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REVIEW ARTICLE

Vascular resection during radical resection of pancreatic adenocarcinomas: evolution over the past 15 years

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Abstract This literature review aimed to critically analyze oncological results of vascular resection during pancreatectomy for adenocarcinoma in the light of the concept evolution of locally advanced tumors and microscopic complete resection. The literature search was conducted in PubMed and Medline for the period June 1994 to December 2012, retaining English as the language of publication. The review of 12 publications indicated that mortality and morbidity rates were not significantly different for pancreatectomy with or without venous resection (VR). Six comparative studies showed worse long-term survival in the VR group, though one meta-analysis, albeit with a significant population heterogeneity, demonstrated that the overall survival between VR and the control group was similar (12% vs. 17%). The compilation of 13 comparative studies showed a significantly lower rate of complete microscopic resection in the VR patient group compared to controls (63% vs. 77%; $P = 0.001$). Concerning pancreatectomy combined to arterial resection, the literature review indicated a significantly greater mortality and morbidity rate and a lower survival rate compared to pancreatic resection alone. Conflicting results concerning the long-term outcome of VR was due to the heterogeneity of the patient population. Since the only chance to cure patients of pancreatic adenocarcinoma is to obtain free resection margins, VR is a valid therapeutic option. But combined arterial resection to pancreatic resection does not appear to be recommended.

Keywords Arterial invasion · Morbidity · Mortality · Pancreatic cancer · Pancreatoduodenectomy · Resectability · Survival · Vascular resection · Venous invasion

Introduction

Pancreatic adenocarcinoma ranked in 2011 as the 4th cause of cancer-related deaths in the United States [1, 2]. The aggressiveness of this cancer is confirmed by an incidence rate almost equal to its mortality with median survival rates of 3 to 4 months and a 5-year overall survival rate of 5% [3]. The cornerstone of curative treatment of pancreatic adenocarcinoma is radical pancreatic tumor resection with negative margins at microscopy (defined as R0 resection) [4, 5], which increases 5-year survival rate to 20% and leads to a median survival rate ranging from 20 to 22 months [6–10]. However, at the time of diagnosis, fewer than 20% of patients have potentially resectable tumors. Although surgery is contraindicated in certain clear-cut clinical situations such as peritoneal carcinomatosis and liver metastases, 30% of pancreatic tumors are locally advanced and justify pancreaticoduodenectomy (PD) with mesenterico-portal vein resection or, more rarely, distal splenopancreatectomy

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(DSP) to achieve R0 resection without increasing morbidity and mortality [11–14]. Both the definition of locally advanced pancreatic tumors and the management of tumors either invading or in contact with the mesenterico-portal venous system have changed over time, in terms of surgical and perioperative treatments including neoadjuvant therapy [13–16]. Patients with resection of the superior mesenteric artery (SMA), celiac trunk (CT) and hepatic artery (HA) were included in the arterial resection group. This arterial group includes heterogeneous studies with small number of patients and different type of surgery (i.e. PD surgery or DSP with the Appleby technique for resection of the celiac trunk) [17]. However, arterial resection is reported to be associated with significantly greater mortality and brings little obvious oncological benefit in terms of survival [17].

The purpose of the present literature review was therefore to critically analyze the oncological benefits of vascular resection during PD for primary pancreatic adenocarcinoma and to discuss the evolution of concepts with respect to microscopic complete resection, venous and arterial resection of "locally advanced" pancreatic tumors.

Method of literature analysis

The literature search was conducted in PubMed and Medline for the period of June 1994 to December 2012, retaining English as language of publication. The keywords used were "portal vein", "superior mesenteric vein", "arterial resection" and "pancreatic adenocarcinoma". The search was then limited by decreasing priority from meta-analysis to randomized controlled trials (RCT) and then to clinical studies (clinical trials). Experimental works were excluded. Comparative studies were analyzed in priority. Literature reviews were only included if they met the standards of evidence-based medicine, that is, systematic reviews (details on the literature review method, review of all articles published on the subject, tabulation and quantitative analysis). The selected 37 studies were then classified according to the international recommendation system assessing scientific quality [18, 19]. Concerning venous resection, the selected studies were 15 comparative studies of pancreatectomies without neoadjuvant therapy [20–34], two literature reviews [13, 35], one meta-analysis [14] and one cohort study [36] (Table 1). Six additional studies from expert centers were selected in view of the detail accuracy of their description of the pancreatectomy resection margins [37–42] (Table 1). Most of these series included pancreaticoduodenectomies (72% to 100%) or total pancreatectomies (0% to 13.7%) and few distal pancreatectomies (0 to 13.7%). Concerning arterial resection (including common hepatic artery (CHA), SMA and CT), we have selected five retrospective studies including three comparative series of more than 19 patients without neoadjuvant therapy and one recent meta-analysis by Molberg et al. [17, 43–48]. Two additional series from expert centers were included in the present review as they concerned patients with previous neoadjuvant therapy [49, 50] (Table 2). In patients with locally advanced tumor located in body or tail of the pancreas and invading CT, DSP associated with arterial resection of CT according to the "modified Appleby technique" was also reported [51, 52]. Three studies with more than 13 patients without neoadjuvant treatment using this technique were included in the present review [44, 53, 54].

All studies were classified as having a low to moderate level of evidence according to the international classification system [18, 19] (Table 1 for venous and Table 2 for arterial resection).

