European Journal of Surgical Oncology 45 (2019) 1912–1918

Contents lists available at ScienceDirect

European Journal of Surgical Oncology

journal homepage: www.ejso.com

International Study Group of Pancreatic Surgery type 3 and 4 venous resections in patients with pancreatic adenocarcinoma:the Paoli-Calmettes Institute experience

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ARTICLE INFO

Article history:
Received 8 April 2019
Received in revised form
7 May 2019
Accepted 1 June 2019
Available online 3 June 2019

Keywords:
Segmental venous resection
Pancreatic adenocarcinoma
folfirinox
Survival

ABSTRACT

Introduction: A new neoadjuvant regimen, together with more aggressive surgeries, appears to have increased the resectability rate in patients with pancreatic ductal adenocarcinoma (PDAC). Our study aimed to evaluate the outcomes of patients who underwent venous resection (VR) during pancreatectomies for PDAC.

Materials and methods: Between 2005 and 2017, 130 patients underwent pancreatectomies with type 3 or 4 (i.e., segmental resection without or with graft interposition, respectively) VR for PDAC. Patients' characteristics, surgical techniques, perioperative management, pathological findings, and outcomes were recorded and compared during 2 inclusion periods: the landmark year for the introduction of the FOLFIRINOX regimen and the hyperspecialization of our pancreatic-surgery team was 2010.

Results: Performance of pancreatectomies with VR steadily increased through the 2 inclusion periods. In the overall series (n = 130), the median overall survival time and the 5-year survival proportion were 26.3 months and 21%, respectively. Upon multivariate analysis, ASA score 3 ($P = 0.01$) and R1 resection margins ($P < 0.01$) were found to be negative independent factors influencing survival. Patients who underwent upfront VR (n = 47) had survival rates similar to those of patients who received neoadjuvant treatment (n = 83). After 2010, more complex VR were performed; however, no difference was found between the 2 periods with respect to postoperative courses, pathologic findings, or survival after a matching process based on patients' characteristics and tumor stages.

Conclusion: Over the last 2 decades, VR during pancreatectomy has been confirmed as a safe procedure despite the increase in technical complexity. Disappointingly, we did not observe any dramatic survival improvement.

Introduction

Surgery remains crucial to effecting a curative treatment in patients with pancreatic ductal adenocarcinoma (PDAC). While arterial resections are still under debate [1], venous resection (VR) in patients with borderline or locally advanced PDAC has been proven to be safe and to provide a substantial survival benefit [2]. During the last decade, the FOLFIRINOX regimen has appeared to increase the number of patients who finally underwent resections [3], and pancreatic surgeons have pushed the limits of VR with complex resection/reconstructions. However, VR is a generic term

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https://doi.org/10.1016/j.ejso.2019.06.003
0748-7983/

Abbreviations

CA19-9	Carbohydrate Antigen 19-9
CT	computerized tomography
DFS	disease-free survival
MRI	magnetic resonance imaging
NCCN	National Comprehensive Cancer Network
OS	overall survival
SPH	sinistral portal hypertension
PDAC	pancreatic ductal adenoma carcinoma
PV/SMV	portal/superior mesenteric vein
VR	venous resection

involving tangential VR together with extreme long segmental VR with the sacrifice of several tributaries and graft interposition. Tangential VR is elected during pancreatectomy for 2 reasons: limited tumor invasion on the venous wall or a tributary invasion ending in the portal/superior mesenteric vein (PV/SMV) (pancreaticoduodenal vein, gastrocolic trunk, etc.). In the first situation, a segmental resection might be preferable for following established oncologic rules [4]. In the second situation, VR is performed to address technical issues. In many reported series, tangential VR have been largely included, which introduced confusion regarding the indication of venous resection: macroscopic tumoral invasion or for technical need [5–7]. In 2014, the International Study Group of Pancreatic Surgery proposed a simple classification for VR [8]. Tangential resections were classified as type 1 (without), or type 2 (with) patch reconstruction, and segmental resections as type 3 (without), or type 4 (with) the need for graft interposition. We supported segmental VR as the optimal way to manage a tumoral invasion of the PV/SMV axis [9], nevertheless there is a lack of large series [10–13], reporting technical matters and outcomes exclusively for PDAC.

The aim of this study was to report our complete experience with type 3 and 4 VR for PDAC, to determine postoperative outcomes and the factors impacting survival.

