Hepatobiliary & Pancreatic Diseases International 18 (2019) 389–394

Contents lists available at ScienceDirect

Hepatobiliary & Pancreatic Diseases International

journal homepage: www.elsevier.com/locate/hbpd

Original Article/Pancreas

The impact of extent of pancreatic and venous resection on survival for patients with pancreatic cancer

Matteo Serenari[a], Giorgio Ercolani[a,*], Alessandro Cucchetti[a], Matteo Zanello[b], Enrico Prosperi[a], Guido Fallani[a], Michele Masetti[b], Raffaele Lombardi[b], Matteo Cescon[a], Elio Jovine[b]

[a] Department of Medical and Surgical Sciences, S. Orsola – Malpighi Hospital, Alma Mater Studiorum – University of Bologna, Bologna, Italy
[b] Department of General Surgery, Maggiore Hospital – Bologna Local Health District, Bologna, Italy

ARTICLE INFO

Article history:
Received 16 January 2019
Accepted 6 June 2019
Available online 10 June 2019

Keywords:
Pancreatic resection
Vascular resection
Pancreatic cancer surgery

ABSTRACT

Background: Borderline resectable pancreatic cancer may require extended resections in order to achieve tumor-free margins, especially in the case of up-front resections, but it is important to know the limits of surgical therapy in this disease. This study aimed to investigate the impact of extent of pancreatic and venous resection on short- and long-term outcomes in patients with pancreatic adenocarcinoma (PDAC).
Methods: This was a retrospective study from a prospectively maintained database of pancreatic resections for PDAC. Short- and long-term outcomes were analyzed in patients having borderline resectable PDAC submitted to up-front total pancreatectomy (TP) or pancreaticoduodenectomy (PD) with simultaneous portal vein (PV) and/or superior mesenteric vein (SMV) resection. Venous resections were carried out as tangential venous resection (TVR) or segmental venous resection (SVR). Patients were divided into 4 groups: (1) PD + TVR, (2) PD + SVR, (3) TP + TVR, (4) TP + SVR. Uni- and multivariate Cox regression analysis were performed to identify factors associated with survival.
Results: Ninety-nine patients were submitted to simultaneous pancreatic and venous resection for PDAC. Among them, 25 were submitted to PD + TVR (25.3%), 12 to PD + SVR (12.1%), 23 to TP + TVR (23.2%), and 39 to TP + SVR (39.4%). Overall, major morbidity (Clavien-Dindo grade ≥ IIIA) was 26.3%. Thirty- and 90-day mortality were 3% and 11.1%, respectively. There were no significant differences among groups in terms of short-term outcomes. Median overall survival of patients submitted to PD + TVR was significantly higher than those to TP+SVR (29.5 vs 7.9 months, $P=0.001$). Multivariate analysis identified TP (HR = 2.11; 95% CI: 1.31–3.44; $P=0.002$) and SVR (HR = 2.01; 95% CI: 1.27–3.15; $P=0.003$) as the only independent prognostic factors for overall survival.
Conclusions: Up-front TP associated to SVR was predictive of worse survival in borderline resectable PDAC. Perioperative treatments in high-risk surgical groups may improve such poor outcomes.

Introduction

Pancreatic cancer is one of the leading causes of cancer-related death worldwide [1]. With regard to loco-regional invasion of pancreatic carcinoma, the International Study Group for Pancreatic Surgery (ISGPS) has recently attempted to distinguish unresectable from borderline resectable tumors [2], basing on the recommendations of the National Comprehensive Cancer Network (NCCN) [3]. In general, a borderline resectable cancer denotes a tumor involving adjacent vascular structures and for which resection, whether technically feasible, will be likely compromised by macroscopic residual disease in the absence of a vascular resection. In order to achieve negative resection margins, extended pancreatectomy with additional resection of adjacent organs involved in continuity, may be also required in some cases [4]. Although recent studies have already demonstrated that standard total pancreatectomy (TP) and pancreaticoduodenectomy (PD) are comparable in terms of short- and long-term outcomes, to what extent pancreatectomy can be considered safe when vascular resection is associated, is still unknown. Little is also known about what factors are associated with overall survival (OS) when simultaneous vascular resection is performed. Identifying high-risk surgical groups and reserving perioperative treatments for those with the poorest prognosis, may potentially improve their survival [2,5,6]. In this context, the objective

* Corresponding author.
E-mail address: giorgio.ercolani2@unibo.it (G. Ercolani).

https://doi.org/10.1016/j.hbpd.2019.06.004
1499-3872/

of the present study was to assess the impact of extent of up-front pancreatic and venous resection on short- and long-term survival in patients with borderline resectable pancreatic adenocarcinoma (PDAC).

