to patients without VR (3.17%, range 0–13.51%), mortality in VR+ patients was increased (3.84%, range 0–13.73%; $P = 0.03$). Whereas, data on 90-day morbidity was available on 3 studies (42,44,47), involving 728 patients. There is also no significant difference between two groups ($P = 0.27$).

A total of 19 retrospective cohort studies (3,499 patients) (9,14,15,19,21,22,25–32,34,36,37,41,47) revealed that the overall postoperative complications showed no significant difference between the two groups ($P = 0.07$). The overall postoperative complications in the VR+ group was 37% (range 20.7–55.6%), compared to the VR- group (34%, range 19.4–63.6%). To allow a more detailed insight, data of wound infection, abdominal abscesses, postoperative bleeding and delayed gastric emptying were extracted.

Pooled analysis revealed that the risk of wound infection ($P = 0.42$) and intra-abdominal abscess ($P = 0.31$) were similar between the two groups. By contrast, the risks of postoperative bleeding ($P < 0.0001$) and delayed gastric emptying ($P = 0.03$) were markedly higher in the VR+ group. Interestingly, patients who underwent pancreatectomy with VR+ revealed less pancreatic fistula (7.9%, range 0–16.3%), than patients without VR- (10.7%, range 2.47–33.3%; $P = 0.0010$).

Seventeen studies (9,10,13,17,20,21,23,27,28,33,37,40,42,43,46,47,49), including 2,469 patients, reported about re-operation rates. Two hundred eighty three patients underwent re-operations, 104 in the VR+ group and 179 in the VR- group, respectively. Pooled analysis of data found that the overall incidence of re-operation in the VR+ group was 12.3% (ranging from 0% to 48%), which was higher when compared to VR- group (11.0% ranging from 0% to 25.33%; $P = 0.008$).

Histopathology

Nine studies (13,17,21,30,34,37,41,46,47), containing 1,445 patients in total, reported the tumor size as a prognostic variable. The average tumor dimension in the VR+ group was 35.7 mm (range, 28.2–47.9 mm), and the dimension in VR- group was 30.8 mm (range, 26.7–41 mm). Patients receiving VR+ were more likely to have bigger tumors than those without VR- ($P < 0.00001$).

Twenty-six studies, including 5,065 patients, reported data on R0 (negative margin) rate. The definition of R0 was determined by the authors of each study. Using a fixed-