Venous resection

Goal and philosophy of venous resection and its limitations

The objective of associated venous resection and reconstruction during pancreatectomy for primary pancreatic adenocarcinoma is to achieve a radical R0 tumor resection when the vein is in contact with the tumor or invaded by it. The rationale for radical surgical excision, that is, with macroscopic and microscopic complete resection (R0), is based on the benefit of a better survival rate in patients with R0 resection (median survival rate: 18–28 months) compared to patients with microscopic incomplete resection (R1) (median survival rate: 14–21 months) in the five largest series from expert centers including more than 250 patients [55–59]. Two studies paying special attention to the microscopic evaluation of the retroperitoneal margins have recently confirmed the same benefit in terms of improved survival when R0 resection was achieved [4, 5]. The surgical goal in pancreatic cancer is thus to perform an R0 resection in order to clearly obtain an increased overall survival rate. However, when performing a PD, there are several tissues margins that have to be taken into consideration to obtain R0 resection. For some of them, such as the biliary, pancreatic, duodenal and vascular margins, obtaining a free margin can be guided by getting routine (and sometimes repeated) frozen section pathological examinations during surgery. However, the posterior retroperitoneal margin can only be analyzed at final pathological examination. It should be emphasized that the definition of an R0 or R1 resection of the retroperitoneal margin, the methodology of retroperitoneal margin analysis at final pathological examination, as well as the technique of surgical dissection of the retroperitoneal margin to intend radical resection have

Table 1 Grade of evidence of studies about pancreatectomies with and without venous resection for pancreatic adenocarcinoma

Year	Authors	Country	Number of patients with and without venous resection	Type of pancreatectomy with associated venous resection			Type of study	Definition of grade of evidence
				PD	DSP	TP		
1996	Harisson [20]	USA	58/274	86.6%	13.4%	13.4%	Retrospective Comparative	Low
1999	Launois [21]	France	14/74	NR	NR	NR	Retrospective Comparative	Low
2001	Bachellier [22]	France	21/66	100%	0	0	Retrospective Comparative	Low
2001	Shibata [23]	Japan	28/46	82.1%	7.2%	10.7%	Retrospective Comparative	Low
2002	Hartel [24]	Germany	68/203	82.3%	0	17%	Retrospective Comparative	Low
2002	Kawada [25]	Japan	28/25	100%	0	0	Retrospective Comparative	Low
2003	Howard [26]	USA	13/23	100%	0	0	Retrospective Comparative	Low
2003	Nakaghori [27]	Japan	33/48	81.8%	18.2%	0	Retrospective Comparative	Low
2004	Poon [28]	China	12/38	100%	0	0	Retrospective Comparative	Low
2004	Nakao [37]	Japan	171/79	NR	NR	NR	Retrospective Comparative	Low
2006	Siriwardana [35]	USA	1334/0	97.7%	2.3%	26.3%[a]	Review	Low
2006	Carrere [29]	France	45/88	100%	0	0	Retrospective Comparative	Low
2007	Al Haddad [34]	USA	22/54	95.3%	4.7%	4.5%	Retrospective Comparative	Low
2007	Fukuda [38]	France	0/37	NR	NR	NR	Retrospective	Low
2007	Chavraty [33]	China	12/75	100%	0	0	Retrospective Comparative	Low
2009	Kanekoa [39]	USA	42/42	100%	0	0	Retrospective Comparative	Low
2010	Ouaissi [30]	Belgium	59/82	88.2%	0	11.8%	Retrospective Comparative	Low
2011	Banz [31]	UK	51/275	100%	0	0	Retrospective Comparative	Low
2012	Wang [32]	Australia	51/50	100%	0	0	Retrospective Comparative	Low
2012	Han [40]	Korea	19/0	100%	0	0	Retrospective	Low
2012	Nakao [41]	Japan	0/297	–	–	–	Retrospective	Low
2012	Castleberry [36]	USA	281/3,582	100%	0	0	Cohort study	Moderate
2012	Ouaïssi [13]	France	NR	NR	NR	NR	Review	Low
2012	Zhou [14]	China	661/2247	NR	NR	NR	Meta-analysis	Moderate
2012	Turrini [42]	France	19/19	100%	0	0	Case-controlled	Moderate

DSP distal splenopancreatectomy ("Appleby procedure"), *NR* not reported, *PD* pancreaticoduodenectomy, *TP* total pancreatectomy

[a] Total pancreatectomy included pancreatoduodenectomy

all been submitted to recent innovative changes (see below).

Prevalence of venous resection

The overall incidence of venous resection during pancreatic resection was 26% according to the 2006 literature review by Siriwardana et al. involving 6333 patients. There was a difference in incidence according to the geographical origin of the series: 15% to 19% in Europe and North America and up to 47% in Asia [35]. These differences may be explained by the use of different strategies and concepts of venous resection that have also changed over time (see below).

Table 2 Grade of evidence for studies concerning pancreatectomies with or without arterial resection for pancreatic adenocarcinoma

Year	Authors	Number of patients with and without arterial resection	Type of study	Type of pancreatectomy with associated arterial resection			Grade of evidence of studies
				PD	DSP	TP	
2007	Hirano [44]	23/23	Retrospective Comparative	0	23%	0	Low
2008	Wang [46]	19/80	Retrospective Comparative	100%	0	0	Low
2008	Stizenber [50]	12/-	Retrospective	50%	16.6%	33.4%	Low
2009	Martin [49]	5/-	Retrospective	NR	NR	NR	Low
2009	Sugiura [48]	26/107[a]	Retrospective Comparative	38.5%	7.7%	53.8%	Low
2009	Amano [43]	23	Retrospective	30.4%	4.4%	65.2%	Low
2010	Bockhorn [47]	29/449	Retrospective Comparative	55.2%	27.5%	17.3%	Moderate
2011	Bachellier [45]	26/26	Case-controlled	NR	NR	NR	Moderate
2011	Mollberg [17]	366/2609	Meta-analysis	NR	NR	NR	Moderate
2011	Tanaka [53]	42	Retrospective	0	0	100%	Low
2012	Yamamoto [54]	13	Retrospective	0	0	100%	Low

DSP distal splenopancreatectomy (“Appleby procedure”), *NR* not reported, *PD* pancreaticoduodenectomy, *TP* total pancreatectomy