Methods

Patient selection

From January 1, 2005 to December 31, 2017, 489 consecutive patients underwent a pancreatectomy for PDAC at Institut Paoli-Calmettes (Marseille, France) of whom 130 (26.6%) required segmental VR and comprised our study population. All patient data were entered prospectively into a clinical database approved by the Institutional Review Board. The study subjects provided informed consent and the study protocol adhered to the tenets of the Declaration of Helsinki. Patients eligible for the present study a) had histologically proven PDAC, b) did not have metastatic tumors, and c) underwent pancreatectomies with type 3 or 4 VR. All patients were initially staged by physical examination, thoraco-abdominal computerized tomography (CT), and Carbohydrate Antigen 19-9 (CA 19-9) serum level determination. Due to period inclusion, patients did not receive routine liver magnetic resonance imaging (MRI) or positron emission tomography. Patients with a preoperative diagnosis of borderline or locally advanced PDAC (according to the 2017 National Comprehensive Cancer Network guidelines, NCCN [14]) received a neoadjuvant treatment. This regimen was elected according to the period of inclusion and multidisciplinary staff decisions. Patients whose tumors were initially staged as resectable and who had a venous invasion found by laparotomy underwent an upfront pancreatectomy with VR.

Surgery

A thorough abdominal exploration was first performed to eliminate carcinomatosis, liver metastasis, and, more recently, para-aortic lymph node metastasis [15]. VR techniques have been previously described [16,17], and included the following major endpoints: a) restrictive intravenous-fluid strategy (lactated Ringer 1 mL/h/kg), b) total disconnection of the retro-portal tissues before venous clamping, which permitted the reduction of venous clamping duration and eliminated the requirement for superior mesenteric artery clamping, and c) liberal policy towards sacrifice of the splenic vein and other tributaries without routine reconstruction with respect to sinistral portal hypertension (SPH) [18]. To ensure venous axis continuity, an end-to-end anastomosis or interposition of a prosthetic graft (appropriately sized ringed polytetrafluoroethylene graft: GORETEX®; WL Gore & Associates, Inc. Flagstaff, AZ, USA) was achieved. At the conclusion of surgery, a summary sheet was amended to include precise patient venous anatomy and resection/reconstruction features, with special attention to sacrificed tributaries. Postoperative curative anticoagulation was introduced only in patients with prosthetic graft reconstructions. All specimens were inked to facilitate margin assessment.

Study parameters

Numerous variables were evaluated: notably, ASA scores; types of neoadjuvant treatment (i.e., chemotherapy alone, chemotherapy followed by chemoradiation, and chemoradiation alone; the precise chemotherapy regimen followed (e.g., FOLFIRINOX or gemcitabine)); localization (i.e., splenic vein, gastric vein, gastrocolic trunk, colica media vein, inferior mesenteric vein, first jejunal vein, ileocolic vein, ileal or jejunal vein) and total number of sacrificed tributaries (except splenic vein), with special mention when 4 or more tributaries were sacrificed); type of PV/SMV reconstruction (i.e., direct anastomosis or graft interposition (diameter (mm) and length (mm)); venous clamping duration (min); surgery duration (min); intraoperative blood loss (mL); perioperative red cell transfusions (i.e., intraoperative and postoperative day 1); margins (less than 1.5 mm was considered to be an involved margin (R1) [19]; node stage (positive nodes, number of examined nodes); pathological invasion of the venous wall, and perineural invasion. Disease staging was established according to the TNM classification of the American Joint Committee on Cancer (AJCC). Morbidity, including relevant (i.e., grade B or C) postoperative pancreatic fistula [20] and hemorrhage, mortality (before hospital discharge and up to 90 days after surgery), length of hospital stays, readmissions, as well as adjuvant treatment administration were also recorded. As 2010 was a landmark year, with the introduction of the FOLFIRINOX regimen, we split the period of inclusion into period 1 (2005–2009) and period 2 (2010–2017). However, the complexity of pancreatectomies with VR performed by individual surgeons was difficult to analyze retrospectively. As a surrogate marker, the complexity rate during each period was then assessed by adding the number of patients with $\geq$4 tributaries sacrificed, arterial resections, and graft interpositions divided by the total number of procedures.