Table 1 The characteristics of included studies included

Reference	Publication (Y)	Study year	Country	No. of patients (VR+ : VR-)	Sex ratio (M:F)	Median age (years)
Fuhrmann <i>et al.</i>	1996	1990–1993	USA	59 (23:36)	33:26	64
Harrison <i>et al.</i>	1996	1983–1995	USA	332 (58:274)	171:161	65.5
Leach <i>et al.</i>	1998	1990–1995	USA	75 (31:44)	42:33	64.8
Launois <i>et al.</i>	1999	1973–1992	France	88 (14:74)	61:27	60
Bachelier <i>et al.</i>	2001	1990–1999	France	87 (21:66)	50:37	62.9
Shibata <i>et al.</i>	2001	–	Japan	74 (28:46)	53:21	61
Kawada <i>et al.</i>	2002	1990–1997	Japan	43 (28:15)	28:15	62.3
Hartel <i>et al.</i>	2002	1980–2001	Germany	271 (68:203)	171:100	61.8
Nakagohri <i>et al.</i>	2003	1992–2001	Japan	81 (33:48)	47:34	62.4
Riediger <i>et al.</i>	2003	1994–2001	Germany	222 (53:169)	122:100	64
Howard <i>et al.</i>	2003	1998–2003	USA	36 (13:23)	21:15	67.4
Poon <i>et al.</i>	2004	1998–2002	China	50 (12:38)	29:21	62.3
Tseng <i>et al.</i>	2004	1990–2002	USA	291 (110:181)	175:116	63.9
Shimada <i>et al.</i>	2006	1996–2004	Japan	149 (86:63)	88:61	62
Carrère <i>et al.</i>	2006	1989–2003	France	133 (45:88)	91:42	60.6
Al-Haddad <i>et al.</i>	2007	1998–2005	USA	76 (22:54)	42:34	70.7
Fukuda <i>et al.</i>	2007	1990–2002	France	121 (37:84)	58:63	66
Kurosaki <i>et al.</i>	2007	1987–2005	Japan	77 (35:42)	43:34	65.1
Illuminati <i>et al.</i>	2008	2000–2005	Italy	137 (29:108)	–	–
Martin II <i>et al.</i>	2009	1999–2007	USA	593 (36:557)	–	–
Kaneoka <i>et al.</i>	2009	1993–2006	Japan	84 (42:42)	–	65.5
Hristov <i>et al.</i>	2010	1993–2005	USA	160 (20:140)	96:64	55.2
Chakravarty <i>et al.</i>	2010	1996–2006	Japan	87 (12:75)	57:30	62.9
Benz <i>et al.</i>	2011	1997–2009	Switzerland	326 (51:275)	171:155	65.3
Murakami <i>et al.</i>	2012	1996–2010	Japan	125 (61:64)	65:60	69
Turley <i>et al.</i>	2012	1997–2008	USA	204 (42:162)	–	65.5
Jeong <i>et al.</i>	2013	1995–2009	South Korea	276 (46:230)	159:117	61.3
Kelly <i>et al.</i>	2013	2000–2007	USA	492 (70:422)	244:248	65.3
Menon <i>et al.</i>	2013	2007–2012	USA	61 (18:43)	27:34	68.5
Ravikumar <i>et al.</i>	2013	1998–2011	UK	1,070 (230:840)	583:487	65.8
Turrini <i>et al.</i>	2013	2000–2010	France	38 (19:19)	–	63.5
Wang <i>et al.</i>	2014	2004–2012	Australia	122 (64:58)	64:58	66.5
Iorgulescu <i>et al.</i>	2014	2004–2012	Australia	34 (17:17)	19:15	63.5
Kulemann <i>et al.</i>	2014	1994–2014	Germany	339 (131:208)	166:173	66
Michalski <i>et al.</i>	2015	2007–2015	Germany	156 (54:102)	–	–
Wang <i>et al.</i>	2015	2009–2013	China	208 (42:166)	141:67	60.3
Marsoner <i>et al.</i>	2016	2003–2016	Austria	221 (47:174)	109:112	66.8
Zhao <i>et al.</i>	2016	2014–2016	China	106 (21:85)	57:49	63.4
Addeo <i>et al.</i>	2017	2006–2014	France	181 (91:90)	106:75	68
Hoshimoto <i>et al.</i>	2017	2007–2015	Japan	122 (21:101)	62:60	67.3
Klein <i>et al.</i>	2018	1989–2015	Germany	160 (40:120)	84:76	64.3

VR, venous resection.

Table 2 Median survival of patients undergoing pancreatectomy with (VR+) or without (VR-) vein resection

Study	Median overall survival (month)		P
	VR+ group	VR- group	
Harrison <i>et al.</i>	13	17	NS
Leach <i>et al.</i>	22	20	NS
Nakagohri <i>et al.</i>	15	10	NS
Poon <i>et al.</i>	19.5	20.7	NS
Tseng <i>et al.</i>	23.43	26.50	NS
Shimada <i>et al.</i>	14	35	0.006
Carrère <i>et al.</i>	15	19	NS
Martin II <i>et al.</i>	18	19	NS
Benz <i>et al.</i>	14.5	14.8	NS
Turley <i>et al.</i>	21.1	20	NS
Jeong <i>et al.</i>	16	12	NS
Menon <i>et al.</i>	31	31	NS
Ravikumar <i>et al.</i>	18.2	18	NS
Wang <i>et al.</i>	18	31	0.016
Iorgulescu <i>et al.</i>	13.8	43.1	0.028
Kulemann <i>et al.</i>	21.6	19.7	NS
Wang <i>et al.</i>	20	26	NS
Zhao <i>et al.</i>	15	19	NS
Addeo <i>et al.</i>	22	27	NS
Hoshimoto <i>et al.</i>	26	29	NS
Klein <i>et al.</i>	10.4	18.6	0.0011
Hristov <i>et al.</i>	21.4	20.8	NS
Howard <i>et al.</i>	13	12	NS

VR, venous resection.

effects model, the incidence of R0 rate in VR+ group was markedly lower comparatively to VR- groups (60.5%, range 35.7–94.4% vs. 68.7%, 47.3–92.9%; $P < 0.00001$).