[a] Including combined pancreatic and venous resection

Predictive factors of venous resection

Tumors located in the uncinate process are associated with a significantly greater rate of venous resection [30]. In historical studies, these tumors were deemed to be unresectable in 90% of cases [60]. A recent study by Kang et al. comparing 25 patients with pancreatic adenocarcinoma in the uncinate process to 72 adenocarcinomas of the pancreatic head showed that tumors located in the uncinate process were significantly more advanced at diagnosis ($P = 0.03$), probably because symptoms appeared later in comparison to tumors located in the pancreatic head close to the common bile duct [61]. Another radiological study comparing 28 adenocarcinomas of the uncinate process to 27 adenocarcinomas of the head of the pancreas reported a significantly greater rate of tumor contact with the superior mesenteric vessels for tumors located in the uncinate process (96% vs. 74%; $P = 0.03$) [62]. The latter tumors often are more advanced and early contact with the mesenteric vessels exposes them to a significantly higher rate of R1 resection and venous resection [30, 63]. Given the oncological requirements of R0 resection, the close contact of the uncinate process with the right edge of the termination of the superior mesenteric vein justifies discussing a philosophy of systematic venous resection for pancreatic tumors located in the uncinate process [30, 42, 64]. Tumor size may also be predictive of the need for venous resection [30], as confirmed in four out of 13 comparative studies [20, 29, 30, 32] (Table 3). Combined venous and pancreatic resection for pancreatic cancer is observed to have a reportedly significantly higher rate of UICC stages 3 and 4 tumors [23, 24, 28, 30]. Despite being an important prognostic factor, lymph node invasion, rated overall between 47% and 79% in patients with venous resection [35], was not observed to be significantly different in the venous resection group (62%) compared to the control group (63%; Table 3) in the compilation of 13 comparative series [20–32]. Perineural invasion was found significantly more frequently in only one series in the venous resection group versus no venous resection pancreatectomy group [24]. Four clinical studies found significantly more undifferentiated tumors in the group of patients with venous resection [24, 26, 29, 30]. All of these histological factors argue in favor of more advanced tumors in patients with venous resection resulting in significantly greater risk of R1 pancreatic resection [5].

Recent changes in defining R1 resection and in the analysis of the retroperitoneal margin

First of all, the definitions of R0–R1 resection at the retroperitoneal margin of the surgical specimen have evolved over time. Furthermore, unlike for rectal cancer where the “lateral margin” has been established to be 1 mm, the minimal clearance to be obtained at the retroperitoneal margin remains to be specified for pancreatic cancer. At the time of writing, there is no consensual definition of R1 resection. Some studies consider that resection should be classified as R1 when tumor cells are in contact with the

Table 3 Studies comparing pathological findings in patients having undergone pancreatectomy with or without venous resection for pancreatic adenocarcinoma

Year	Authors	Country	wVR		With VR		*P*-value	wVR *n* (%) R0	With VR *n* (%) R0	*P*-value	wVR *n* (%) N +	With VR *n* (%) N +	*P*-value	wVR Size (mm)	VR Size (mm)	*P*-value	Rate of venous invasion
			n	Stage (*n* (%)) 0–1 2 3 4	*n*	Stage (*n* (%)) 0–1 2 3 4											
1996	Harisson [20]	USA	274	–	58	–	–	209 (76%)	43 (74%)	NS	152 (55%)	30 (52%)	NS	35	40	0.01	–
1999	Launois [21]	France	74	–	14	–	–	–	2 (14%)	–	–	6 (43%)	–	–	50	–	3/14 (21%)
2001	Bachellier [22]	France	66	8 (12%) 12 (18%) 30 (46%) 16 (24%)	21	0 5 (24%) 4 (19%) 12 (57%)	NS	48 (73%)	13 (62%)	NS	–	–	–	41	47.9	NS	14/21 (67%)
2001	Shibata [23]	Japan	46	5 (11%) 4 (9%) 20 (43%) 17 (37%)	28	0 0 4 (14.3%) 24 (85.7%)	0.006	38 (82%)	20 (71%)	NS	–	–	–	–	–	–	12/28 (43%)
2002	Hartel [24]	Germany	203	27 (13%) 50 (27%) 124 (62%) 2 (1%)	68	0 6 (9%) 6 (9%) 56 (82%)	0.001	149 (73%)	42 (62%)	NS	126 (62%)	50 (73%)	NS	30	32	NS	56/68 (82%)
2002	Kawada [25]	Japan	15	–	28	–	–	9 (60%)	10 (37%)	NS	13 (87%)	24 (86%)	NS	42	47	NS	21/28 (75%)
2003	Howard [26]	USA	23	6 (26%) 5 (22%) 12 (52%) 0	13	4 (31%) 9 (69.2%) 0 0	NS	19 (83%)	10 (75%)	NS	13 (56%)	7 (54%)	NS	27	33	NS	13/13 (100%)
2003	Nakaghori [27]	Japan	48	–	33	–	–	38 (79%)	25 (76%)	NS	41 (85%)	32 (97%)	NS	33	39	NS	17/33 (51.5%)
2004	Poon [28]	China	38	15 (40%) 5 (13%) 16 (42%) 2 (5%)	12	2 (16.6%) 2 (16.6%) 2 (16.6%) 6 (50%)	0.002	32 (84%)	11 (92%)	NS	8 (21%)	3 (33%)	NS	35	30	NS	6/12 (50%)
2006	Carrere [29]	France	88	–	45	–	–	75 (85%)	37 (82%)	NS	55 (63%)	33 (73%)	NS	26.7	31.8	0.01	29/45 (64%)
2010	Ouaissi [30]	Belgium	82	20 (24%) 58 (71%) 0 4 (5%)	59	10 (17%) 37 (62.7%) 11 (18.7%) 1 (1.6%)	0.0006	71 (87%)	34 (58%)	0.001	56 (68%)	43 (73%)	NS	22	30	0.05	24/59 (41%)
2011	Banz [31]	UK	275	2 (0.7%) 272 (99%) 0 1 (0.3%)	51	1 (2%) 50 (98%) 0 0	NS	174 (63%)	25 (49%)	NS	228 (83%)	41 (80%)	NS	30	30	NS	25/47 (53%)
2012	Wang [46]	Australia	50[a]	3 (6%) 37 (74%) 5 (10%) 2 (4%)	51	0 45 (90%) 3 (6%) 2 (4%)	NS	39 (78%)	28 (55%)	0.014	35 (67%)	35 (70%)	NS	31	40	0.003	39/51 (76%)
Total			1244		481			901/1170 (77%)	305/481 (63.4%)	<0.001	727/1170 (62%)	304/481 (63%)	0.1648	–	–	–	