Methods

Study design and population

Data from a prospectively collected shared database from two institutions of the same city (S.Orsola-Malpighi Hospital and Maggiore Hospital, Bologna, Italy) between 2004 and 2016 were retrieved. The data search included patients having borderline PDAC [3] submitted to pancreatectomy with simultaneous portal vein (PV) and/or superior mesenteric vein (SMV) resection. Patients were divided into four groups on the extent of pancreatic and vascular resection: (1) PD + tangential venous resection (TVR), (2) PD + segmental venous resection (SVR), (3) TP + TVR, and (4) TP + SVR. The study protocol was conformed by the ethical guidelines of the 1975 *Declaration of Helsinki* (6th revision, 2008) as reflected in a priori approval by the institution's human research committee. Informed consent was obtained from each patient included in the study.

Variable analysis

Preoperative evaluation included abdominal ultrasonography and computed tomography (CT). Magnetic resonance imaging (MRI) and endoscopic ultrasound (EUS) with fine-needle aspiration (FNA) were also performed when clinically indicated. When necessary, obstructive jaundice was treated with the placement of plastic stent through endoscopic retrograde cholangiopancreatography (ERCP) or percutaneous transhepatic cholangiography (PTC). Distortion/narrowing/occlusion of the mesenterico-portal veins with a technical possibility of reconstruction were accepted as indication for explorative laparotomy. In contrast, celiac trunk/aorta infiltration, engagement (>180°) of the superior mesenteric artery or thrombosis of the mesenterico-portal axis with cavernomatous transformation evidenced either by preoperative imaging or intraoperation were considered as absolute contraindications for curative surgery. Post-operative complications were routinely recorded. The definition of postoperative complications was adopted from ISGPS [7-9]. Complications were classified according to the Clavien classification of surgical complications [10] and grade ≥ IIIA was considered as "major" complications. Post-operative mortality was defined as death within the first 30 and 90 days after surgery. Multivisceral resection was defined as a resection of further organs other than pancreas and the vascular structures. Data on adjuvant therapy were collected when possible. Microscopic invasion (R1) of resection margins was defined as cancer cells microscopically present < 1 mm from the margin, according to the Royal College of Pathologists guidelines [11]. Data regarding depth of venous wall invasion were not reported in this study.

Surgical technique

After abdominal exploration, patients were considered potentially eligible for resection in absence of peritoneal dissemination, arterial infiltration of the celiac trunk or mesenteric root encasement. For masses located right to the mesenteric/portal axis, Whipple PD was the procedure of choice. Central tumor location in the pancreatic corpus or multifocal tumors were usually treated with TP. Bile duct and pancreatic section margins were routinely checked by frozen section to confirm tumor-free margin. Mobilization of the specimen was performed before vascular resection, hereby resulting in *en-bloc* resection that includes the involved vessel as the last step of the operation. Whether tangential resection of the lateral SMV/PV (TVR) or SVR was performed depended on tumor extent. TVR in case of attachment of the tumor to the right-sided SMV/PV was usually reconstructed by direct closure of the defect or with a small patch. When more than one-third of the lateral wall had to be resected, SVR was performed. The preferred reconstruction technique after segmental resection was primary end-to-end anastomosis. Tension-free anastomosis was facilitated by mobilization of the mesenteric root. When a tension-free anastomosis was not technically obtained, continuity was restored by interposition of an allogeneic cadaveric graft.

Statistical analysis

Continuous variables were expressed as medians and interquartile ranges (IQR), and the values in the different groups were compared using the Mann–Whitney *U* test. Categorical variables were expressed as prevalence, and the groups were compared using the Chi-squared test or the Fisher's exact test, as appropriate. OS was computed from the day of surgery until the death of the patient, and the last follow-up visit was treated as censoring event. Differences in survival were investigated using the Kaplan–Meier estimate and the log-rank test. Uni- and multivariate Cox regression analyses were performed to examine the impact of patient, tumor and resection characteristics on long-term survival. Prognostic factors with $P < 0.100$ in univariate analysis were entered into a multivariate regression model to determine independent predictors. Two-sided P values were considered statistically significant at $P < 0.05$. The statistical analysis was carried out using SPSS Version 13.0 software (SPSS Inc., Chicago, IL, USA).

