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ORIGINAL ARTICLE – PANCREATIC TUMORS

Pancreatectomy with Mesenteric and Portal Vein Resection for Borderline Resectable Pancreatic Cancer: Multicenter Study of 406 Patients

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ABSTRACT

Purpose. The role of pancreatectomy with en bloc venous resection and the prognostic impact of pathological venous invasion are still debated. The authors analyzed perioperative, survival results, and prognostic factors of pancreatectomy with en bloc portal (PV) or superior mesenteric vein (SMV) resection for borderline resectable pancreatic carcinoma, focusing on predictive factors of histological venous invasion and its prognostic role.

Methods. A multicenter database of 406 patients submitted to pancreatectomy with en bloc SMV and/or PV resection for pancreatic adenocarcinoma was analyzed retrospectively. Univariate and multivariate analysis of factors related to histological venous invasion were performed using logistic regression model. Prognostic factors were analyzed with log-rank test and multivariate proportional hazard regression analysis.

Results. Complications occurred in 51.9 % of patients and postoperative death in 7.1 %. Histological invasion of the resected vein was confirmed in 56.7 % of specimens. Five-year survival was 24.4 % with median survival of 24 months. Vein invasion at preoperative computed tomography (CT), N status, number of metastatic lymph nodes, preoperative serum albumin were related to pathological venous invasion at univariate analysis, and vein invasion at CT was independently related to venous invasion at multivariate analysis. Use of preoperative biliary drain was significantly associated with postoperative complications. Multivariate proportional hazard regression analysis demonstrated a significant correlation between overall survival and histological venous invasion and administration of adjuvant therapy.

Conclusions. This study identifies predictive factors of pathological venous invasion and prognostic factors for overall survival, including pathological venous invasion, which may help with patients' selection for different treatment protocols.

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Pancreatic carcinoma represents the fourth-leading cause of cancer-related death in the United States with 46,420 estimated new cases for 2014 and 35,590 deaths.[1] In Europe, 103,773 new cases are estimated in 2012,[2] and 8.15 deaths/100,000 in men and 5.62/100,000 in women

are predicted for 2015.[3] Surgical resection represents the only potentially curative treatment for pancreatic adenocarcinoma: 5-year survival for patients undergoing complete surgical resection approaches 25 %.[4] Unfortunately, approximately 80 % of patients are inoperable for locally advanced or metastatic disease.[5] Superior mesenteric vein (SMV) and portal vein (PV) invasion is frequent because of the proximity of these vessels to the uncinate process and pancreatic head. Potentially curative surgery is possible in these patients combining pancreatic resection with en bloc resection of the PV-SMV venous axis.[6] Single-center reports, systematic reviews, and meta-analyses have shown the feasibility and the advantages of this approach, which may provide survival results comparable to those obtained with standard pancreatectomy without venous resection.[7–10] Other studies have stressed the role of histological venous invasion as prognostic factor, reporting worst survival in patients with venous invasion confirmed by pathological examination.[11,12] A recent study has even questioned the utility of aggressive surgery in these cases.[13] The objective of this study is to report the analysis of a large multicenter series of 406 patients with borderline resectable pancreatic cancer submitted to pancreatectomy with en bloc venous resection in eight Italian specialized surgical units. Our purpose is to analyze perioperative and survival results of this technique and to identify predictive factors of histological venous invasion. We also define the prognostic role of histological venous invasion and identify other prognostic factors of overall survival.

PATIENTS AND METHODS

The study is a retrospective analysis of a multicenter prospectively collected database of patients submitted to pancreatectomy with en bloc SMV and/or PV resection for pancreatic adenocarcinoma. Between January 1987 and December 2014, a total of 406 consecutive patients were treated in eight referral Italian centers. Only patients with borderline resectable pancreatic cancer were included in this study. Borderline pancreatic cancer was defined according to NCCN guidelines, version 2.2015. Collected data included: patients characteristics, preoperative workup, tumor characteristics, surgical treatment, postoperative outcomes, histological tumor features, postoperative adjuvant therapies, and survival.