Statistical analysis

Data analyses were performed using GraphPad Prism software, version 6 (GraphPad Software Inc., La Jolla, CA, USA) and SAS statistical software version 9.1 (SAS Institute, Inc., Cary, NC, USA). The

categorical factors were compared using the Fisher's exact test; the continuous variables were compared using the Student t-test. The association between categorical factors and overall survival (OS) and disease-free survival (DFS) rates were assessed using the Kaplan-Meier method (based on the date of diagnosis and the censor date, November 1, 2018) and were tested using the log-rank test. To ensure a relevant comparison between the 2 periods with respect to survival, we performed a one-to-one matching procedure based on neoadjuvant treatment, arterial resection, number of tributaries sacrificed, the need for a graft interposition, TNM staging, perineural invasion, vein invasion, and adjuvant treatment. Statistical significance was set at *P value* < 0.05. Prognostic factors with $P < 0.1$ in univariable analysis or those well-known to impact PDAC survival were entered into a multivariable regression model to determine independent predictors.

Results

Patient characteristics, surgeries, and postoperative courses

In the whole population (n = 130), 83 patients (64%) received a neoadjuvant treatment (Table 1). Thirteen patients (10%) required the sacrifice of more than 4 venous tributaries. Direct reconstruction of the PV/SMV (type 3) was achieved in 114 patients (90%), and graft interposition (type 4) was required in 13 patients (10%); in 3 patients, no venous reconstruction of the PV/SMV axis was performed due to a pre-existing thrombosis and sufficient porto-mesenteric shunts. In 2 patients of whom the PV/SMV axis was reconstructed, all the tributaries and the jejunal vein were sacrificed without any reconstruction. Only one patient required reconstruction of both gastric and splenic veins due to an intraoperative SPH. Morbidity and 30-(90) days mortality rates were 61% and 4.5% (6%), respectively. No patient experienced a delayed clinically relevant SPH within the follow-up period. Type of surgical procedures done and the postoperative courses are shown on Table 2.

Table 1
Clinical characteristics.

Sex Ratio M/F	0.69
Mean Age (±SD)	64.7 (±9.72)
Mean BMI (±SD)	24 (±3.96)
>5% Weight Loss (%)	68 (52.3)
Jaundice (%)	93 (71.5)
Biliary Stenting (%)	90 (69.2)
Abdominal Pain (%)	58 (44.6)
Mean CA 19−9 Serum Level (UI)(±SD)	
At Diagnosis (after jaundice resolution)	721 (±1041)
Before Surgery	216 (±380)
Tumor Location	
Head (%)	112 (86.2)
Body (%)	14 (10.8)
Tail (%)	4 (3)
Neoadjuvant Treatment (%)	83 (63.8)
Chemotherapy Alone (%)	58 (44.6)
Chemotherapy and Chemoradiation (%)	10 (7.7)
Chemoradiation Alone (%)	15 (11.5)
Chemotherapy Regimen	
Folfirinox (%)	61 (46.9)
Gemcitabine (%)	8 (6.2)
ASA score	
1/2 (%)	102 (78)
3 (%)	28 (22)

(**BMI**: **B**ody **M**ass **I**ndex; **CA 19-9**: **C**arbohydrate **A**ntigene **19-9**).

Table 2
Surgery and postoperative courses.

Type of Surgery	
PD	112 (86.2)
Total Pancreatectomy	2 (1.5)
Distal Pancreatectomy	16 (12.3)
Associated Resected Organs (%)	32 (24.6)
Right Colon	14
Transverse Colon	4
Splenic Flexure	9
Partial Gastrectomy	11
Total Gastrectomy	3
Duodenojejunal Junction	6
Kidney	4
Supra Renal Gland	8
Sacrificed/Reconstructed Tributaries	
*Splenic Vein	64/1
Gastric Vein	22/1
*Infracolic Vein	42/0
Gastrocolic Trunk	29/0
Colica Media Vein	27/0
First Jejunal Vein	51/0
Ileocolic Vein	5/0
Ileal or Jejunal Vein	6/0
****Sacrificed Tributaries > 4 (%)**	13 (10)
****Median Sacrificed Tributaries (range)**	1 (0−7)
Arterial Resection (%)	11 (8.5)
Celiac Axis	6
Superior Mesenteric Artery	3
Hepatic Artery	2
Reconstruction of Venous Axis	
End-to-End Anastomosis (Type 3)	114 (87.7)
PTFE graft (Type 4)	13 (10)
No Reconstruction	3 (2.3)
Median Graft Diameter (mm)/Length (mm)	10/100
Mean Venous Clamping Duration (mn) (±SD)	18.3 (±9.24)
Mean Intraoperative Blood Loss (mL) (±SD)	310 (±137)
Mean Operation Duration (mn) (±SD)	403 (±86.3)
Morbidity (%)	79 (60.8)
Grade B or C POPF	18 (13.8)
Hemorrhage	6 (4.6)
Reintervention	9 (6.9)
Delayed Gastric Emptying	28 (21.5)
30-Days Overall Reconstruction Thrombosis	8 (6.2)
30-Days PTFE graft Thrombosis	5 (38.5)
30-Days End-to-End Anastomosis Thrombosis	3 (2.6)
30-days Mortality (%)	6 (4.6)
90-days Mortality (%)	8 (6.2)
Length of Hospital Stay (Days) (±SD)	16 (±7.71)
Readmission (%)	15 (11.5)