[a] Information's data about classification was detailed only for 47 patients. Classification of the 7th edition (2010) of the American Joint Committee on Cancer Staging Manuel (AJCC) was used. Stage 0–1 = Stage 0, IA, IB; Stage 2 = Stage IIA, IIB; Stage 3 = Stage III and Stage 4 = Stage IV

NS not significant, *VR* venous resection, *wVR* without VR retroperitoneal section (0 mm margin) [5, 57], while others prefer to use the definition of "International Union against Cancer" and consider a 1-mm margin necessary to classify the resection as R0 [65–67]. However, this 1-mm margin is insufficient according to Chang et al. who demonstrated by multivariate analysis in 365 patients that a tumor clearance greater than 1.5 mm at the retroperitoneal section was an independent predictor of long-term survival [68]. The impact on survival of the tumor clearance at the retroperitoneal resection margin has also been demonstrated by others [4].

Secondly, the method used for the analysis of the retroperitoneal margin at final pathological examination has also evolved. To achieve a precise determination of tumor clearance at the retroperitoneal margin, pathologists have over the years generalized the use of black ink over the whole retroperitoneal margin [65, 67]. Accordingly, the reported rate of microscopic incomplete resections has significantly increased with systematic inking of the retroperitoneal margin compared to when not inking the surgical specimen (84% vs. 52%; $P = 0.009$) [5, 65, 67]. This important feature explains why it is nonsense to compare R0-R1 resection rates in different series, particularly over a long period of time, due to the lack of standardization of the pathological examination leading to a significant underestimation of microscopic invasion of the resection margins. The impact of R0-R1 resection using such standardized pathological examination has also been correlated to patients' survival. The recent study by Rau et al. on 128 resected pancreatic adenocarcinomas reported a significantly increased median survival in patients with microscopic radical R0 resection (18.6 vs. 13.8 months; $P < 0.04$) [4]. Similarly, a recent work by Delpero et al. involving 150 patients confirmed the importance of R0 resection with a significantly lower disease-free survival rate at 2 years in patients with a R1 resection (R1: 26.5% vs. R0: 42%; $P = 0.02$) [5]. These series justify the goal of radical R0 resection with standardization of the histological examination of the excised tissue.

Two studies further report how beside inking the whole retroperitoneal margin, the surgeon in the operating room can also clearly separately identify by multicolor coded inking the margins of the mesenterico-portal vein groove, superior mesenteric artery groove and the posterior margin. Microscopic invasion of the retroperitoneal margin at the superior mesenteric artery groove was thus observed to be an independent predictor of overall survival [5, 69]. These refinements in the analysis of the retroperitoneal margin clearly show that venous resection is only one of the steps towards obtaining sufficient posterior retroperitoneal clearance to reduce local recurrence. The current goal is to obtain posterior retroperitoneal clearance greater than 1 mm and to identify the location of any possible retroperitoneal margin invasion by different colored inking of the superior mesenteric artery and vein grooves.

Radicality of venous resection and its impact on survival

Despite a lack of significant difference, 11 comparative studies have shown a lower R0 resection rate in the group of patients with venous resection (37% to 92%) [13, 20, 22–27, 29, 31, 32], with a significant difference in two series [13, 32]. The compilation of 13 comparative studies showed a significantly lower rate of R0 resection in the group of patients with venous resection compared with those without venous resection (77% vs. 63.4%; $P = 0.001$; Table 3) [20–27, 29–32]. A recent study conducted by the MD Anderson Center specifically analyzed predictors of R1 microscopic incomplete resection in a large series of patients and showed that patients with vascular resection (venous or arterial) had a significantly greater rate of R1 resection (R1 rate in vascular resection: 22% vs. R1 rate without venous resection 12%; $P = 0.02$) [70] and that 50% of R1 resected patients underwent vascular resection [57]. However, in the latter series, vascular resection was predictive of microscopic incomplete resection only in univariate statistical analysis [57]. A similar study by Rau et al. on 128 pancreatic adenocarcinomas confirmed that the R1 resection rate was significantly greater in the group of patients with venous resection (22% vs. without venous resection 2%; $P < 0.003$) [4]. The work of Delpero et al. also revealed that patients with venous resection had a 63% greater rate of R1 resection (defined by a distance smaller than 1.5 mm between the last tumor cell and inking the venous retroperitoneal margin), which was significantly greater than for patients without venous resection after multivariate statistical analysis [5]. Yamamoto et al. recently reported in a series of 132 patients a significant positive correlation between infiltration of retroperitoneal fat on abdominal computed tomography (CT) (in 3 grades), histologic retroperitoneal margin invasion risk and overall survival: survival was correlated with retroperitoneal margin invasion, regardless of the risk of venous invasion (45.9% survival at 5 years for patients with venous invasion with grade 1 retroperitoneal fat invasion on abdominal CT vs. 0% for patients with venous invasion with grade 2–3 retroperitoneal fat invasion on abdominal CT) [71]. Therefore, venous resection may be justified in order to optimize subsequent clearance of the pancreatic tumor resection [71, 72]. An essential element of the "oncological resectability" is not represented as much by venous invasion itself, but rather by the contribution of venous resection to achieve R0 resection with sufficient clearance at the retroperitoneal margin.

In reviewing the literature, Siriwardana et al. reported that microscopic venous invasion was encountered in 63% at final pathological examination [35]. Nakao et al. reported that the vein was microscopically invaded in only one half of the tumors with unilateral contact [41]. Additionally, venous invasion by the tumor is a prognostic factor for survival in Asian series [37–39] but not in Western series [30, 31]. For Asian surgeons, the depth of invasion of the venous wall (from intima to adventitia) is also considered as a predictor of survival [40, 41, 73]. However, the sensitivity of preoperative imaging to predict venous invasion is often low. A recent study by Ishikawa et al. [74] reported that in 297 venous resections unilateral tumor contact to the mesenterico-portal system was responsible for microscopic invasion of the vein in only 51% of cases [41]. Finally, when the tumor is in contact with a vein, the issue is not whether the vein is invaded or not (1 out of 2), but the potential for achieving R0 resection, which may therefore justify also performing venous excision. The radicality of surgical resection was not compared between TP and PD in the different reported series. The percentage of TP was even too small to demonstrate any difference between the two procedures.