Preoperative Workup and Treatment

Diagnosis of pancreatic adenocarcinoma was initially made by imaging and confirmed by pathological examination. Only patients with confirmed pathological diagnosis of pancreatic adenocarcinoma were included. Preoperative workup included contrast-enhanced thoracoabdominal computed tomography (CT); abdominal contrast-enhanced magnetic resonance (MR) was performed in selected patients according to results of CT scan or in case of contraindication of CT scan. Echo-endoscopy with fine-needle aspiration was not systematically performed at the beginning of this series. Positron emission tomography (PET) was used only in highly selected cases. Indication and protocols of neoadjuvant treatment was established case by case by the multidisciplinary tumor board of each single center, according to patients and tumors' characteristics and to the expected probability to obtain an R0 resection.

Surgery

Patients underwent pancreaticoduodenectomy, left spleno-pancreatectomy, or total pancreatectomy according to the location and extent of the tumor. Standard lymphadenectomy was performed as previously described.[14] Venous invasion was suspected by preoperative imaging and intraoperatively diagnosed in case of not dissociable adherence between the tumor and the PV/SMV axis. The technique of venous resection and reconstruction included tangential resection with primary suture or patch interposition, segmental resection with end-to-end venous anastomosis or venous graft interposition or vascular prosthesis interposition. Venous resection and reconstruction were defined according to the International Study Group of Pancreatic Surgery (ISGPS) as follows: type 1 = partial venous excision with direct closure (venorrhaphy) by suture closure; type 2 = partial venous excision using a patch; type 3 = segmental resection with primary veno-venous anastomosis; and type 4 = segmental resection with interpose venous conduit and at least two anastomoses.[15] The splenic vein was ligated, or preserved, or ligated and reimplanted according to tumor location and surgeon's choice. The technique of vascular reconstruction and the type of pancreatic, biliary, and enteric anastomoses depended on operating surgeon's choice.

Definition of Clinical Outcomes

Postoperative complications were defined according to the ISGPS.[16,17] Postoperative mortality was defined as death occurring during the first 30 days after surgery or during hospitalization. Overall survival was calculated from the date of surgery to the date of death.

Pathological Examination

Pathologists with specific experience on pancreatic oncology examined the specimens. A microscopic positive resection margin (R1) was defined as presence of tumor cells within 1 mm from the margin in the absence of macroscopic evidence of residual tumor, which was

classified as R2. Margins were classified according to the recommendation of the ISGPS.[15]

Adjuvant Therapies and Follow-up

Adjuvant chemotherapy or radiochemotherapy were administered according to the evaluation of the multidisciplinary tumor board of each single institution, basing on performance status and tumor characteristics. Follow-up consisted on physical examination and CA 19-9 determination every 3 months and thoraco-abdominal CT scan every 6 months during the first 2 years. After 2 years physical examination, CA 19-9 determination and CT scan were performed every 6 months.

Statistical Analysis

Data were prospectively collected by every center and retrospectively analyzed. Qualitative variables were compared using the Chi square test, and quantitative variables were analyzed using Student's *t* test. Univariate and multivariate analysis of factors related to histological venous invasion were performed using logistic regression model. Multivariate analysis included variables significant at univariate analysis. Univariate analysis of factors related to postoperative morbidity and mortality was performed using logistic regression model. The survival rates were estimated using the Kaplan–Meier method. The log-rank test was used to compare survival curves of subgroups, with continuous variables dichotomized around the median value. Multivariate proportional hazard regression (Cox model) analysis of prognostic factors was performed. Two-sided *P* values were computed; $P < 0.05$ was considered statistically significant. All analyses were performed using MedCalc for Windows, version 10.2.0.0 (MedCalc Software, Belgium).

RESULTS

Patients' Characteristics

The study population was composed by 229 men (56.4 %) and 177 women (43.6 %). Patients' characteristics are listed in Supplemental Table 1. A total of 235 patients (57.9 %) had one or more comorbidity; 182 patients had cardiovascular comorbidities (44.8 %), 43 had respiratory comorbidities (10.6 %), and 105 (25.9 %) had metabolic comorbidities.