(**PD: P**ancreatico**D**uodenectomy; **POPF: P**ost-**O**perative **P**ancreatic **F**istula) (°number of patients (splenectomy were not included); °°number of organs; *not recorded when sacrificed during distal pancreatectomies; **splenic vein excluded).

Pathologic findings

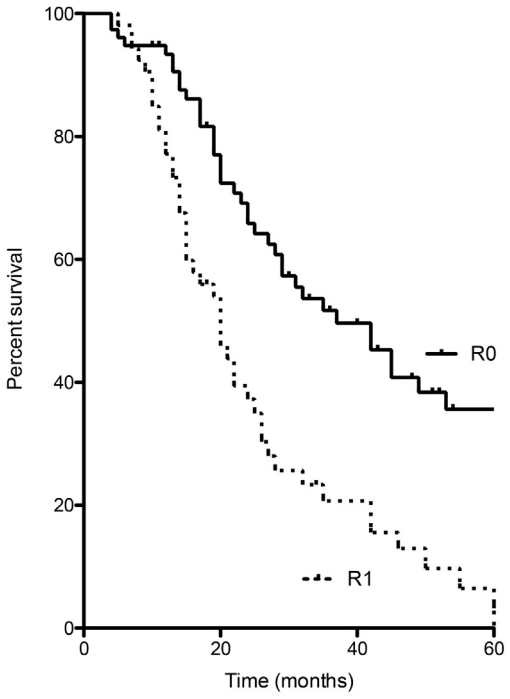
Positives lymph nodes were found in 84 patients (64.6%). The mean numbers of examined lymph nodes during periods 1 and 2 were 14 and 17 respectively ($P = 0.14$) and the percentages of positive lymph nodes were 48% and 69% respectively ($P = 0.062$). Positive (R1) margin resections were assessed in 53 patients (40.8%), and venous invasion was affirmed in 57 patients (43.8%).

Survival

The mean follow-up period was 34 months. Disease recurrence occurred in 92 patients (73%). The median OS time from diagnosis was 26.3 months; the OS proportions at 1-, 3-, and 5-years were 86%, 38.5%, and 21%, respectively. Upon multivariate analysis (Table 3), ASA score 3 ($P = 0.01$) and R1 resection margins ($P < 0.01$)

Table 3
Univariate and multivariate analysis of factor influencing overall survival.

	P Univariate	*Hazard Ratio* *P* Multivariate
ASA score 3	**<.01**	1.93 [1.16–3.23] **.012**
Neoadjuvant Treatment	.83	–
Folfirinox Regimen	.51	–
Sacrificed Tributaries > 4 (%)	**.013**	1.54 [.74–3.21] .25
Arterial Resection	.7	–
Graft Reconstruction	.26	–
Morbidity	.63	–
Perioperative Red Cell Transfusion	.31	–
Lymph Nodes Invasion	**.015**	1.31 [.8–2.14] .28
R1 Resection Margin	**<.01**	1.87 [1.19–2.94] **<.01**
Adjuvant Therapy	.27	–



Log-rank test : ***<.001***

Subjects at risk

Time (months)	**0**	**12**	**24**	**36**	**48**	**60**
R0	77	67	42	24	18	13
R1	53	42	18	9	6	2

Fig. 1. Overall survival according to resection margin status.

were found to negatively influence both the OS (median survival of R1 versus R0 resection: 20 months vs 37 months, respectively ($P < 0.001$); hazard ratio = 1.87 [1.19–2.94]; Fig. 1); and the DFS ($P = 0.03$). The preoperative factor that favored R0 resection margins was the neoadjuvant treatment (73% vs 51%, $P = 0.02$), as identified solely by univariate analysis. Patients who underwent upfront VR had OS rates at 5 years comparable to those of patients who received neoadjuvant treatment (12.7% vs 9%, $P = 0.8$), irrespective of the regimen received (Fig. 2 a,b).

