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Original Research

Evolution of pancreatectomy with en bloc venous resection for pancreatic cancer in Italy. Retrospective cohort study on 425 cases in 10 pancreatic referral units

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ABSTRACT

Introduction: The aim of this study is to analyze the evolution of pancreatectomy with venous resection in 10 referral Italian centers in the last 25 years.

Methods: A multicenter database of 425 patients submitted to pancreatectomy with venous resection between 1991 and 2015 was retrospectively analyzed. Patients were classified in 5 periods: 1 (1991–1995); 2 (1996–2000); 3 (2001–2005); 4 (2006–2010); 5 (2011–2015). Indications and outcomes were compared according to the period of surgery.

Results: Nineteen patients were operated in period 1, 28 in period 2, 91 in period 3, 140 in period 4, and 147 in period 5. Use of neoadjuvant therapy increased from 0% in period 1 and 2–12.1% in period 5. Postoperative complications ranged from 46.3% to 67.8%, and mortality from 5.3% to 9.2%. Median survival progressively increased, from 6 months in period 1–16 months in period 2, 24 months in period 3 and 4 and 35 months in period 5 ($p = 0.004$). Period, venous and nodal invasion were significant prognostic factors for survival.

Conclusion: Management and outcomes of pancreatectomy with venous resection have evolved in the last 25 years in Italy. Improvement in patients' multidisciplinary management has lead to significant improvement of median survival.

1. Introduction

Pancreatic cancer represents the fourth-leading cause of cancer-related death in the United States. It is estimated that in 2017, 53670 cases of pancreatic cancer will occur with 43090 deaths [1]. In Europe, 103773 new cases were reported in 2012 [2]. Surgical resection represents the only potentially curative treatment for pancreatic adenocarcinoma, with 5-year survival approaching 25% for patients undergoing R0 pancreatectomy [3]. Unfortunately, the majority of patients are not resectable at diagnosis, for locally advanced or metastatic disease [4]. Superior mesenteric vein (SMV) and/or portal vein (PV) invasions are frequent for anatomical reasons, because these vessels are close to the uncinate process and pancreatic head. Patients with venous invasion may undergo potentially curative surgery, combining pancreatic resection with en bloc resection of the PV-SMV venous axis [5]. The feasibility of this approach has been demonstrated by single

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institution series, reviews and meta-analysis, and synchronous venous resection is nowadays a common practice during pancreatectomy [6,7]. Furthermore, the use of neoadjuvant and adjuvant therapies has been demonstrated to ameliorate the long-term survival in these patients [8–10]. The aim of this study is to evaluate the evolution of pancreatectomy with synchronous venous resection in ten Italian pancreatic surgical units. Our hypothesis is that the improvement in multidisciplinary management, use of neoadjuvant therapy, surgical techniques, postoperative management may have improved the long-term survival in this setting.

2. Materials and methods

A multicenter database of patients submitted to pancreatectomy with en-bloc SMV and/or PV resection for pancreatic adenocarcinoma was retrospectively analyzed. All patients undergoing pancreatectomy with synchronous PV or SMV resection for pancreatic cancer were included. Patients with metastatic pancreatic cancer and patients undergoing pancreatectomy with synchronous arterial resections (hepatic artery, celiac trunk, superior mesenteric artery) were not included. The study was a cohort study. Part of these data has been reported in a previous study [4]. Between January 1991 and December 2015, a total of 425 consecutive patients were treated in ten referral Italian academic centers. Last follow-up was performed in December 2017. Collected data included: patients' characteristics, preoperative work-up, preoperative therapies, tumor characteristics, surgical treatment, postoperative outcomes, histological tumor features, postoperative adjuvant therapies and survival. The study was conducted in accordance with the declaration of Helsinki and registered at Researchregistry.com. The work has been reported in line with the STROCSS criteria [11]. Ethical approval was obtained by participating institutions. No protocol was “a priori” published for this study. Sample size calculation was not needed in this type of study. As a quality control, the included centers should have a mean number of retrieved lymph nodes ≥ 10.

2.1. Preoperative work-up 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 work-up included contrast-enhanced thoraco-abdominal 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 (gemcitabine with or without oxaliplatin, Folfirinox) 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.