Preoperative Workup and Treatment

Mean tumor diameter at CT scan was 32.0 ± 14.05 mm. PV and/or SMV invasion was diagnosed in 81.7 % of cases at CT scan. Tumor occlusion/thrombosis of the PV or SMV was detected in 12 patients (2.9 %).

TABLE 1 Surgical procedures performed in 406 patients submitted to pancreatectomy with PV or SMV resection for pancreatic adenocarcinoma

Variable	%
Procedure	
Pancreaticoduodenectomy	74.1
Whipple	25.1
Pylorus preserving	49.0
Left spleno-pancreatectomy	21.4
Total pancreatectomy	4.4
Resected vein	
Portal vein	52.2
Superior mesenteric vein	26.4
PV-SMV confluence	21.4
Venous resection/reconstruction according to ISGPS	
Type 1	44.7
Type 2	6.8
Type 3	38.8
Type 4	9.7

SD standard deviation, *PV* portal vein, *SMV* superior mesenteric vein, *ISGPS* international study group of pancreatic surgery, *N* number

Contrast-enhanced MR was performed in 26.1 % of cases and echoendoscopy in 22.4 %, whereas staging laparoscopy was never used and PET only in nine cases. Preoperative biliary drainage was performed in 22.9 % of patients. Neoadjuvant chemotherapy was administered to 23 patients, and radiotherapy alone in 1 case.

Surgery

The majority of patients underwent pancreaticoduodenectomy (74.1 %), whereas 87 (21.4 %) underwent left spleno-pancreatectomy and 18 (4.4 %) total pancreatectomy (Table 1). Mean time of venous clampage was 16.96 ± 6.67 (range 5–30) minutes. Mean length of venous resection was 19.6 ± 16.15 (range 3–100) mm. Mean operative time was 469.6 ± 139.9 min, and blood loss 318.7 ± 132.4 ml.

Postoperative Outcomes

Complications occurred in 51.9 % of patients (Table 2). Thrombosis of the reconstructed PV/SMV axis occurred in seven patients. Ninety-eight patients were transfused in the postoperative period, and mean intensive care unit stay was 2.78 ± 4.29 days. Mean hospital stay was 19.84 ± 11.16 (median 17) days.

TABLE 2 Postoperative morbidity and mortality of 406 patients submitted to pancreatectomy with PV or SMV resection for pancreatic adenocarcinoma

Variable	*N*	%
Overall complications	211	51.9
Mortality	29	7.1
Pancreatic fistula	42	10.34
Grade A	19	4.68
Grade B	16	3.94
Grade C	7	1.72
DGE	101	24.87
Grade A	37	9.11
Grade B	38	9.36
Grade C	16	3.94
Grade not reported	10	2.46
Biliary anastomotic leak	10	2.46
Intestinal anastomotic leak	1	0.25
Postoperative bleeding	35	8.62
Relaparotomy	23	5.66
PV-SMV thrombosis	7	1.72
Abdominal abscess	38	9.36
Need of postoperative abdominal drain	48	11.82
Intestinal ischemia	4	0.98
Wound infection	17	4.18
Urinary tract infection	3	0.74
Cardiovascular complications	12	2.95
DVT/PE	7	1.72
Acute renal failure	3	0.74
Liver failure	1	0.25
Pancreatitis	1	0.25
Enteric fistula	3	0.74
Pneumonia	4	0.98
Multiorgan failure	10	2.46

N number, *DGE* delayed gastric emptying, *PV* portal vein, *SMV* superior mesenteric vein, *DVT/PE* deep venous thrombosis/pulmonary embolism

Pathological Analysis

Mean tumor diameter was 34.8 ± 15.03 (range 2–125) mm. Histological invasion of the resected vein was confirmed in 56.7 % of specimens (Supplemental Table 2). Mean numbers of retrieved and metastatic lymph nodes were respectively 34.3 ± 22.89 and 3.45 ± 4.56.

Adjuvant Therapies and Survival

Adjuvant therapy was administered to 72.2 % of patients and 7.4 % of those had radiochemotherapy. Adjuvant therapy was not administered in 27.8 % of patients. Among those, causes of nonadministration of postoperative therapy were postoperative complications (81.5 %), weakness/inability to support adjuvant therapy or patients' refuse (13.2 %), or early recurrence (5.3 %). Mean follow-up duration was 42.7 months. Median overall survival was 24 months. Five-year survival was 24.4 % as showed in Supplemental Fig. 1.