Results

Demographics and histological data

In total, 940 patients underwent pancreatic surgical resection within the study period. Ninety-nine patients underwent PD or TP with simultaneous SMV/PV resection for PDAC. Distal resections and vena cava and/or arterial combined resection were excluded to obtain more comparable and homogenous groups of patients. Demographic and operative characteristics are summarized in Table 1. Median age of patients was 68 years (IQR 61-72). PD was performed in 37 patients (37.4%), whereas TP in 62 (62.6%). Vascular resections included TVR with simple venous suture ($n = 44$) or with vein patch reconstruction ($n = 4$). SVR included resections with primary end-to-end anastomosis ($n = 39$) or with interposition graft ($n = 12$). Histology revealed neoplastic vein infiltration in 54 patients (54.5%) whereas 45 patients (45.5%) had only vascular adherences. Tumor-free (R0) resection margins ($n = 57$) accounted for 57.6% on final histology.

Follow-up

Major complications (Clavien-Dindo grade ≥ IIIA) occurred in 26.3% of patients (Table 2). Pancreatic fistula occurred in 27.0% of all PD. Thirty- and 90-day mortality were 3% and 11.1%, respectively. Vascular thrombosis complicated the postoperative course in two patients and was lethal in one, who died on postoperative day 4. Besides vascular complications, five patients died due to sepsis and two patients due to postoperative hemorrhage. Three patients died after discharge due to hypoglycaemia in two cases and unexpected progression of disease in one case. All but one death occurred after TP. Median hospital stay was 15 days (IQR 12-22).

None of the patients received neoadjuvant treatment. Eighty-seven patients died returning a median survival of 15.6 months, with 1-, 3-, and 5-year survival probabilities of 59.0%, 16.1% and

Table 1
Demographics and operative characteristics ($n=99$).

Variables	Values
Age (yr, median, IQR)	68 (61–72)
Sex (M/F)	43/56
Diabetes mellitus	22 (22.2%)
ASA score	
1–2	47 (47.5%)
3–4	52 (52.5%)
CA 19–9 (U/mL, median, IQR)	213 (90–656)
Preoperative biliary drainage	
ERCP	44 (44.4%)
PTC	6 (6.1%)
None	1 (1.0%)
Voice preoperative biliary drainage	
FNA	48 (48.5%)
Vascular invasion at imaging	
EUS	24/37 (64.9%)
CT	26/71 (36.6%)
MRI	1/20 (5.0%)
Pancreatic resection	
Pancreaticoduodenectomy	37 (37.4%)
Total pancreatectomy	62 (62.6%)
Vascular reconstruction	
Venorrhaphy	44 (44.4%)
End-to-end anastomosis	39 (39.4%)
Graft insertion	12 (12.1%)
Patch	4 (4.0%)
Operative time (min, median, IQR)	345 (287–405)
Multivisceral resection	14 (14.1%)

IQR: Interquartile range; M: Male; F: Female; ASA: American Society of Anesthesiologists; ERCP: Endoscopic retrograde cholangiopancreatography; PTC: Percutaneous transhepatic cholangiography; FNA: Fine-needle aspiration; EUS: Endoscopic ultrasound; CT: Computed tomography; MRI: magnetic resonance imaging.

Table 2
Short-term outcomes of all patients ($n=99$).

Variables	Values
Clavien-Dindo grade ≥ IIIA	26 (26.3%)
Pancreatic fistula[a]	10 (27.0%)
A	7 (7.1%)
B	2 (2.0%)
C	1 (1.0%)
DGE	18 (18.2%)
PPH	14 (14.1%)
Portal vein thrombosis	1 (1.0%)
Arterial thrombosis	1 (1.0%)
Hospital stay (d, median, IQR)	15 (12–22)
30-day mortality	3 (3.0%)
90-day mortality	11 (11.1%)

[a] For 37 patients underwent pancreaticoduodenectomy. DGE: Delayed gastric empty; PPH: Post post-pancreatectomy hemorrhage; IQR: Interquartile range.

8.7%, respectively. Taking main histological features, it was observed that survival of patients without vascular involvement was on the border of significance compared to patients with histological proven vascular infiltration (17.4 months vs. 13.7 months; $P=0.054$). No significant difference in survival was seen between patients with tumor positive (R1: 12.9 months) and tumor-free (R0: 16.2 months) resection margins ($P=0.134$). Uni- and multivariate analysis identified TP (HR = 2.11; 95% CI: 1.31–3.44; $P=0.002$) and SVR (HR = 2.01; 95% CI: 1.27–3.15; $P=0.003$) as the only independent prognostic factors for OS (Table 3).