2.2. 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 [12]. Venous invasion was suspected by preoperative imaging and intra-operatively 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 (venorraphy) 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 [13]. The splenic vein was ligated, or preserved, or ligated and re-implanted 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. All surgeries were performed by experienced academic pancreatic surgeons.

2.3. Definition of clinical outcomes

Postoperative complications were defined according to the ISGPS [14–16]. 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.

2.4. 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 [13].

2.5. Adjuvant therapies and follow-up

Adjuvant chemotherapy (gemicitabine based regimen, with or without cisplatin, with or without oxaliplatin) 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 in the first two years. After two years physical examination, CA 19-9 determination and CT scan were performed every 6 months.

2.6. Periods of surgery

Patients were classified in 5 periods: 1 (from 1991 to 1995); 2 (from 1996 to 2000); 3 (from 2001 to 2005); 4 (from 2006 to 2010); 5 (from 2011 to 2015). Indications, perioperative treatment, results and outcomes were compared according to the period of surgery.

2.7. Statistical analysis

Data were prospectively collected by every center and retrospectively analyzed. Qualitative variables were compared using the chi-square test, while quantitative variables were analyzed using Student's *t*-test and ANOVA. 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).

3. Results

3.1. Patients' characteristics and preoperative treatments

The study population was composed by 239 men (56.2%) and 186 women (43.8%). Mean age was 66.8 years. Nineteen patients were operated in period 1, 28 in period 2, 91 in period 3, 140 in period 4, and

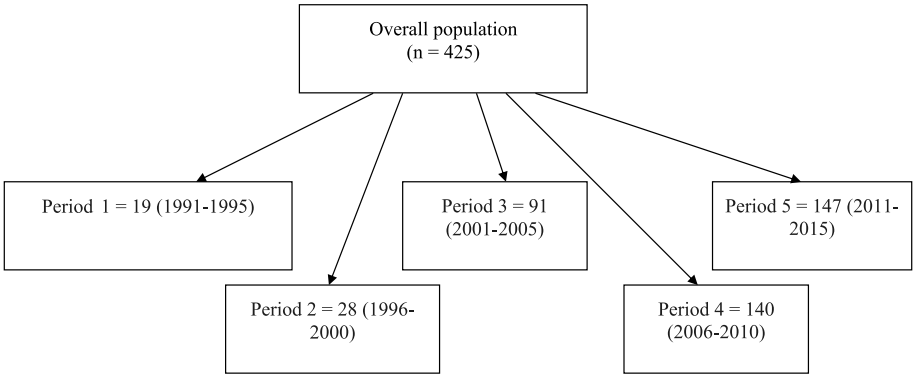

Fig. 1. Overall population undergoing pancreatectomy with synchronous PV or SMV resection, and distribution according to the time frame.

Table 1
Preoperative characteristics and procedures in a series of 425 patients submitted to pancreatectomy with PV or SMV resection for pancreatic adenocarcinoma in Italy according to the period of surgery.

Variable	Period 1	Period 2	Period 3	Period 4	Period 5	p
Number	19	28	91	140	147	
Mean Age, years	65	67.5	66.1	67.8	66.6	0.680
Mean ASA score	2.2	2.3	2.3	2.5	2.4	0.326
Comorbidities	42.1%	60.7%	47.6%	58.3%	64.0%	0.1057
CV comorbidities	15.8%	35.7%	41.7%	51.9%	49.6%	**0.0294**
Respiratory comorbidities	15.8%	7.1%	11.7%	9.5%	11.3%	0.8878
Metabolic comorbidities	15.8%	21.4%	16.4%	33.9%	28.1%	0.0902
Preoperative biliary drainage	10.5%	10.7%	14.3%	26.1%	30.6%	**0.0175**
Neoadjuvant therapy	0%	0%	1.5%	4.6%	12.1%	**0.0057**
Procedure						**0.0064**
PD	73.7%	67.9%	72.5%	82.9%	73.5%	
DP	26.3%	14.3%	23.1%	14.3%	23.8%	
TP	0%	17.8%	4.4%	2.8%	2.7%	
Resected vein						**0.0089**
PV	42.1%	50%	54.3%	52.9%	49.7%	
SMV	47.4%	42.9%	34.3%	26.9%	21.1%	
PV/SMV	10.5%	7.1%	11.4%	20.2%	29.2%	
Mean Operative time, min	625	497.9	487.7	447.9	463.9	0.062

PV, portal vein; SMV, superior mesenteric vein; ASA score, American Society of Anaesthesiology score; CV, cardiovascular; PD, pancreaticoduodenectomy; DP, distal pancreatectomy; TP, total pancreatectomy; min, minutes.
Significant values (< 0.05) are reported in bold.