Predictive Factors of Histological Venous Invasion

At univariate analysis, significant predictive factors of histological venous invasion were: vein invasion at preoperative CT, N status, number of metastatic lymph nodes, and preoperative serum albumin (Table 3). Vein invasion at preoperative CT was the only significant factor at multivariate analysis (0.0212).

Predictive Factors of Postoperative Morbidity and Mortality

The only factor significantly associated with postoperative complications at univariate analysis was the use of preoperative biliary drain (Table 4). Multivariate analysis was not performed because only one factor was significant at univariate analysis. Univariate analysis did not find any significant correlation between perioperative factors and postoperative mortality.

Analysis of Prognostic Factors

Log-rank test showed a significant correlation between histological venous invasion, vein occlusion at preoperative CT, N status, number of metastatic lymph nodes, administration of adjuvant therapy, and overall survival (Table 4). Survival curves are shown in Fig. 1 and Supplemental Figs. 2–5. Multivariate proportional hazard regression analysis demonstrated a significant correlation

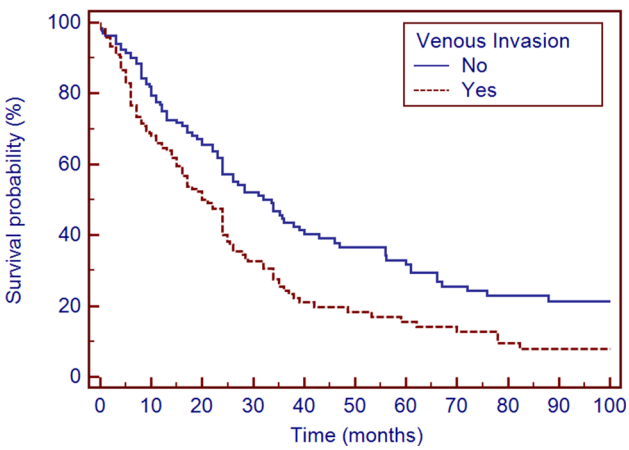

FIG. 1 Overall survival according to histological venous invasion

TABLE 3 Predictive factors of pathological venous invasion

Variable	Univariate analysis			*P*	Multivariate analysis		*P*
	SE	OR	CI		CI	OR	
Age	0.01	1.02	0.99–1.04	0.0771			
ASA	0.35	1.19	0.60–2.38	0.6197			
Sex = F	0.21	1.35	0.89–2.04	0.1559			
Comorbidity = 0	0.22	0.71	0.47–1.09	0.1219			
CA 19-9	0.01	1.0	0.99–1.0	0.4730			
Albumine	0.33	0.48	0.25–0.92	0.0262	0.25–1.02	0.50	0.0577
Bilirubine	0.02	1.01	0.97–1.06	0.6617			
Haemoglobin	0.1	0.9	0.74–1.1	0.3068			
CRP	0.08	1.02	0.87–1.19	0.8048			
Tumor diameter at CT	0.01	0.99	0.97–1.02	0.4797			
Vein invasion At CT	0.37	2.54	1.24–5.20	0.0107	1.17–7.0	2.87	0.0212
Vein occlusion at CT	0.80	2.87	0.60–13.76	0.1880			
Use of neoadjuvant therapy	0.45	0.52	0.21–1.27	0.1537			
Length of resected vein	0.02	1.01	0.98–1.05	0.4375			
Tumor diameter (histology)	0.01	1.00	0.99–1.02	0.6274			
N = 0	0.25	0.41	0.25–0.68	0.0004	0.16–1.40	0.47	0.1751
No. metastatic lymph nodes	0.24	2.16	1.3–3.51	0.0019	0.92–1.16	1.03	0.5863
R = 1	0.26	0.79	0.47–1.31	0.3579			
Perineural invasion = 0	0.31	0.64	0.35–1.18	0.1523			
Microvascular invasion = 0	0.31	0.83	0.45–1.53	0.5479			

Results of univariate and multivariate analysis

SE standard error, *CI* confidence interval, *OR* odds ratio, *N* nodal status according to the American Joint Committee on Cancer (AJCC) TNM staging of Pancreatic Cancer 2010, *N* number, *ASA* American Society of Anesthesiology score, *F* female, *R* resection margin, *CT* computed tomography, *CRP* C reactive protein, *CA 19-9* carbohydratic antigen 19-9

between overall survival and histological venous invasion, and administration of adjuvant therapy.