Effect of pancreatectomy and vascular resection on survival

When PD + TVR, PD + SVR, TP + TVR and TP + SVR were compared, age, American Society of Anesthesiologists (ASA) score, CA 19-9 levels and diabetes were comparable among these groups (Table 4). No differences were found in regards to tumor size (maximal transverse diameter), nodal status (N stage) and lymph node ratio. Histology did not reveal difference in terms of true vascular invasion, whereas positive microscopic resection margins (R1) were significantly different among the 4 groups ($P=0.007$). When comparing survival features (Fig. 1), median OS was significantly better after PD + TVR (29.5 months) than after TP + SVR (7.9 months) ($P=0.001$). PD + SVR had intermediate survival rates (13.7 months) and was not significantly different compared to TP + TVR (18.9 months) ($P=0.480$).

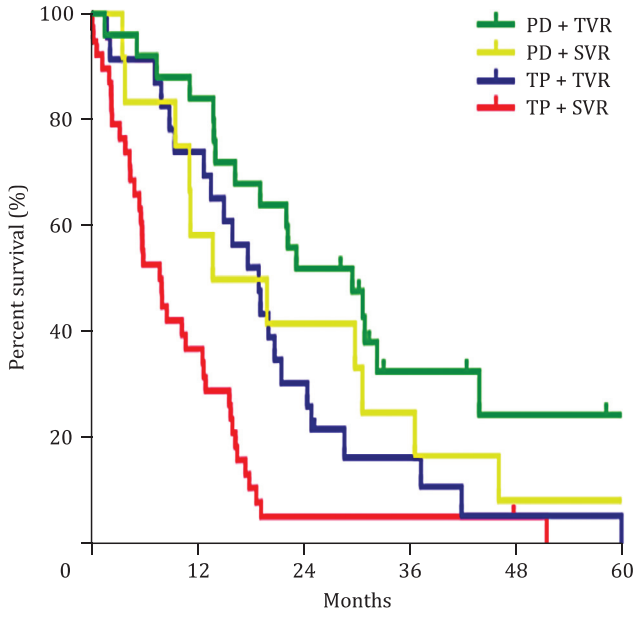

Fig. 1. Overall survival between patients submitted to total pancreatectomy (TP) or pancreato-duodenectomy (PD) with concomitant segmental venous resection (SVR) or tangential venous resection (TVR).

Discussion

This study includes 99 consecutive up-front pancreatectomies with simultaneous venous resection for borderline resectable PDAC. TP and SVR were independently associated with OS, whereas, among all combinations of pancreatic and vascular resection, TP associated to SVR showed the worst survival feature.

Borderline resectable cancer represents approximately 30–40% of stages at diagnosis [12]. Such surgical approach is currently endorsed by expert consensus suggesting it as the standard of practice for PDAC locally involving the PV and/or SMV [13]. The preoperative evaluation of resectability/vascular involvement is commonly accomplished using radiologic and endoscopic techniques; however, it is often difficult to distinguish real tumor infiltration from inflammatory adhesion basing on imaging results alone [14]. For this reason, our two centers share a common surgical strategy which consists of a systematic preventive venous resection whenever invasion is macroscopically suspected [15]. In fact, venous excision or even multivisceral resection increases the chance of complete tumor clearance [5,16-19]. In our study, histology revealed real neoplastic vein infiltration in about half of the patients, and a R0 resection margin status of 57.6% [11]. Although many studies, including ours, did not establish pathological evidence of tumor invasion in the PV/SMV as a negative prognostic factor for survival [17,20-24], patients with extended pancreatectomy were demonstrated to have a significantly higher rate of R1 margins compared to standard resections [5,25,26], representing simply the epiphenomenon of a more extended disease rather than a consequence of tumor size, anatomical location [27],

Table 3
Univariate and multivariate Cox regression analysis for overall survival.