Mortality and morbidity related to venous resection (Table 4)

Twelve out of the 13 comparative studies available did not find any significant difference in terms of postoperative morbidity and mortality when venous resection was combined with pancreatic resection [20, 22–30, 32]. Only one series reported a significantly greater mortality in the group of patients with venous resection (13.7% vs. 5.1%; $P = 0.021$) [31]. The distribution of TP varied from 0 to 54% in the different reported series with only one study reporting a significant percentage of TP with venous resection [22]. However, the specific morbidity and mortality rate of total pancreatectomy combined with venous resection were not reported in these different studies (Table 4).

However, a cohort study also reported significantly greater morbidity (39.9% vs. 33.3%; $P = 0.02$) and mortality (5.7% vs. 2.9%; $P = 0.008$) in patients with venous resection [36], underlining the strong importance of the center effect. It can therefore be considered that venous resection combined with PD does not increase postoperative morbidity and mortality.

Long-term survival following venous resection (Table 5)

The benefits of venous resection during PD for pancreatic cancer remain difficult to define. Survival was considered worse after venous resection in six out of the 15 analyzed series [21, 22, 28–30, 34], but with statistical significance in only two studies [21, 30]. In the largest Asian series of venous resection reported by Nakao et al. [64], venous resection was observed to be a prognostic factor of poor survival by multivariate statistical analysis. These results are confirmed by a recent study by the same team including 463 patients, of whom 297 had benefited from venous resection during pancreatic resection [41]. Finally, a recent meta-analysis [14] did not observe any difference in survival with the knowledge that this meta-analysis included heterogeneous series of patients with respect to selection and therapeutic management, particularly as it included patients with neoadjuvant therapy. The long-term outcome was also not compared between TP and PD in the different series. The percentage of TP was even too small to demonstrate any difference between the two procedures.

Definition and evolution of the concept of venous resection

The definition of tumor resectability divides pancreatic tumors into “resectable”, “borderline resectable” and “unresectable” tumors [16]. Technical tumor resectability must also be differentiated from oncological resectability (R0 resection that will provide a survival benefit to the patient) [13–15]. Indeed, a tumor can be considered borderline when resectability is technically possible though it is associated with a high risk of microscopic incomplete resection (R1) [15]. According to the “*National Comprehensive Cancer Network*”, resectable tumors are unequivocally represented by tumors limited to the pancreas without vascular contact (venous or arterial) and without distant metastasis [15, 16]. Metastatic tumors, tumors with mesenterico-portal venous invasion with or without thrombosis or with arterial (hepatic artery, superior mesenteric artery or celiac trunk) invasion are considered to be unresectable [15, 16]. The definition of oncological resectability in France is currently also based on the degree of circumferential venous invasion, the tumor being considered as unresectable when venous invasion is greater than half the vein circumference, or if the proximal superior mesenteric vein is invaded by pancreatic cancer (http://www.tncd.org). This recommendation is based on a 64% risk of R1 resection when the tumor is more than 180° in contact with the venous system [64, 74, 75]. In summary, pancreatic tumors with venous involvement may be considered as “borderline resectable tumors”, at least from the oncological point of view, according to the degree of venous invasion. On one hand, some teams such as the MD Anderson’s Cancer Center believe that the presence of vascular invasion (mesenterico-portal venous system or superior mesenteric artery), whatever its extent, should be classified as a borderline lesion given the high risk of R1 resection at the retroperitoneal margin and suggest that neoadjuvant therapy should be offered initially followed by surgical resection based on the tumor response [16, 30, 70].

Table 4 Morbidity and mortality rates in comparative series between patients with or without venous resection (upper and bottom line, respectively) for pancreatic adenocarcinoma

Year	Authors	Country	N wVR VR	Type of pancreatectomy with associated venous resection			Morbidity rate	*P*-value	Mortality rate	*P*-value	Mean blood loss (ml)	*P*-value	Mean operative time (minutes)	*P*-value	Mean hospital stay (days)	*P*-value
				PD	DSP	TP										
1996	Harisson [20]	USA	274	84.3%	9.2%	6.5%	–	–	9 (3%)	NS	1200	<0.01	348	<0.01	15	0.01
			58	72.4%	13.8%	13.8%	–		3 (5%)		1900		440		22	
1999	Launois [21]	France	74	21.5%	0	78.5%	–	–	10 (13%)	NS	–	–	–	–	20	NS
			14				–		0		–	–	–	–	23	
2001	Bachellier [22]	France	66	81.9%	0	18.1%	30 (45%)	NS	–	–	–	–	410	0.0001	–	–
			21	47.6%	0	52.4%	8 (38%)		–		–		503		–	
2001	Shibata [23]	Japan	46	82.6%	10.9%	6.5%	12 (26%)	NS	2 (4%)	NS	958	<0.05	362	<0.05	–	–
			28	82.1%	10.7%	7.2%	9 (32%)		1 (4%)		1583		462		–	
2002	Hartel [24]	Germany	203				45 (22%)	NS	6 (3%)	NS	800	0.0001	360	0.0001	17	NS
			68	83%	0	17%	18 (28%)		3 (4%)		1500		395		21	
2002	Kawada [25]	Japan	15	67%	0	33%	9 (60%)	NS	1 (7%)	NS	2095	NS	414	<0.05	59.6	NS
			28	100%	0	0	13 (46%)		1 (4%)		3083		551		68.8	
2003	Howard [26]	USA	23	100%	0	0	10 (43%)	NS	1 (4%)	NS	848	0.01	342	0.01	10	0.03
			13	100%	0	0	7 (54%)		1 (8%)		1567		408		14	
2003	Nakaghori [27]	Japan	48	70.8%	29.2%	0	–	–	–	–	–	–	–	–	–	–
			33	81.8%	18.2%	0	–		–		–		–		–	
2004	Poon [28]	China	38	100%	0	0	16 (42%)	NS	1 (2.6%)	NS	800	NS	570	NS	15	NS
			12	100%	0	0	5 (42%)		0		800		660		23	
2006	Carrere [29]	France	88				56 (64%)	NS	5 (6%)	NS	658	NS	420	0.02	24.6	NS
			45	100%	0	0	25 (55.5%)		2 (4%)		812		480		22.6	
2010	Ouaissi [30]	Belgium	82	92.7%	0	7.3%	45 (55%)	NS	1 (1%)	NS	400	0.230	420	0.9235	18.5	NS
			59	88.2%	0	11.8%	31 (52.5%)		1 (2%)		600		480		21	
2011	Banz [31]	UK	275	100%	0	0	78 (27.5%)	NS	14 (5.1%)	0.021	–		–		10	NS
			51	100%	0	0	14 (27.5%)		7 (13.7%)		–		–		11	
2012	Wang [32]	Australia	50	100%	0	0	18	NS	0	NS	502	<0.01	384	<0.001	12	NS
			51	100%	0	0	15		0		788		468		14	