147 in period 5, as showed in Fig. 1. Patients' characteristics according to the period of surgery are listed in Table 1. The five groups were comparable concerning age, sex, ASA score, and overall comorbidities. The rate of cardiovascular comorbidities was significantly different between the 5 groups, and varied from 15.8% in period 1–51.8% in period 4. Use of neoadjuvant therapy significantly increased during time, ranging from 0% in period 1–12.1% in period 5. Preoperative biliary drainage use was significantly different and increased during time, from 10.5% in period 1–30.6% in period 5.

3.2. Surgery, histological results, and postoperative outcomes

Concerning the type of procedure, pancreaticoduodenectomy was the most frequent, and ranged from 67.9% of cases in period 2–82.9% in period 4, as showed in Table 1.

The percentage of resection of the portal vein, the superior mesenteric vein, or both is listed in Table 1. Resection of the PV/SMV confluence augmented from 10.5% in period 1–29.2% in period 5. A trend for operative time diminution was observed, from 625 min in period 1 to 464 in period 5.

At pathological analysis, a significant difference was detected in tumor size and percentage of T3/T4 tumors, as showed in Table 2. The rates of histologically confirmed venous invasion, nodal invasion and mean number of metastatic nodes were comparable. The mean number of retrieved lymph nodes was significantly different between the 5 periods, and progressively increased from 20.8 to 39.2. The percentage of patients undergoing incomplete resection (R1 or R2) was also significantly different, with a decrease of positive margin from 55.5% in period 1–21.4% in period 5.

Concerning overall morbidity and mortality, no significant differences were detected. Rate of POPF and DGE were different between the 5 groups, as listed in Table 2. Other complications, including thrombosis of the reconstructed vein, were comparable. Hospital stay was similar in the different temporal periods.

3.3. Survival and prognostic factors

Overall median survival was 24 months for the entire cohort, with a 5-year survival of 24%. Survival analysis according to the period of surgery showed a progressive and significant improvement of overall median survival, which ranged from 6 months in period 1–35 months in period 5, as showed in Fig. 2. Log-rank test showed a significant correlation between histological venous invasion, N status, period of surgery and overall survival (Table 3). Survival curves are showed in Figs. 2–4. Multivariate proportional hazard regression analysis confirmed a significant correlation between overall survival and histological venous invasion, N status, and period of surgery.

4. Discussion

Portal vein and/or superior mesenteric vein invasion is a frequent finding in patients with pancreatic cancer. Moore et al., in 1951 [17] and Asada et al., in 1963 [18] reported the first resections and reconstructions of the portal-mesenteric venous axes during pancreatectomy. In 1973, Fortner [19] proposed “regional pancreatectomy”, which involved a systematic resection of the major peripancreatic vessels and soft-tissue clearance, in the effort to improve patients' long-term survival. However, subsequent experiences with this procedure showed no survival benefit, and increase of postoperative morbidity [20]. Therefore, most surgeons started to consider venous invasion as a contraindication to potentially curative pancreatic surgery. In the 1990s, however, several reports have suggested the feasibility with acceptable mortality and morbidity of pancreatectomy combined with portal an/or superior mesenteric vein resection [21–23]. Survival analyses showed comparable outcomes to those observed after pancreatectomy without venous resection [6,21–23]. Venous resections

Table 2
Histological results and postoperative outcomes of 425 patients submitted to pancreatectomy with PV or SMV resection for pancreatic adenocarcinoma in Italy according to the period of surgery.