Periods of inclusion

Twice the numbers of VR were performed during period 2 than period 1 (15% versus 7.5%, respectively, $P < 0.01$); Chemotherapy alone ($P < 0.01$) was the preferred neoadjuvant treatment during period 2, with a special focus on the FOLFIRINOX regimen (61 patients; 90%). During period 2, surgery ($P = 0.01$) and venous clamping ($P < 0.01$) durations were shorter, blood loss was lower ($P = 0.03$), and complex procedures were performed more often ($P < 0.01$) than in period 1. No difference was found between the 2 periods with respect to postoperative courses or pathologic findings. Before and after the matching process, no differences in OS or DFS rates were observed between the 2 periods ($P = 0.35$ and $P = 0.14$, respectively).

Discussion

Our study showed that VR (type 3 and 4) is safe procedure that provide interesting survival benefits.

Our department has historically been focused on pancreatic surgery; moreover, the annual volume of pancreatectomies and VR has steadily increased during the past 2 decades. This has led to the formation of a dedicated pancreatic-surgery team since 2010, with correspondingly increasing experience. Consequently, more complex resections were achieved through the period of the study; as we noted, there were more sacrificed tributaries, arterial resections, and prosthetic replacements during period 2. We elected to focus on type 3 and 4 VR, as we supported these as the appropriate techniques to ensure optimal oncologic resections. However, several large series have reported employment of all types of VR (type 3 and 4 rates varied from 44% to 81%, respectively [9,11,21–24] for different pancreatic pathologies (i.e., not only for PDAC)). Here, we report one of the largest monocentric series involving type 3 and 4 VR focused on PDAC; with some limitations. First, the retrospective study design had corresponding drawbacks. Second, due to the long period of inclusion, disparities between hyperspecialization of surgeons, changes in neoadjuvant regimens, and improvement of specimen pathologic analysis probably occurred. Moreover, our experience and the sample size might permit some discussion with substantial arguments.

Neoadjuvant treatment

According to the 2017 NCCN guidelines [14], patients with no or "limited" venous contact (≤180° without vein contour irregularity) are deemed resectable, can undergo upfront pancreatectomy, and a VR could be achieved without neoadjuvant treatment in this setting. For patients who received neoadjuvant treatment, we noted a drastic change as chemotherapy became the most frequently administered regimen in period 2, probably due to the promising results of the FOLFIRINOX regimen on both resectability [3,21,22] and survival [23,24]. In our series, we did not observe any benefit in patients who received neoadjuvant treatment with the FOLFIRINOX regimen as compared with patients who underwent upfront surgery. However, we refrained from drawing any hasty conclusions regarding the effectiveness of FOLFIRINOX. Indeed this judgement might be dismissed, because the two populations were probably not precisely comparable with respect to the initial staging of the tumors. For example, we could not compare a patient who underwent an upfront resection for PDAC with a limited venous invasion to a patient who had an initially complex venous Nakao type D [25] invasion and became resectable after neoadjuvant treatment. The definitive impact of neoadjuvant treatment on patients who require VR must be affirmed through rigorous, precise, and reproducible initial staging and a prospective