DISCUSSION

Pancreatic adenocarcinoma with PV and/or SMV invasion is still a matter of debate. Even if case series and meta-analyses have shown the feasibility and suggested the efficacy in terms of postoperative outcomes of pancreatectomy combined with venous resection, some questions are still unresolved and doubts have arisen.[7–10,18,19] Recent studies have focused on the significance of pathological venous invasion on survival, and in May 2015 Okabayashi and colleagues even suggested reconsidering the role of aggressive surgery in patients with venous invasion.[13] In their recent study, they analyzed data of 160 patients undergoing pancreatectomy with venous resection. Median overall survival was 48.0 months in the group without pathological venous invasion and 18.0 months in the group with venous invasion. These results led the authors to question the role of pancreatectomy with combined venous resection.

In this study, we report the analysis of a large series of 406 patients undergoing pancreatectomy combined with PV/SMV axis resection. Our results were interesting. We demonstrated a significant correlation at univariate analysis between preoperative biliary drain and postoperative morbidity. Van der Gaag already had reported the association between preoperative biliary drain and complications in a randomized trial, which included patients submitted to standard pancreaticoduodenectomy.[20] This is the first study to report this finding in patients undergoing pancreatic resection combined with venous resection.

It is well known that a considerable percentage of patients, ranging from approximately 10 to 55 %, has non-dissociable tumor adherence with the PV/SMV axis requiring venous resection but does not have confirmed pathological venous invasion.[9,18] So, we analyzed the correlation between preoperative and pathological factors and histological venous invasion. Venous invasion at CT was the only independent predictive factor of venous invasion, and careful examination of preoperative CT pancreatic protocol remains the best method to predict pathological venous invasion.[21]

TABLE 4 Analysis of prognostic factors: log-rank test and multivariate proportional hazard regression (Cox model) analysis

Log-rank test					Multivariate analysis		
Variable	%	Median OS	5-y OS p (%)	*P*	CI	HR	*P*
Age				0.5268			
<68	47.7	26	22.4				
≥68	52.3	24	26.4				
BMI				0.5851			
<23.1	49.4	28.25	22.0				
≥23.1	50.6	28.5	24.1				
Comorbidity				0.2784			
No	42.1	24	25.4				
Yes	57.9	24	19.0				
CA 19-9				0.3638			
<179	49.4	33.67	24.3				
≥179	50.6	24	21.1				
Tumor diameter at CT				0.6689			
<30 mm	41.0	25.42	14.1				
≥30 mm	59.0	33.67	25.5				
Vein invasion at CT				0.1080			
No	18.3	28.33	24.0				
Yes	81.7	22	11.6				
Vein occlusion				0.0132	0.54–3.85	1.44	0.4668
No	97.1	34	26.5				
Yes	2.9	18	0				
Preoperative biliary drain				0.7609			
No	77.1	24	21.4				
Yes	22.9	25.42	10.7				
Neoadjuvant therapy				0.1221			
No	94.1	24	18.5				
Yes	5.9	75.8	34.2				
Resected vein				0.9966			
VP	52.2	24	22.5				
VMS	26.4	24	17.0				
VP-VMS confluence	21.4	24	17.3				
Resected venous length				0.2644			
<15 mm	45.2	35.25	35.1				
≥15 mm	54.8	28.5	31.6				
Tumor diameter at histology			0.2473				
<30 mm	46.5	26	19.1				
≥30 mm	53.5	22	17.0				
T[a]				0.6746			
T 1	0.9	64	50.0				
T 2	7.1	26	38.5				
T 3	84.9	24	19.3				
T 4	6.8	28	23.6				
Perineural invasion				0.7116			
No	57.6	34	25.4				
Yes	42.4	31	29.4				