Variable	Period 1	Period 2	Period 3	Period 4	Period 5	p
Number	19	28	91	140	147	
Mean Tumor size, mm	42.4	50	34.8	34.8	32.5	**0.001**
Mean n. of retrieved nodes	20.8	21.8	22.8	32.8	39.2	**< 0.001**
Mean n. of metastatic nodes	2.9	2.6	3.3	3.4	3.5	0.957
T3/T4 tumors	52.6%	87.5%	93.4%	98.1%	96.2%	**< 0.0001**
N+ patients	73.7%	79.2%	78.1%	77.2%	71.8%	0.8939
Histological venous invasion	57.9%	50%	52.8%	55.1%	60.3%	0.7747
Resection margin invasion	55.5%	60%	37.9%	28.6%	21.4%	**0.0020**
Postoperative Mortality	5.3%	7.1%	9.2%	8.3%	8.3%	0.9841
Overall Complications	52.6%	67.8%	50.6%	46.3%	50%	0.3593
POPF	15.8%	30.8%	12.3%	5.8%	12.6%	**0.0086**
DGE	47.4%	57.7%	35.1%	21.6%	24.4%	**0.0009**
PV-SMV thrombosis	5.2%	3.8%	0%	1.2%	3.3%	0.5234
Mean In hospital stay, days	21.2	21.0	18.7	19.5	20.3	0.783
Median survival, months	6	16	24	24	35	**0.0004**

PV, portal vein; SMV, superior mesenteric vein; mm, millimetres; n., number; T, tumor staging according to the American Joint Committee on Cancer (AJCC) TNM staging of Pancreatic Cancer (2010); N, nodal status according to the American Joint Committee on Cancer (AJCC) TNM staging of Pancreatic Cancer (2010); POPF, postoperative pancreatic fistula; DGE, delayed gastric emptying.
Significant values (< 0.05) are reported in bold.

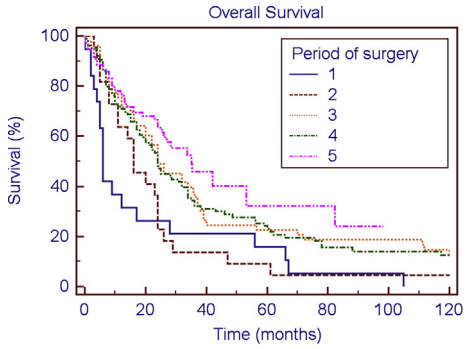

Fig. 2. Overall survival of patients submitted to pancreatectomy with en-bloc venous resection according to the period of surgery.

have nowadays become part of the routine practice of pancreatic surgeons, accounting for approximately 10–20% of cases in referral centers [24,25]. Patients with tumor contact with the SMV or PV at imaging are defined as resectable or borderline resectable according to NCCN guidelines, unless the infiltrated venous segment cannot be resected and reconstructed safely [26]. The evolution of surgical indications for tumor with venous invasion has been gradual, and advancements in imaging, perioperative managements, surgical techniques, perioperative treatments have play a role in increasing the safety of venous resection, and the survival results. In this article, we analyze the experience of ten Italian referral centers from 1990 to 2015, comparing patients' characteristics and results according to the period of surgery. Our objective has been to evaluate if the improvement in multidisciplinary management, use of neoadjuvant therapy, surgical techniques, postoperative management may have ameliorated the long-term survival in this setting.

Concerning the characteristics of the patients, with did not find significant differences in age, ASA score and overall comorbidities, even if the percentage of patients with cardiovascular comorbidities increased in the latter 3 periods. Use of preoperative biliary drainage significantly and gradually increased during time. Neoadjuvant therapy was not administered at the beginning of the experience, and rose to 12.1% of cases in the latter 5-year period from 2011 to 2015. Even if not significant, a trend versus better survival for patients having neoadjuvant therapy was noted (median survival, 24 versus 36 months), and neoadjuvant therapy may have contributed to improvement of survival outcomes during time. The reported rate of neoadjuvant therapy administration is in accordance with NCCN guidelines until 2014 [26], which advocated up-front surgery in fit patients with borderline resectable cancers and a high probability to obtain an R0 resection. In 2015, NCCN experts have 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 [26]. 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. The last version of NCCN guidelines states that although there is no high-level evidence supporting its use, most NCCN Member Institutions now prefer an initial approach involving neoadjuvant therapy, as opposed to immediate surgery, for patients with borderline resectable disease [26]. Actually, upfront resection in patients with borderline resectable disease is no longer recommended, as of the 2016 version of these guidelines. Potential theoretical benefits of neoadjuvant therapy in patients with venous invasion are [27–31]: 1) reduction of tumor volume with subsequent potential increase in R0 rate; 2) precocious treatment of micro-metastases; 3) avoid surgery for patients who develop distant metastases or became unresectable; 4) augmentation of the proportion of patients who receive radio or chemotherapy. On the other side it should be underlined that a significant percentage (up to 50–60%) of patients with pancreatic cancer undergoing neoadjuvant therapy has disease progression and will not receive surgery [32,33]. Furthermore, the capacity of neoadjuvant therapy to increase R0 rate is still questioned for pancreatic cancer [34].