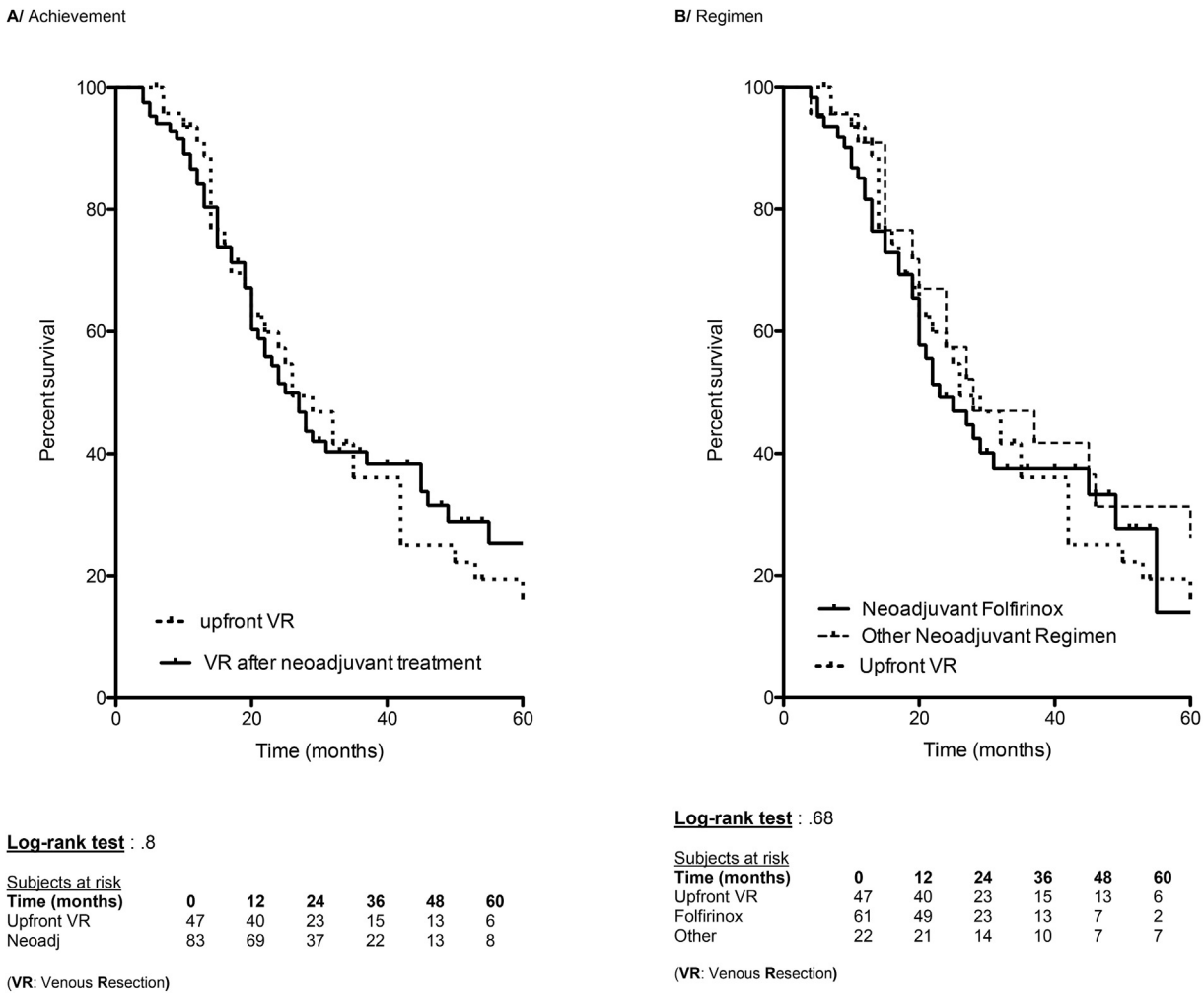


Fig. 2. Overall survival according to neoadjuvant treatment.

clinical trial—not through retrospective studies.

Surgery and postoperative courses

According to our technical approach to VR, splenic veins (49%) and PV/SMV tributaries (10% of patients with more than 4 tributaries ligated) were liberaly sacrificed because of direct involvement or to facilitate VR. However, this policy could lead to an intraoperative or delayed SPH. Delayed SPH is rare [26] and clinically irrelevant for patients with advanced PDAC who have relatively short expected survivals [18]. In contrast, intraoperative SPH requires venous tributary reconstruction. Consequently, we supported "on-demand" instead of routine tributary reconstruction. In our study, only one patient needed both splenic and gastric vein reconstruction due to an intraoperative SPH, and we did not observe clinically relevant delayed SPH during the follow-up period. Thus, we supported the fact that type 3 or 4 VR did not require routine splenic vein (as previously reported [27]) or tributary reconstruction, if no SPH was observed intraoperatively. This substantially simplified the venous reconstruction and reduced operative duration. To the extreme, we did not perform any reconstruction (i.e., neither of the tributaries nor of the PV/SMV axis itself) in 3 patients [28] because of pre-operative thrombosis and sufficient porto-mesenteric shunts, and in other 2 patients, we only reconstructed the PV/SMV axis after sacrificing all tributaries.