DSP distal splenopancreatectomy (“Appleby procedure”), *NS* not significant, *PD* pancreaticoduodenectomy, *TP* total pancreatectomy, *VR* venous resection, *wVR* without VR

Table 5 Comparison of survival of patients with (VR) or without venous resection (wVR) pancreatic resection of pancreatic adenocarcinoma

Year	Authors	Country	With and without VR	N	Median survival (months)	*P*-value	Overall survival rate (%)				*P*-value
							1 year	2 years	3 years	5 years	
1996	Harisson [20]	USA	wVR	274	17	NS	–	–	–	–	–
			VR	58	13		–	–	–	–	–
1999	Launois [21]	France	wVR	74	15	0.032	–	34.0	–	8.0	0.032
			VR	14	5		–	15.0	–	0.0	
2001	Bachellier [45]	France	wVR	66	12.2	NS	51.0	24.0	–	–	NS
			VR	21	12.0		53.0	21.5	–	–	
2001	Shibata [23]	Japan	wVR	46	–	NS	33.0	–	9.0	8.0	NS
			VR	28	–		31.0	–	13.0	9.0	
2002	Hartel [24]	Germany	wVR	203	–	–	–	–	–	23.0	NS
			VR	68	–		–	–	–	24.0	NS
2002	Kawada [25]	Japan	wVR	15	–	NS					NS
			VR	28	–						
2003	Howard [26]	USA	wVR	23	12	NS	60.0	–	–	–	NS
			VR	13	13		83.0	–	–	–	
2003	Nakaghori [27]	Japan	wVR	48	10	NS	41.0	13.0	–	8.0	NS
			VR	33	15		58.0	9.0	–	9.0	
2004	Poon [28]	China	wVR	38	20.7	NS	–	–	–	–	NS
			VR	12	19.5		–	–	–	–	
2006	Carrere [29]	France	wVR	88	19	NS	–	–	25.0	–	NS
			VR	45	15		–	–	22.0	–	
2007	Al Haddad [34]	USA	wVR	54	11.5	NS	64.7	49.6	33.5	25.1	NS
		USA	VR	22	8.6	NS	41.9	30.0	20.0	–	
2007	Chavraty [33]	China	wVR	54	–	NS	44.4	–	12.2	–	–
			VR	22	–		50.0	–	16.7	–	
2010	Ouaissi [30]	Belgium	wVR	82	18.7	0.032	–	–	–	29.0	0.032
			VR	59	17.5		–	–	–	11.0	
2011	Banz [31]	UK	wVR	275	14.5	NS	–	–	–	–	
			VR	51	14.8		–	–	–	–	
2012	Wang [32]	Australia	wVR	50	–	–	–	–	–	–	–
			VR	51	–	–	–	–	–	–	

NS not significant

On the other hand, most European and French surgical teams distinguish between tumors with venous invasion smaller than 180° (defined as "locally-advanced resectable tumors), for which R0 resection is possible [22, 29] without using neoadjuvant therapy (not shown so far to be beneficial in this situation [76]) and tumors with venous invasion greater than 180° (defined as "locally-advanced unresectable tumors"), for which the high risk of R1 resection does not justify immediate resection but rather primary neoadjuvant therapy [64, 74, 75], including chemotherapy or chemoradiation therapy followed by resection only in case of tumor response (which may affect up to 33% of patients and then up to 79% of R0 resection in a highly selected group of patients) [76].

Different strategies of venous resection must be taken into consideration when analyzing the different series of venous resection during PD for pancreatic cancer. Indeed, interpretation of the data has changed according to the adopted strategy. The concept of "*venous resection by necessity*" corresponds to the resection of a vein invaded by tumor contiguity to ensure a macroscopically complete resection and to avoid an R2 resection. However, even during surgical dissection, venous invasion may be difficult to differentiate from peritumoral inflammation. This may explain why microscopic invasion is absent in 50% of the resected veins when resection is only based on intraoperative surgical findings. Dissecting a supposed venous tumor invasion may also result in tumor breakdown and thus in a palliative resection. On the other hand, Siriwardana et al. found in their literature review that microscopic venous invasion was encountered in 63% at final pathological examination [35]. The concept of "*primary venous resection*" is based on routine venous resection when and only when tumor contact or invasion is demonstrated on preoperative imaging studies without attempting any surgical dissection of the vein and leading to a "monobloc non-touch resection" [21, 30, 41, 57]. This approach aims to perform oncological R0 resection avoiding the risk of microscopic venous invasion and not taking care of the final pathological venous invasion status. This oncological goal justifies systematic venous resection, even in cases of unilateral venous contact, to avoid incomplete excision, possibly R1 in half of the cases. The concept of "*systematic preventive venous resection*" is based on routine venous resection whatever venous contact or invasion is present or absent and whatever the results of preoperative imaging studies [42].