Variables	Univariate			Multivariate		
	95% CI	HR	*P* value	95% CI	HR	*P* value
Age	0.96–1.00	0.98	0.199	–	–	–
Female	0.77–1.80	1.19	0.443	–	–	–
Tumor position						
Head/uncinate process	Ref.	Ref.	Ref.	–	–	–
Body and tail	0.58–2.54	1.22	0.595	–	–	–
Diffuse	0.61–4.70	1.70	0.303	–	–	–
Multivisceral resection	0.73–2.33	1.31	0.363	–	–	–
TP vs. PD	1.48–3.80	2.37	**<0.001**	1.31–3.44	2.11	**0.002**
SVR vs. TVR	1.62–3.91	2.51	**<0.001**	1.27–3.15	2.01	**0.003**
Clavien-Dindo grade ≥ IIIA	0.48–1.26	0.78	0.311	–	–	–
N stage (N1 vs N0)	0.63–1.93	1.10	0.727	–	–	–
Resection margin (R1 vs R0)	0.84–1.98	1.29	0.245	–	–	–
Tumor grade						
G1	Ref.	Ref.	Ref.	–	–	–
G2	0.43–2.44	1.03	0.941	–	–	–
G3/G4	0.68–3.86	1.62	0.271	–	–	–
Perineural invasion	0.73–2.29	1.29	0.397	–	–	–
Vascular infiltration	0.94–2.25	1.46	0.087	0.97–2.39	1.52	0.067
Adjuvant chemotherapy	0.41–0.99	0.64	**0.043**	0.42–1.03	0.65	0.068

Ref.: Reference; 95% CI: 95% Confidence interval; HR: Hazard ratio; TP: Total pancreatectomy; PD: Pancreaticoduodenectomy; SVR: Segmental venous resection; TVR: Tangential venous resection.

Table 4
Comparison between patients undergoing TP and PD for PDAC with TVR or SVR.

Variables	PD+TVR ($n=25$)	PD+SVR ($n=12$)	TP+TVR ($n=23$)	TP+SVR ($n=39$)	*P* value
Age (yr, median, IQR)	68 (61–73)	64 (57–73)	68 (61–76)	69 (60–72)	0.950
Sex (M/F)	12/13	6/6	11/12	14/25	0.681
Diabetes mellitus	4 (16.0%)	3 (25.0%)	7 (30.4%)	8 (20.5%)	0.553
ASA Score					0.112
1–2	17 (68.0%)	4 (33.3%)	10 (43.5%)	16 (41.0%)	
3–4	8 (32.0%)	8 (66.7%)	13 (56.5%)	23 (59.0%)	
CA 19–9 (U/mL, median, range)	208 (83–398)	117 (21–1458)	243.5 (101–617)	220 (56–1420)	0.868
Operative time (min, median, IQR)	315 (265–375)	380 (302–458)	350 (287–405)	370 (285–435)	0.465
Multivisceral resection	1 (4.0%)	1 (8.3%)	4 (17.4%)	8 (20.5%)	0.266
Tumor position					
Head/uncinate process	25 (100%)	12 (100%)	20 (87.0%)	29 (74.4%)	0.090
Body and tail	0	0	2 (8.7%)	7 (17.9%)	
Diffuse	0	0	1 (4.3%)	3 (7.7%)	
Tumor size (mm, median, IQR)	30.0 (25.0–35.0)	30 (25.5–37.5)	30.0 (25.0–40.0)	33.0 (25.0–40.0)	0.495
N stage					0.715
N0	3 (12.0%)	2 (16.7%)	5 (21.7%)	9 (23.1%)	
N1	22 (88.0%)	10 (83.3%)	18 (78.3%)	30 (76.9%)	
LN ratio (median, IQR)	0.12 (0.06–0.28)	0.09 (0.06–0.14)	0.12 (0.06–0.28)	0.09 (0.02–0.14)	0.246
Perineural invasion	23 (92.0%)	9 (75.0%)	17 (73.9%)	32 (82.1%)	0.382
Resection margin					**0.007**
R0	21 (84.0%)	7 (58.3%)	8 (34.8%)	21 (53.8%)	
R1	4 (16.0%)	5 (41.7%)	15 (65.2%)	18 (46.2%)	
Histologic vascular invasion	10 (40.0%)	7 (58.3%)	13 (56.5%)	24 (61.5%)	0.390
Clavien-Dindo grade ≥ IIIA	5 (20.0%)	3 (25.0%)	8 (34.8%)	10 (25.6%)	0.709
Hospital stay (d, median, IQR)	14 (10–19)	15 (12–25)	15 (10–19)	16 (12–25)	0.183
30-day mortality	0	0	0	3 (7.7%)	0.190
90-day mortality	1 (4.0%)	0	2 (8.7%)	8 (20.5%)	0.093
Adjuvant chemotherapy	18 (72.0%)	5 (41.7%)	16 (69.6%)	18 (46.2%)	0.078