Despite more complex resections being performed during period 2, we did not observe higher blood loss, longer venous clamping/operative durations, or higher morbidity/mortality rates. This confirmed that type 3 and 4 VR can be relatively safely performed in high-volume centers that bring together experienced surgeons and experienced physicians involved in perioperative complex oncologic surgery. This probably contributed to the substantial rate of patients who were able to receive adjuvant treatment (61.5%). Indeed, pancreatectomy for advanced PDAC is a highly morbid surgery that may expose patients to altered postoperative courses, and hence may preclude adjuvant treatment. To our opinion, the major contribution of experienced and high-volume surgical teams is to reduce the impact of surgery to allow achievement of optimal therapeutic plans.

Pathologic findings

The rate of histologically confirmed venous invasion was 44% for the entire cohort and 66% in cases of R1 resection, comparable to the range of 56%–78% reported in the literature [29–31]. The effect of vessel-wall tumor invasion on clinical outcomes is unclear. Several series have reported that venous tumor invasion, *per se,* and/or the depth of tumor invasion were both negative prognostic factors [32,33] while others [5,29,30,34] have suggested that they do not appear to affect survival rates. In our series, we found no significant association between these factors and survival. When intraoperatively the tumor invades the vein, it could be shown that

this macroscopic involvement is not supported by microscopic tumoral invasion. However, this supposed tumor associated fibroinflammatory reaction on the venous axis might be an unrecognized tumoral invasion [35,36] and explain the comparable survival among patients with macroscopic/microscopic involvement.

In our study, the R1 resection rate was 40.8%, which did not increase between the 2 inclusion periods despite deep changes in the specimen pathological analysis. Concomitantly with the implementation of a standardized sampling protocol [37], the R1 resection rate increased [38]. A higher rate of R1 resections in PDAC is not necessarily an indicator of low-quality surgery, but rather, of high-quality pathology. Indeed, we expected a higher R1 resection rate during period 2; however, this did not occur. We hypothesize that this stable R1 resection rate between the 2 periods actually reflects a higher quality of surgical techniques.

Survival

Our population achieved an attractive 26 months of median OS time, which is similar to the median survival of patients without VR [39–41], but higher than that of patients with unresected disease [40,42]. This reinforces the key impact of resection in patients with borderline or locally advanced PDAC, even when complex VR is required. In our series, neoadjuvant treatment independently increased the R0 resection rate (as reported in other series [43–45]), but without any benefit to the survival (irrespective of the regimen followed). The benefit and the regimen of neoadjuvant treatment (chemotherapy or chemotherapy followed by chemoradiation) over upfront surgery in patients requiring VR is still under debate. Neoadjuvant therapy could reduce the lymph node invasion [43,44,46,47], downsize the tumor, and, hence, increase the chance of R0 resection. The other way to employ this therapy would be as a “Darwinism” treatment, to spare patients from a useless surgery; initially unrecognized systemic microscopic disease might be identified at restaging [21,24,48]. Recently, a randomized controlled trial showed a clear benefit from neoadjuvant chemoradiation on survival in an intention-to-treat analysis [27]; however, we required more strong evidence as is expected from other ongoing randomized trials. Another relevant strategy would be to more extensively explore patients with borderline or locally advanced PDAC at diagnosis, to avoid a surgical strategy in patients with unknown metastatic disease, which would, consequently, confuse the results of trials. In that case, routine hepatic MRI [49] and laparoscopy with para-aortic lymph node picking [50–52] might be discussed at diagnosis to clearly establish the role and type of neoadjuvant treatment required. In the last two decades; although we extended our indication towards more advanced tumors; survival outcomes remain stable at a favourable level. Mainly progress has been reported in the rate of patients who undergo resection because of changes in neoadjuvant regimens [53,54] and the increased experience of surgeons with more complex resections. Because of the design of our study (i.e., not an intention-to-treat analysis, which precluded determination of the resectability rate of the 2 periods), we could not highlight this improvement.

Conclusion

Our series showed that vascular resection types 3 and 4 during pancreatectomy were safe. Obviously, resection remains playing a crucial role in patients with PDAC. It appears that neoadjuvant treatment strongly impacted margin resection status but not survival. We believe that this finding must not advocate for upfront VR in borderline or locally advanced PDAC, but instead, highlight the need for prospective trials to determine which patients and which tumors could benefit the most from neoadjuvant regimen.

Declarations of interest

None.

Declarations of interest

None.

Funding/disclosures

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Acknowledgment

We would like to thank Editage (www.editage.com) for English language editing. We did not preregister this study in any an independent, institutional registry.

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