Survival analysis

To evaluate the effect of VR, the median survival and the 1-, 2-, 3-, and 5-year overall survival were extracted and compared between the two groups. Data on median overall survival were available for 23 studies (Table 2). Four studies identified VR as a negative prognostic factor ($P=0.006$, $P=0.016$, $P=0.028$, and $P=0.0011$, respectively). Pooled analysis of data from 12 studies (11,19-21,33,35,39-41,44,48,49) showed that VR+ patients have significantly shorter median survival ($P=0.0001$). Furthermore, patients who received VR had worse 1- (13,24,25,30,31,39,44,45,47,48), 3- (18,24-26,30,37,39,47,48), and 5-year (10,14,15,18,21-24,36,39,45,47,48) survival (Table 3). Analysis of long-term survival revealed that 1-year survival rate was decreased in VR+ group (62.9%) compared to VR- group (76.6%) ($P=0.0009$). Similarly, 3-year survival rates and 5-year survival rates were lower in VR+ group (24.5% vs. 29.4% for 3-year survival, $P=0.02$ and 12.7% vs. 15.4% for 5-year survival, $P=0.001$).

Type of venous reconstruction

The venous reconstruction techniques included end-to-end anastomosis, patch venoplasty, venorrhaphy, and graft interposition. Data on the type of venous reconstruction were available for 18 studies (10,11,13,15-18,26-30,35,36,38,43,44,47) with 932 patients. Generally, the selection of different vessel reconstruction techniques depended on the length of the vessel infiltration. The most common reconstruction method was an end-to-end

Table 3 Long-term outcomes in patients undergoing pancreatectomy with (VR+) or without (VR-) vein resection

Outcome of interest	VR+ group	VR- group	Risk ratio	95% CI	P	Heterogeneity P , I^2
1-year survival	237/377	772/1,008	0.86	0.78, 0.94	0.0009	$I^2=0\%$, $P=0.49$
2-year survival	69/188	247/622	0.90	0.72, 1.11	0.33	$I^2=11\%$, $P=0.35$
3-year survival	79/322	189/643	0.76	0.61, 0.95	0.02	$I^2=0\%$, $P=0.48$
5-year survival	90/708	236/1,537	0.64	0.49, 0.83	0.0010	$I^2=57\%$, $P=0.004$

VR, venous resection.

anastomosis (531 patients, 57.0%), which was normally performed by a continuous running 5-0 polypropylene suture. If the involvement of the vein was longer than 5 cm, an interposition vascular graft was considered in order to perform a tension-free anastomosis. Launois *et al.* (12) reported that a distance of up to 8 cm could be covered by end-to-end anastomosis after mobilizing of the mesenteric base. No data were available for the mortality, morbidity, and survival for the different types of venous reconstruction.

Discussion

This systematic review investigated the perioperative outcomes and long-term outcomes in patients suffered from pancreatectomy with or without VR. The study demonstrated the overall postoperative complications were similar between the two groups. Moreover, patients in the VR+ group showed a relatively higher mortality and worse 1-, 3-, 5-year survival.

Pancreatectomy combined with VR provides a possibility of a radical treatment option for patients with pancreatic cancer. Although VR can be performed feasibly and safely (50), the outcomes of VR remain discrepant. Pancreatectomy combined with VR was first reported by Moore *et al.* (51) in 1951. However, subsequent studies demonstrated that there was no survival benefit from VR. Moreover, VR was also associated with increased morbidity and mortality. Therefore, venous infiltration was considered as a contraindication to surgery for pancreatic cancer. With deepened understanding and development of operative techniques, pancreatectomy combined with VR can achieve similar morbidity and mortality compared to standard pancreatectomy.