TP: Total pancreatectomy; PD: Pancreatoduodenectomy; PDAC: Pancreatic ductal adenocarcinoma; TVR: Tangential venous resection; SVR: Segmental venous resection; IQR: Interquartile range; M: Male; F: Female; ASA: American Society of Anesthesiologists; LN: Lymph node.

mobilization margins [28] or a difference in histological processing and sampling standards [29]. This finding was also confirmed in our study, where the rate of R1 resections ranged from 41.7% to 65.2% in the SVR/TP groups, compared to only 16.0% in the PD + TVR group. However, the only independent predictors of survival were TP and SVR, suggesting that these two surgical features, especially when combined, represents a surrogate of a more advanced disease. Even though it seems to be obvious that a more extended operation is associated to a poorer prognosis, the last reports aiming to compare standard TP vs. PD showed no differences in terms of short- and long-term outcomes [30,31]. On the contrary, when vascular or multivisceral resection was associated, TP was found to carry a higher risk for in-hospital mortality [5], whereas no differences existed after comparison of different venous reconstructions [32,33]. In our study, for the first time, TP and SVR (i.e. PV/SMV resection reconstructed by end-to-end anastomosis with or without graft interposition) were predictive of worse survival in borderline resectable PDAC. Moreover, TP + SVR revealed 20.5% 90-day mortality while other combinations ranged from 0–8.7% and this could be explained by the relative high number of associated multivisceral resections, other than by the more complex vascular resections (and

reconstructions) performed. Besides oncological aspects, long-term life-threatening complications co-related with the apancreatic state which characterizes the patients who underwent TP, may have affected negatively the survival outcomes of the TP groups. However, we were unable to ascertain the cause of death in some patients of our series but we acknowledge that this important aspect, consequent to the type of pancreatectomy performed, surely requires further dedicated studies [34].

This study has other limitations. First, we are aware that selection bias may have affected the allocation of TP vs. PD, although this would have not changed our findings. Similarly to our finding, Hartwig et al. [5] performed TP in 33.2% of their patients who had an extended resection, compared with only 13.7% in those having a standard resection. This confirms the presence of the same bias, which is that TP may have been performed in place of PD due to the extent of vascular or multivisceral resection, trying to achieve tumor-free margins. Second, the small number of patients included may have prevented significances in baseline characteristics. Third, all patients received up-front surgery without neoadjuvant therapy. This was in accordance with NCCN 2014 Guidelines [35]. Up-front resection in patients with borderline resectable disease is no longer recommended, as of the 2016 (end of our study) version of these guidelines. However, even though neoadjuvant therapy has been demonstrated to potentially improve the long-term prognosis of patients with borderline resectable tumors, no randomized phase III trials have compared the approach of neoadjuvant therapy in borderline resectable disease versus up-front surgery. We do not know whether the results presented would have been better than expected if the more recent chemotherapy protocols had been used. Nevertheless, according to the most recent (2018) NCCN guidelines, which state that “a borderline resectable lesion can be defined as one in which there is a higher likelihood of an incomplete resection”, it is increasingly important to assess preoperatively the extent of pancreatic and vascular resection in order to identify high-risk features that would probably benefit more from preoperative treatments rather than surgery alone [36,37].

In conclusion, radical resection is the only chance of cure for pancreatic malignancies and preventive vascular resection is justified in case of macroscopically suspected venous involvement. The high probability of obtaining poor survival features if up-front TP and SVR are performed, suggests that perioperative treatments in these high-risk surgical groups should be further analyzed.

Contributors

EG and JE proposed the study. SM and CA performed the research and wrote the first draft. ZM, PE, FG, MM, LR, and CM collected and analyzed the data. All authors contributed to the design and interpretation of the study and to further drafts. JE is the guarantor.

Funding

None.

Ethical approval

This study was approved by the Ethics Committee of University of Bologna.

Competing interest

No benefits in any form have been received or will be received from a commercial party related directly or indirectly to the subject of this article.