Concerning the resected vein segment, it is interest to remark that the rate of resection of both the PV and SMV (venous confluence) significantly increased during time, from 10.5% to 29.2%, which is probably related to advancements in surgical experience and techniques. A trend for diminution of operative time was also noted.

Looking at histological results, we highlight the significant augmentation of complete resection along time, with a gradual R1 rate diminution from 55.5% in period 1–21.4% in period 5, probably linked to several factors, such as patients' selection, increased surgical experience, preoperative therapies. A negative resection margin was associated with a trend for better median survival (26 versus 22 months), even if this result was not significant. Furthermore, a significant and consistent augmentation of the number of retrieved nodes, which is considered an indicator of quality of surgery [35] has been demonstrated, related in our opinion to wider lymphadenectomy (quality of

Table 3
Analysis of prognostic factors: log-rank test and multivariate proportional hazard regression (Cox model) analysis. Continuous variables are dichotomized around the median value.

Log-rank test				Multivariate analysis			
Variable	%	Median OS	5-yOS (%)	p	CI	HR	p
Age				0.5811			
< 68	48.2	26	21.8				
≥68	51.8	24	26.2				
Comorbidity				0.3961			
No	40.4	24	24.2				
Yes	59.6	24	19.2				
Tumor diameter				0.1678			
< 30 mm	33.2	27	20.1				
≥30 mm	66.8	23	16.5				
Vein invasion				**0.0001**	**1.34–2.45**	**1.8**	**0.0001**
No	44.4	33.7	31.6				
Yes	55.6	21	16				
Preoperative biliary drain				0.7544			
No	74.4	24	20.9				
Yes	25.6	25.42	10.7				
Neoadjuvant therapy				0.1514			
No	94.2	24	18				
Yes	5.8	36	33.2				
Resected vein				0.9728			
PV	48.7	24	22.6				
SMV	30.3	24	16.5				
PV-SMV	21.0	24	14.2				
Confluence							
T3/4				0.2007			
No	7.7	56	46.4				
Yes	92.3	24	19.8				
Resection margin				0.8751			
R0	70.4	26	24.3				
R+	29.6	22	23.6				
Number of retrieved lymph nodes				0.8807			
< 30	46.7	25.4	25.9				
≥30	53.3	24.2	23.2				
N status				**0.0001**	**1.08–2.24**	**1.56**	**0.0170**
N0	26.1	39	45.7				
N1	73.9	22	14.2				
Period				**0.0004**	**0.67–0.85**	**0.75**	**< 0.0001**
1	4.5	6	15.8				
2	6.6	16	9.1				
3	21.4	24	22.6				
4	32.9	24	23				
5	34.6	35	32.1				

PV, portal vein; SMV, superior mesenteric vein; T, tumor staging according to the American Joint Committee on Cancer (AJCC) TNM staging of Pancreatic Cancer (2010); N, nodal status according to the American Joint Committee on Cancer (AJCC) TNM staging of Pancreatic Cancer (2010); R, resection margin; mm, millimeters.
Significant variables at multivariate analysis are reported in bold.

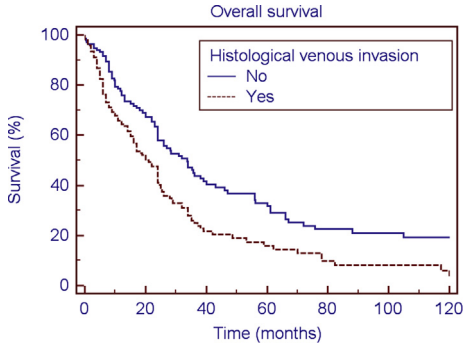

Fig. 3. Overall survival of patients submitted to pancreatectomy with en-bloc venous resection according to histological venous invasion.