TABLE 4 continued

Log-rank test					Multivariate analysis		
Variable	%	Median OS	5-y OS p (%)	*P*	CI	HR	*P*
Microvascular invasion				0.2749			
No	76.1	19	33.9				
Yes	23.9	35	16.5				
Resection margin				0.0621			
R0	72.4	27	24.4				
R+	27.6	22	26.9				
Number of retrieved lymph nodes				0.3360			
<30	48.0	26	27.8				
≥30	52.0	24	21.9				
Number of metastatic lymph nodes				0.0012	0.60-2.33	1.18	0.6279
0–2	55.2	35.25	37.7				
>2	44.8	23	8.4				
N status				0.0003	0.75–4.92	1.92	0.1764
N0	24.4	39	45.4				
N1	75.6	22	14.3				
Histological venous invasion				0.0002	1.34-5.08	2.60	0.0052
No	43.3	33.67	31.7				
Yes	56.7	20	15.5				
Adjuvant chemotherapy				0.0195	1.35–4.89	2.57	0.0041
No	27.8	19	11.2				
Yes	72.2	34	24.8				

Continuous variables are dichotomized around the median value

N number, *SD* standard deviation, *BMI* body mass index, *ASA score* American Society of Anaesthesiology score, *CA 19-9* antigene carboidratico 19-9, *CT* computed tomography, *PV* portal veinm, *SMV* superior mesenteric vein, *ISGPS* international study group of pancreatic surgery, *T* tumor, *N* nodal status, *R* resection margin

[a] patients with in situ tumors excluded

With univariate analysis, we found a significant correlation between venous invasion and lymph nodal diffusion and with preoperative serum albumin value. The presence of nodal metastases and the number of metastatic nodes were significantly associated with venous invasion, corroborating the hypothesis that venous invasion is not only a consequence of the intimate anatomic relationship between the pancreas and the PV/SMV axis, but also a sign of aggressiveness of the disease.[22] In the light of these findings, further studies might add careful preoperative evaluation of radiological nodal status to tumor/vein interface analysis at CT in an effort to better predict the presence of pathological venous invasion. Serum albumin level is an indicator of patients' nutritional status. Preoperative albumin level has been correlated to postoperative complications and to overall survival.[23–25] In this study, we found a significant correlation between pathological venous invasion and preoperative albumin level. Interpretation of this data may further strengthen the hypothesis that pathological venous invasion is a sign of more advanced/aggressive disease, which may be associated to malnutrition.[26] Concerning postoperative outcomes, we observed mortality and morbidity rates comparable to other series.[27–29] Regarding specific complication, acute thrombosis of the reconstructed vein occurred in seven patients (1.7 %), showing that the procedure has specific and potentially serious risks. Despite the nonnegligible rates of mortality and complication, we obtained 5-year survival of 24.4 % months with a median survival of 24 months. These data confirm that pancreatectomy with venous resection is worthwhile in the overall study population. If we analyze survival according to presence of pathological venous invasion, we note 5-year and median overall survival of 33.7 % in patients without pathological venous invasion, significantly higher than in patients without pathological venous invasion (20 % at 5 years). These results confirm the important role of pathological venous invasion as prognostic factors, as reported by

others.[11,12,30–32] However, other studies did not detect the prognostic role of venous invasion, but the small number of included patients limits them.[33,34]

Patients with venous occlusion/thrombosis had worse results: at 5 years survival was 0 % and median survival was 18 months, approaching survival obtained by medical treatment alone, and raising questions about the utility of up-front surgery in this group (only 1 patient with venous occlusion had neoadjuvant therapy, without tumor regression).[35] The other prognostic factors were the use of adjuvant therapy with median survival of 19 months in patients without adjuvant therapy and 34 in those having chemotherapy and parameters of lymph nodal spread: N status and number of metastatic nodes. These factors are well-known prognostic factors in patients submitted to standard pancreatectomy.[36–38] Our results confirm their role in patients undergoing venous resection. At present, the prognostic role of resection margin in patients with borderline resectable tumors was demonstrated only by some studies, whereas in other studies it was not a significant prognostic factor for overall survival. The complex relationship between histologic venous invasion, venous resection, and negative resection margins should be further studied and explained.