References

[1] Siegel R, Naishadham D, Jemal A. Cancer statistics, 2013. CA Cancer J Clin 2013;63:11–30.
[2] Bockhorn M, Uzunoglu FG, Adham M, Imrie C, Milicevic M, Sandberg AA, et al. Borderline resectable pancreatic cancer: a consensus statement by the International Study Group of Pancreatic Surgery (ISGPS). Surgery 2014;155:977–988.
[3] National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology (Version 1) 2012.
[4] Hartwig W, Vollmer CM, Fingerhut A, Yeo CJ, Neoptolemos JP, Adham M, et al. Extended pancreatectomy in pancreatic ductal adenocarcinoma: definition and consensus of the International Study Group for Pancreatic Surgery (ISGPS). Surgery 2014;156:1–14.
[5] Hartwig W, Gluth A, Hinz U, Koliogiannis D, Strobel O, Hackert T, et al. Outcomes after extended pancreatectomy in patients with borderline resectable and locally advanced pancreatic cancer. Br J Surg 2016;103:1683–1694.
[6] Konstantinidis IT, Warshaw AL, Allen JN, Blaszkowsky LS, Castillo CF, Deshpande V, et al. Pancreatic ductal adenocarcinoma: is there a survival difference for R1 resections versus locally advanced unresectable tumors? What is a "true" R0 resection? Ann Surg 2013;257:731–736.
[7] Wente MN, Bassi C, Dervenis C, Fingerhut A, Gouma DJ, Izbicki JR, et al. Delayed gastric emptying (DGE) after pancreatic surgery: a suggested definition by the International Study Group of Pancreatic Surgery (ISGPS). Surgery 2007;142:761–768.
[8] Wente MN, Veit JA, Bassi C, Dervenis C, Fingerhut A, Gouma DJ, et al. Postpancreatectomy hemorrhage (PPH): an International Study Group of Pancreatic Surgery (ISGPS) definition. Surgery 2007;142:20–25.
[9] Bassi C, Dervenis C, Butturini G, Fingerhut A, Yeo C, Izbicki J, et al. Postoperative pancreatic fistula: an international study group (ISGPF) definition. Surgery 2005;138:8–13.
[10] Clavien PA, Barkun J, de Oliveira ML, Vauthey JN, Dindo D, Schulick RD, et al. The Clavien-Dindo classification of surgical complications: five-year experience. Ann Surg 2009;250:187–196.
[11] Campbell F, Cairns A, Duthie F, Feakins R. Dataset for the histopathological reporting of carcinomas of the pancreas, ampulla of Vater and common bile duct. R Coll Pathol 2017.
[12] Ghaneh P, Costello E, Neoptolemos JP. Biology and management of pancreatic cancer. Gut 2007;56:1134–1152.
[13] Adams RB, Allen PJ. Surgical treatment of resectable and borderline resectable pancreatic cancer: expert consensus statement by Evans et al. Ann Surg Oncol 2009;16:1745–1750.
[14] Porembka MR, Hawkins WG, Linehan DC, Gao F, Ma C, Brunt EM, et al. Radiologic and intraoperative detection of need for mesenteric vein resection in patients with adenocarcinoma of the head of the pancreas. HPB (Oxford) 2011;13:633–642.
[15] Turrini O, Ewald J, Barbier L, Mokart D, Blache JL, Delpero JR. Should the portal vein be routinely resected during pancreaticoduodenectomy for adenocarcinoma? Ann Surg 2013;257:726–730.
[16] Kulemann B, Hoeppner J, Wittel U, Glatz T, Keck T, Wellner UF, et al. Perioperative and long-term outcome after standard pancreaticoduodenectomy, additional portal vein and multivisceral resection for pancreatic head cancer. J Gastrointest Surg 2015;19:438–444.
[17] Nakao A, Kaneko T, Takeda S, Inoue S, Harada A, Nomoto S, et al. The role of extended radical operation for pancreatic cancer. Hepatogastroenterology 2001;48:949–952.
[18] Shimada K, Sano T, Sakamoto Y, Kosuge T. Clinical implications of combined portal vein resection as a palliative procedure in patients undergoing pancreaticoduodenectomy for pancreatic head carcinoma. Ann Surg Oncol 2006;13:1569–1578.
[19] Yekebas EF, Bogoevski D, Cataldegirmen G, Kunze C, Marx A, Vashist YK, et al. En bloc vascular resection for locally advanced pancreatic malignancies infiltrating major blood vessels: perioperative outcome and long-term survival in 136 patients. Ann Surg 2008;247:300–309.
[20] Müller SA, Hartel M, Mehrabi A, Welsch T, Martin DJ, Hinz U, et al. Vascular resection in pancreatic cancer surgery: survival determinants. J Gastrointest Surg 2009;13:784–792.
[21] Riediger H, Makowiec F, Fischer E, Adam U, Hopt UT. Postoperative morbidity and long-term survival after pancreaticoduodenectomy with superior mesenterico-portal vein resection. J Gastrointest Surg 2006;10:1106–1115.
[22] Bachellier P, Nakano H, Oussoultzoglou PD, Weber JC, Boudjema K, Wolf PD, et al. Is pancreaticoduodenectomy with mesentericoportal venous resection safe and worthwhile? Am J Surg 2001;182:120–129.
[23] Banz VM, Croagh D, Coldham C, Tanière P, Buckels J, Isaac J, et al. Factors influencing outcome in patients undergoing portal vein resection for adenocarcinoma of the pancreas. Eur J Surg Oncol 2012;38:72–79.
[24] Fuhrman GM, Leach SD, Staley CA, Cusack JC, Charnsangavej C, Cleary KR, et al. Rationale for en bloc vein resection in the treatment of pancreatic adenocarcinoma adherent to the superior mesenteric-portal vein confluence. Pancreatic Tumor Study Group. Ann Surg 1996;223:154–162.
[25] van Geenen RC, ten Kate FJ, de Wit LT, van Gulik TM, Obertop H, Gouma DJ. Segmental resection and wedge excision of the portal or superior mesenteric vein during pancreatoduodenectomy. Surgery 2001;129:158–163.
[26] Wang F, Arianayagam R, Gill A, Puttaswamy V, Neale M, Gananadha S, et al. Grafts for mesenterico-portal vein resections can be avoided during pancreatoduodenectomy. J Am Coll Surg 2012;215:569–579.