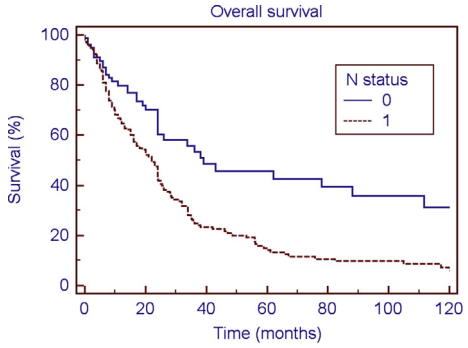

Fig. 4. Overall survival of patients submitted to pancreatectomy with en-bloc venous resection according to nodal status defined according to the American Joint Committee on Cancer (AJCC) TNM staging of Pancreatic Cancer (2010).

surgery) and better pathological analysis (quality of pathological analysis). Concerning postoperative outcomes, no significant differences in postoperative mortality or overall complications were found. However, the rate of postoperative pancreatic fistula and delayed gastric emptying were significantly different, with a diminution in the latter periods. We explain these data with increase of surgical experience, as for surgical margins and lymphadenectomy. The most remarkable

results concern postoperative survival. Actually, survival significantly improved during time, starting from a median survival of 6 months in period 1–35 months in period 5. These data are encouraging and reflects the efficacy of the efforts done to ameliorate management of pancreatic cancer with venous involvement. Concerning prognostic factors, period of surgery was significantly associated with survival at univariate and multivariate analysis. We believe that several aspects played a role in this improvement, including preoperative treatments, such as administration of neoadjuvant therapy or wider use of biliary drainage if indicated, better surgical techniques, with better tumor clearance, improvement in postoperative management. Histological venous invasion and nodal invasion were found to be significantly associated with worst survival, also. Several recent studies have focused on the significance of pathological venous invasion on survival, and Okabayashi and colleagues have even suggested to re-considerate the role of aggressive surgery in patients with venous invasion [36]. 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 lead the authors to question the role of pancreatectomy with combined venous resection. In our population, we demonstrated medial survival of 33.7 months in patients without pathological venous invasion, significantly higher than in patients without pathological venous invasion (21 months). Our results confirm the important role of pathological venous invasion as prognostic factors, as reported by others [37–39]. Patients with nodal disease had also significantly lower survival, confirming the well-known prognostic role of nodal metastases [40].

4.1. Limits

This study has several limits to be considered: first of all, its retrospective nature, which may represent a potential source of bias in retrieving relevant data. Furthermore, the inclusion period is long, and may include heterogeneous patients undergoing heterogeneous treatment protocols. Also the vascular resection techniques and the surgeons' experience in this setting evolved during this time frame. However, the main aim of the study is to show the amelioration of the results during time, and for this reason a long time frame was necessary. Whereas the patients' overall survival was reported by all centers, data on disease-free survival and type of recurrence were lacking for the majority of patients. We considered that retrieval of these data retrospectively would be a potential source of major bias, considering the large inclusion period, and considering that not all centers had a data collection system covering the whole inclusion period. Strengths of the study are the number of included patients, which is remarkable. Furthermore, all included centers are referral centers for pancreatic surgery.

5. Conclusions

The study shows that pancreatectomy with combined venous resection for pancreatic cancer has evolved in Italy during the last 25 years. Preoperative management has changed, with a more frequent use of neoadjuvant therapy and preoperative biliary drainage. The rate of complete resections and the number of retrieved nodes has increased, in line with advancements of surgical techniques. Median survival gradually increased from 6 months at the beginning of the experience to 35 months in the latter period. Period of surgery, nodal involvement and histological vein invasion were significant prognostic factors at multivariate analysis.

Our results are encouraging and highlight the evolution of pancreatectomy with venous resection in Italy. Increase of multidisciplinary management and experience at referral centers may lead to further improvement of survival in this setting.

Conflicts of interest

No conflicts of interests.

Funding

No founding was received.

Ethical approval

Ethical approval was obtained by participating institutions.

Research registration unique identifying number (UIN)

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Author contribution

GN, NP, GR have made substantial contributions to conception and design, acquisition of data, analysis and interpretation of data; 2) have been involved in drafting the manuscript and revising it critically for important intellectual content; 3) have given final approval of the version to be published; and 4) agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

ADP, MR, EJ, FM, GLG, PC, GB, GT, FF, LDC, NN, UB have made substantial contributions to acquisition of data, analysis and interpretation of data; 2) have been involved in revising the manuscript critically for important intellectual content; 3) have given final approval of the version to be published; and 4) agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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