Recent innovative techniques: surgical dissection of the retroperitoneal margin to intend radical resection

Because the microscopic retroperitoneal tumor extent is unknown at the time of surgical resection, the use of an appropriate technique is mandatory to achieve radical retroperitoneal tumor clearance. Several techniques have recently been reported to achieve this goal [64, 77, 78]. The SMA first approach should be routinely used early during surgical resection in order to explore retroperitoneal tumor invasion. This artery-first approach during PD is generally carried out through a right-sided route after Kocher maneuver but can also be done through a left-sided route after lowering the duodeno-jejunal flexure or by an infracolic route as described by the Nakao team [64, 77]. This technique offers several oncological benefits, such as facilitating interaortocaval lymphadenectomy at the origin of the SMA and checking resectability at the retroperitoneal margin but it also has some technical advantages, such as preventing hemorrhage by preservation of the venous return and facilitating venous resection during PD. The principle is to approach the SMA at its origin, to ensure arterial resectability, to pursue the dissection in the sheath of the SMA for complete resection of the retroportal lamina and to minimize handling of the tumor. Vascular control of the SMA and dissection of the right hemi-circumference of the SMA to the right of the celiac trunk associated with a pancreatic pseudo-hanging maneuver allowed to obtain complete retroperitoneal clearance. If a monobloc tumor mobilization is achieved, the length of venous resection can be adapted according to the oncological requirements [79]. The length of venous resection is usually limited and the use of a venous bypass is never necessary. The SMA first approach therefore allows easy performance of venous resection at the end of the dissection and allows adjusting the length of the vascular resection according to the oncological requirements.

Arterial resection

Goal of arterial resection and its limitations

As for the venous resection, the goal of arterial resection during PD is to obtain a microscopically healthy retroperitoneal margin with the final objective to cure the patient. The concept of such an extended resection was developed a long time ago by Fortner et al. [80]. However, it is established that when major retroperitoneal arteries (such as the SMA) are invaded, invasion of the retroperitoneal nerve plexus already ranges from 60.8% to 88.4% [17]. This explains why in the setting of a so-called "locally-advanced tumor" with arterial invasion, neoadjuvant chemoradiation therapy is usually administered as the primary therapeutic option [49, 50].

Prevalence of arterial resection

The prevalence and results analysis of combined arterial and pancreatic resections are difficult to determine. First of all, because arterial resection is observed to be associated with venous resection in 51.7% to 96% of the patients in the literature analysis (Table 6), then because every series concerns fewer than 30 patients. However, in the meta-analysis by Molberg et al. including 26 studies, the rate of arterial resection was 14% [17]. Additionally, most patients underwent arterial resection within the frame of "locally advanced tumors", that is, when SMA contact was over 180° [16] or in case of contact with the hepatic artery [50] and having received neoadjuvant treatment [17]. Very few patients underwent primary arterial resection without previous neoadjuvant treatment [43, 45–48]. The issue or arterial resectability is thus difficult to address, even during surgery. Primary anterior approach of the superior mesenteric artery has been recently suggested through an inframesocolic route, or a right- or left-sided approach depending on tumor location [77].

In case of locally advanced pancreatic adenocarcinoma of the body of the pancreas invading the celiac trunk, DSP with resection of CT according to the "modified apple by procedure" was reported [51, 52], capitalizing on the circulation through the gastroduodenal artery to maintain liver perfusion [51]. Other authors have proposed to reduce the risk of ischemic complications of the stomach or liver by using preoperative embolization of the common hepatic artery (CHA) in order to maintain the arterial blood flow to the hepatobiliary system through collaterals via SMA, pancreaticoduodenal arcades and gastroduodenal artery [44, 53, 54]. This technique had the great advantage to decrease or quasi abolish the requirement for arterial reconstruction after CT resection.

Predictive factors of arterial resection

Tumor location into the pancreatic parenchyma is an important predictive factor of arterial tumor invasion. Indeed, a comparative radiological study reported a significantly greater risk of tumor contact with superior mesenteric vessels (SMA and SMV) for tumors located in the uncinate process compared to other tumors of the pancreatic head (96% vs. 74%; $P = 0.03$), especially concerning the SMA (82% vs. 52%; $P = 0.02$) [62]. Tumor size may also be involved, with two series reporting lesions larger than 5 cm [44, 45].

Radicality of arterial resection and its impact on survival (Tables 6,7)

Molberg et al. reported that the R0 resection rate was lower after arterial resection (74.8% vs. 60%) but the difference was not significant [17]. Following sensitivity analysis due to population heterogeneity and after excluding one study, the authors found a significant difference concerning R0 resection rate in disfavor of arterial resection ($P = 0.004$). However, most patients had received preoperative chemoradiation therapy. Microscopic arterial invasion was 44% overall in Molberg's series [17]. It ranged from 20% to 34% in the six retrospective series [32, 43, 45, 47, 48] that contain detailed information on this feature, which is much lower than the 67% rate of microscopic venous invasion after pancreatic resection combined with mesenterico-portal resection [35] and limits the analysis of the impact on survival [17]. However, in the case-controlled study by Bachellier et al. [45] concerning 26 patients with arterial resection without neoadjuvant therapy, arterial invasion was reported as an independent predictive factor of poor survival, although the latter observation only concerned four patients. In the three studies with more than 13 patients using DSP with CT resection the radical resection rate varied from 31% to 92% [44, 53, 54]. In the study of Yamamoto et al. [54], the radical resection R0 was significantly lower in patients with DSP combined with CT resection (31% vs 74%; $P = 0.02$). These results could not be allowed to draw significant conclusions about the real impact of arterial resection of CT on the improvement of radicality of surgical resection.