[27] Kelly KJ, Winslow E, Kooby D, Lad NL, Parikh AA, Scoggins CR, et al. Vein involvement during pancreaticoduodenectomy: is there a need for redefinition of "borderline resectable disease"? J Gastrointest Surg 2013;17:1209–1217.
[28] Jamieson NB, Foulis AK, Oien KA, Going JJ, Glen P, Dickson EJ, et al. Positive mobilization margins alone do not influence survival following pancreatico-duodenectomy for pancreatic ductal adenocarcinoma. Ann Surg 2010;251:1003–1010.
[29] Esposito I, Kleeff J, Bergmann F, Reiser C, Herpel E, Friess H, et al. Most pancreatic cancer resections are R1 resections. Ann Surg Oncol 2008;15:1651–1660.
[30] Satoi S, Murakami Y, Motoi F, Sho M, Matsumoto I, Uemura K, et al. Reappraisal of total pancreatectomy in 45 patients with pancreatic ductal adenocarcinoma in the modern era using matched-pairs analysis: multicenter study group of pancreatobiliary surgery in Japan. Pancreas 2016;45:1003–1009.
[31] Xiong J, Wei A, Ke N, He D, Chian SK, Wei Y, et al. A case-matched comparison study of total pancreatectomy versus pancreaticoduodenectomy for patients with pancreatic ductal adenocarcinoma. Int J Surg 2017;48:134–141.
[32] Ravikumar R, Sabin C, Abu Hilal M, Bramhall S, White S, Wigmore S, et al. Portal vein resection in borderline resectable pancreatic cancer: a United Kingdom multicenter study. J Am Coll Surg 2014;218:401–411.
[33] Murakami Y, Satoi S, Motoi F, Sho M, Kawai M, Matsumoto I, et al. Portal or superior mesenteric vein resection in pancreatoduodenectomy for pancreatic head carcinoma. Br J Surg 2015;102:837–846.
[34] Balzano G, Maffi P, Nano R, Mercalli A, Melzi R, Aleotti F, et al. Autologous islet transplantation in patients requiring pancreatectomy: a broader spectrum of indications beyond chronic pancreatitis. Am J Transplant 2016;16:1812–1826.
[35] Tempero MA, Malafa MP, Behrman SW, Benson AB 3rd, Casper ES, Chiorean EG, et al. Pancreatic adenocarcinoma, version 2.2014: featured updates to the NCCN guidelines. J Natl Compr Canc Netw 2014;12:1083–1093.
[36] Delpero JR, Boher JM, Sauvanet A, Le Treut YP, Sa-Cunha A, Mabrut JY, et al. Pancreatic adenocarcinoma with venous involvement: is up-front synchronous portal-superior mesenteric vein resection still justified? A survey of the Association Française de Chirurgie. Ann Surg Oncol 2015;22:1874–1883.
[37] Nakao A, Kanzaki A, Fujii T, Kodera Y, Yamada S, Sugimoto H, et al. Correlation between radiographic classification and pathological grade of portal vein wall invasion in pancreatic head cancer. Ann Surg 2012;255:103–108.