In this study, we demonstrated that the overall postoperative complications were similar between the two groups, which underline that VR can be performed safely. Although the mortality is higher in the VR group, it is notable that these patients suffered from larger tumors, reduced R0 rates, longer operation time, as well as increased perioperative blood loss. Subgroup analysis for postoperative complications revealed that the risks of postoperative bleeding and delayed gastric emptying were markedly higher in the VR group, which is accordant with the fact that patients undergoing VR received relatively more complex surgery and had longer operation time. In line with our results, Carrère *et al.* (21) reported that the risk of pancreatic fistula was significantly decreased in the VR+ group, since patients in VR+ group revealed a more fibrotic

pancreatic remnant. Furthermore, tumor topography and volume may also contribute to this phenomenon. Our study demonstrated that patients in VR+ group tended to have larger tumors, which consequently may lead to more frequent obstruction and a dilated main-pancreatic duct, which enables a safe anastomosis.

Regarding histopathology, there was no significant difference between VR- and VR+ group in the rate of lymph node metastasis. However, compared with VR- group, patients in VR+ group tended to suffer from larger tumors and lower R0 resection rate, which may imply that they tended to have more aggressive and malignant tumors. Riediger *et al.* (22) investigated patients from both groups with margins negative or margins positive specimens, and reported markedly increased survival in margins negative group. Consistent with our previous study (2), we found that R1 resection in pancreatic head resection frequently associated with impaired survival both in the meta-analysis and in our cohort. Moreover, patients with R1 resection were suffering from advanced tumor disease, including larger tumor size, high rate of lymph node metastasis. Similar benefits of radical resection were also revealed by Neuhaus *et al.* (52) for hilar cholangiocarcinoma. Hence, radical excision with large tumor-free margins remains to be essential for solid tumors.

Consistent with some other meta-analyses, our findings demonstrate that VR during pancreatectomy is associated with worse survival (53-55). The shorter survival of patients who suffered from VR seems to be attributable to larger tumor size and the higher rate of positive margins. Yu *et al.* (55) reported in 2014 that the VR+ group and the VR- group had similar 1-year survival and 3-year survival. Yet at 5-year, VR+ group showed a worse survival ($P=0.03$). The higher number of patients and possibly more advanced disease of the involved patients in our study may explain the different results that are obtained here. More importantly, the data points out that patients with negative margin have significantly better 2- and 5-year survival (55). VR provides the opportunity of achieving R0 resection for the patients with venous infiltration, following with an obvious survival advantage (5-year survival: 25%) compared to the palliative setting only (5-year survival: 7%). Therefore, pancreatectomy combined with VR seems to be justified in the patients with vein infiltration since VR can offer the chance of radical margin-free surgery.

There are several limitations in this systematic review. First, 5 studies (56-60) were excluded because data on VR could not be separated from arterial resection in these

studies. Furthermore, the heterogeneity of the included studies is another limitation of this review. The studies included in this systematic review were published from 1996 to 2018. The techniques of surgery and perioperative care have since been further developed and changed including different protocols of adjuvant chemotherapy. As a consequence, the results of short-term and long-term outcomes might have been influenced by this long time window. Moreover, besides these developments, the existence of surgical experience and protocol disparities in different surgery centres can also contribute to statistical heterogeneity. Another limitation is that randomized controlled trial (RCT) is not available on this topic, since VR is necessary to achieve R0 resection in patients with vein infiltration and it is highly impossible to randomize patients into VR- and VR+ groups.

In conclusion, VR in pancreatic cancer is a safe and feasible procedure. Given the great benefit of R0 resection and the fact that patients have miserable outcomes and survival in the palliative setting only, extended resection including VR is required for the purpose of achieving radical resection, which is considered to be the best option to achieve long-term survival for patients with solid tumors. Future studies with larger case series from high-volume pancreatic cancer surgery centres are necessary to demonstrate the true impact of VR, especially when regarding novel neoadjuvant therapy protocols.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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