The role of neoadjuvant therapy in patients with suspected venous invasion has been questioned.[39–44] In this study, only 5.9 % of patients had neoadjuvant therapy, in accordance with NCCN guidelines until 2014. Potential theoretical benefits of neoadjuvant therapy in patients with borderline resectable tumors are: (1) reduction of tumor volume and subsequent potential increase in R0 rate; (2) early treatment of micrometastases; (3) exclusion from surgery of patients who develop distant metastases or became unresectable; (4) augmentation of the proportion of patients receiving radio or chemotherapy.[39–41] However, on the other side a significant percentage (up to 50–60 %) of borderline resectable patients with pancreatic cancer undergoing neoadjuvant therapy has disease progression and is excluded from surgery, losing the only chance of possible cure.[42,43] Furthermore, the capacity of neoadjuvant therapy to increase R0 rate is still questioned for pancreatic cancer.[44] In this study, only 5.9 % of patients had neoadjuvant therapy. This is in accordance with NCCN guidelines until 2014, which advocated up-front surgery in fit patients with borderline resectable cancers and a high probability to obtain an R0 resection (which was obtained in 72.4 % of our patients, a percentage similar to what is obtained in resectable patients in the literature). Some authors, mainly Kelly and colleagues had even questioned the utility of neoadjuvant therapy in patients undergoing pancreatectomy with venous resection and their study has been the most important among those advocating up-front surgery.[44] They treated 492 patients with pancreatic cancer with up-front surgery, including 70 of them who had venous resection; R0 rate and survival was similar in patients with or without venous resection, and the authors concluded that in case of venous invasion and possibility of safe resection and reconstruction neoadjuvant therapy was not indicated. The last version of NCCN guidelines in 2015 has slightly changed in favor of neoadjuvant therapy, stating that patients with borderline resectable disease have the option of upfront resection (category 2B) with adjuvant therapy or neoadjuvant therapy followed by restaging and resection in patients without disease progression precluding surgery.[45] Although there is no high-level evidence supporting its use, most NCCN members in 2015 prefer an initial approach involving neoadjuvant therapy and for this reason upfront surgery has been downgraded to category 2B. So, we believe that our low rate of neoadjuvant therapy is acceptable considering that the majority of patients were treated before 2014, in the light of the results of the study by Kelly and colleagues and NCCN recommendations.

This study has several limits to be considered: first of all, its retrospective nature. However, data were extracted from prospectively collected databases. Another limit is the lack of analysis of disease-free survival, which was not reported by all centers, and therefore was not taken into account. The latter limit is the length of inclusion period, which may lead to heterogeneity. However, little has changed in surgical techniques, perioperative therapies and adjuvant therapies for pancreatic cancer from 1987 to 2014, so we believe that this bias does not compromise report of postoperative and survival outcomes.

Strengths of the study are the number of included patients, which is remarkable. Furthermore, the use by all centers of the definitions proposed by the ISGPS leads to homogeneity of definitions. We also remark that experienced pancreatic surgeons performed all the procedures with standardized technique.

CONCLUSIONS

The study shows that venous invasion at preoperative CT is related to pathological venous invasion at multivariate analysis. Preoperative biliary drainage and postoperative complications are significantly correlated. Survival results are encouraging with 5-year survival of 24.4 % and median survival of 24 months. Mortality and morbidity are similar to those observed after standard pancreatectomy. The study demonstrates the role of pathological venous invasion as relevant prognostic factors, with 5-year and median survival of 33.7 % and 31.7 months in patients without pathological venous invasion, significantly higher than those of patients without pathological venous invasion (20 % at 5 years and median

of 15.5 months). Other detected prognostic factors were vein occlusion at preoperative CT, lymph nodal involvement, number of metastatic lymph nodes and use of adjuvant therapies.

Our data confirm the feasibility and efficacy of pancreatectomy with combined venous resection and identify predictive factors of venous invasion and prognostic factors, which may help in patients' selection for different treatment protocols. In the future, the role of neoadjuvant therapies should be clarified.

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