Mortality and morbidity related to arterial resection (Tables 6,7)

Even in the hands of experienced teams, postoperative mortality remains high with a median of 11.8% (range from 0% to 45%) [17]. Despite numerous biases (patients with neoadjuvant therapy, mortality recorded at 30 or at 60 days), Molberg et al. [17] reported both a significantly increased mortality rate in PD with arterial resection compared to PD without arterial resection (five times higher, $P < 0.0001$) and a significantly increased morbidity rate (median 53.6% [16.7–100%]; $P = 0.006$) [17]. In the three studies reporting the Appleby procedure, the mortality rates were very low (0 to 4.8%) but the morbidity varied from 43% to 92%, a feature that was significantly greater compared to these observed for DSP without arterial resection (92% vs. 60%; $P = 0.05$). The high postoperative mortality (especially for PD) and morbidity rates are obvious limitations for potential benefits in terms of long-term survival.

Long-term survival following arterial resection

In the study of Molberg et al., the overall survival was significantly lower (49.1% at 1 year, 8.3% at 3 years and 0% at 5 years) in patients with arterial resection [17]. Among the six retrospective studies including more than 20 patients, only Bachellier et al. reported similar survival rates in patients with arterial resection [45]. Concerning DSP

Table 6 Comparative series of patients undergoing pancreatic resection with or without vascular (arterial and/or venous) resection for pancreatic adenocarcinoma

Authors	Year	Inclusion period	Numbers of pancreatic/arterial resection	Type of pancreatic resection	Arterial resection				VR	Artery invaded (%)	Vein invaded (%)	R0	Mortality rate (%)	Morbidity rate (%)	Median survival (months)	Overall survival (%)			
				PD DSP TP	SMA	CT	HA	RHA								1 year	2 years	3 years	5 years
Wang [32]	2008	1998–2005	80	100% 0 0	–	–	–	–	–	–	–	–	5.3%	23.5%	13	56%	–	19%	13%
			19	100% 0 0	–	–	–	–	–	–	–	–	0%	36.8%	7	16%	–	0%	0%
Sugiura [48]	2009	1978–2007	107[a]	–	–	–	–	–	–	–	–	–	–	–	–	77.4%	36.5%	24%	–
			26	38.5% 7.7% 53.8%	8	8	10	0	96.1%	–	–	–	–	–	9	38%	6%	6%	–
Amano [43]	2009	2005–2009	23	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
			23	30.4% 4.4% 65.2%	12	6	12	6	86.9%	26.1%	20%	78.3%	4.3%	73.9%	12	51.2%	–	23.1%	–
Bockholm [47]	2010	1994–2007	449	94.8% 0 5.1%	–	–	–	–	–	–	–	85.3%	4%	19.8%	15.8	51.7%	–	–	–
			29	55.2% 27.5% 17.3%	3	8	18	0	51.7%	–	–	66%	14%	37.9%	14	31%	–	–	–
Bachellier [45]	2011	1990–2008	26	46.1% 19.2% 34.6%	–	–	–	–	76.9%	–	29%	80.7%	3.8%	38.4%	–	50%	–	17.6%	–
			26		4	8	9 + 4 left	3	80.7%	15.4%		80.7%	7.6%	53.2%	–	65.9%	–	22%	–

CT celiac trunk, *DSP* distal splenopancreatectomy, *HA* hepatic artery, *PD* pancreaticoduodenectomy, *RHA* right hepatic artery, *SMA* superior mesenteric artery, *TP* total pancreatectomy, *VR* venous resection, *wVR* without VR

[a] Included combined pancreatic and venous resection

Table 7 Series of celiac axis resection ("modified Appleby procedure")

Authors	Year	Inclusion period	Numbers of pancreatic/Arterial resection	Type of pancreatic resection	Arterial resection				Venous resection (%)	Artery invaded (%)	Vein invaded (%)	R0 resection (%)	Mortality rate (%)	Morbidity rate (%)	Median survival (months)	Overall survival (%)		
				DSP	SMA	CT	HA	RHA								1 year	2 years	5 years
Hirano [44]	2007	1998–2005	23	100%	0	23	0	0	69.5%	8.6%	81.5%	91%	0%	48%	21	71%	–	42%
Yamamoto [54]	2011	1978–2007	58	100%	0	0	0	0	0	–	–	74%	0	60.3%	20.8	–	25.4%	–
			13	100%	0	13	0	0	–	15.4%	69.2%	31%	0	92.3%	21	–	45.9%	–
Tanaka [53]	2012	2005–2009	42	100%	0	42	0	0	67%	–	–	92.8%	4.8%	43%	24	–	–	25%

CT celiac trunk, *DSP* distal pancreatectomy, *HA* hepatic artery, *RHA* right hepatic artery, *SMA* superior mesenteric artery

combined with CT resection, the median survival was more than 20 months in the three reported studies and was similar to DSP without arterial resection in the comparative study of Yamamoto et al. [44, 53, 54] (Table 7). Despite strict patient selection, these disappointing results do not justify to extend PD or LP to arterial resection for pancreatic adenocarcinoma.

Conclusions

Radical R0 resection surgery is the standard for achieving curative treatment of pancreatic cancer. Combining venous resection during PD meets this oncological requirement without increasing the morbidity and mortality of the procedure. Recent advances in defining the tumor clearance of the surgical specimen have changed concepts and indications of venous resection during PD. The current therapeutic objective is to achieve surgery with a posterior retroperitoneal resection margin that justifies primary venous resection, especially in case of venous contact, or even systematic vein resection when the tumor is located in the uncinate process. Technically, a first approach of the SMA with venous resection at the end of the dissection is oncologically sound and limits the extent of venous resection to meet the oncological requirements, thus limiting the use of venous bypass and venous graft. Concerning arterial resection the disappointing results despite strict patient selection do not justify such extended surgery for pancreatic adenocarcinoma. The use of neoadjuvant therapy is discussed in the context of a protocol when primary R0 resection cannot be achieved. Along with the discussion of clinical targeting of patients undergoing neoadjuvant therapy, knowledge of the molecular events contributing to the transformation of pancreatic cells into tumor cells will also help to develop new therapeutic targets to improve patient prognosis. It would also be beneficial to define judicious strategies for early detection as these tumors are currently discovered too late [13, 81–84].

Conflict of interest None declared.

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