Mesenterico-portal vein resection in patients with pancreatico-duodenal cancer is safe and may increase survival

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ABSTRACT

INTRODUCTION: Pancreatic cancer is one of the most serious gastrointestinal cancers, and in the US and Europe it is a leading cause of cancer-related mortality. Radical surgery is the only option available for long-term survival. The aim of this study was to describe the surgical technique and the results of portal vein/superior mesenteric vein resection in patients with pancreatic cancer.

MATERIAL AND METHODS: Between 1 April 2009 and 1 April 2013, 354 patients underwent resection for pancreatic malignancy. A total of 47 portal vein/superior mesenteric vein resections were performed in 22 men and 25 women.

RESULTS: A total of 44 patients (93.7%) had ductal adenocarcinomas. In all, 39 patients (83%) had T3 tumours, and 38 patients (80.9%) had involvement of lymph nodes. Furthermore, 29 patients (62%) had a pancreatico-duodenectomy, 15 patients (32%) a total pancreatectomy and three patients (6%) had a distal pancreatectomy. Six patients (17%) were reconstructed with interposition grafts, and vessels (83%) were reconstructed with an end-to-end anastomosis in the remaining 39 patients. Surgical morbidity was 29.8%, and 19.1% had non-surgical complications. The perioperative mortality (30 days) was 0%. The median survival was 25.2 months (confidence interval: 19-31.4).

CONCLUSION: Resection of the portal vein/superior mesenteric vein is a safe procedure. It is not associated with an increased perioperative morbidity and mortality. This latter finding is in accordance with the findings in other high-volume centres. The median survival was far better than expected, especially since our material included a considerable number of patients with lymph node metastases.

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Pancreatic cancer is one of the most serious gastrointestinal cancers, and in the United States and Europe it is the fourth and sixth leading cause of cancer-related mortality, respectively [1, 2]. Radical surgery is the only curative option available. However, only 15-20% of tumours are resectable as the majority of patients will either have locally advanced disease or distant metastases at diagnosis [3]. While metastatic disease is defined according to the tumour-node-metastasis (TNM) classification, there is no consensus on the definition of locally advanced disease. It is generally accepted that tumours involving more than 180° of the circumference of the superior mesenteric artery or celiac trunk are locally advanced and may be technically resectable [4]. However, these patients usually do not become long-term survivors [5]. Since more than 75% of malignant pancreatic tumours are found in the head of the pancreas, the majority of tumours will have a close relation to the adjacent vessels, which may result in tumour infiltration of the mesentericoportal transition. In the past, the involvement of the veins was regarded a sign of non-resectability, but in recent years several high-volume centres have published data which show that neither mortality nor morbidity is increased when resection of the portal vein/superior mesenteric vein (PV/SMV) is performed along with the tumour-bearing part of the pancreas [6-8]. At the same time, there is growing agreement that venous involvement is not necessarily a sign of locally advanced disease but rather a result of the anatomical location of the tumour in relation to the vessels [9]. Furthermore, recent studies have shown that long-term survival after PV/SMV resection is not different from survival in patients who did not undergo PV/SMV resection if clear resection margins could be achieved [8, 10].

Resection of the PV/SMV was first performed systematically in the 1970s by Fortner, who at that time advocated a very aggressive approach to surgery for pancreatic cancer [11]. The aggressive technique, however, came into disrepute due to high perioperative morbidity and mortality. Development of new surgical techniques and advances in intensive therapy has today reduced the perioperative morbidity and mortality.

Because of the lack of an effective adjuvant oncological treatment, most high-volume centres now routinely offer PV/SMV resections.

In Denmark, the incidence of pancreatic cancer is approximately 900 cases per year. 20% of the patients are candidates for surgery, while 40% have non-resectable tumours or are not operable due to their medical condition at the time of diagnosis [12]. The remaining 40% or about 350 patients have various degrees of lo-

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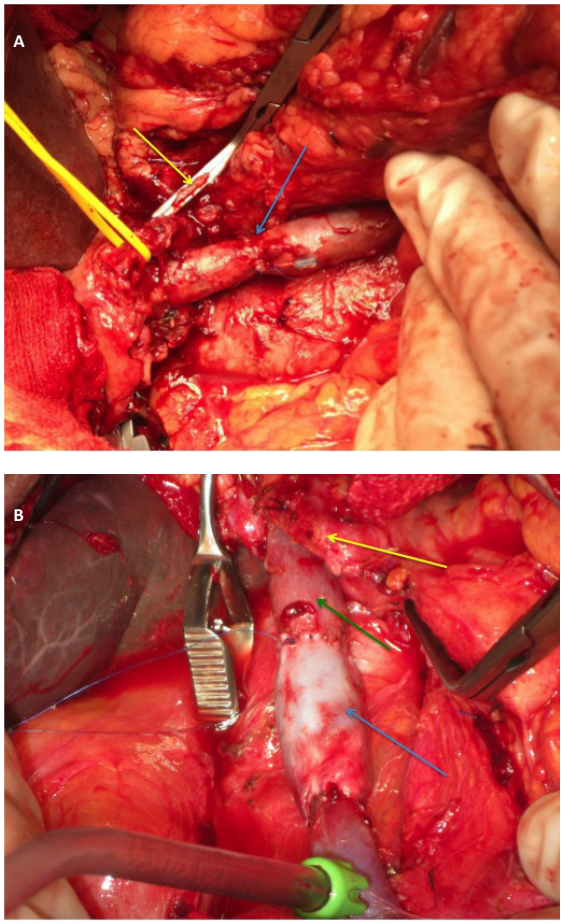
FIGURE 1



A. Portal vein/superior mesenteric vein resection with direct end-to-end anastomosis at site of resected portal vein/superior mesenteric vein. Blue arrow = end-to-end anastomosis. Yellow arrow = vascular clamp on splenic vein. Yellow band around common hepatic artery. **B.** Portal vein/superior mesenteric vein resection with interposition graft. Green arrow = portal vein. Blue arrow = interposition graft. Bulldog clamp on transected hepatic duct. Yellow arrow = common hepatic artery.

cally advanced disease, a major part of them with PV/SMV involvement.

According to several new studies, the patients of this group are candidates for resection [6-8, 10].

The purpose of this survey was to describe the surgical technique and results of PV/SMV resection in patients with pancreatico-duodenal cancer in the first large Danish material from a single high-volume tertiary referral centre for pancreatic surgery.

MATERIAL AND METHODS

Between 1 April 2009 and 1 April 2013, 354 patients had pancreatico-duodenal resections for malignant disease in our institution. A total of 47 (13.3%) patients had resection of either the portal vein, the mesentericoportal confluence, the superior mesenteric vein or a combination of these resections.

Resectability was evaluated at our multidisciplinary team conference in the presence of radiologists, nuclear physicians, oncologists and surgeons. For all patients, diagnostic imaging included a three-phase multi-detector-row computed tomography and, if needed, supplementary magnetic resonance imaging and/or positron emission tomography-computed tomography. The surgeon and an anaesthetist evaluated the operability of patients with resectable tumours. Biliary obstruction was alleviated before the operation by endoscopic retrograde biliary drainage or percutaneous transhepatic cholangiography-guided drainage.

The preoperative risk assessment was graded according to the American Society of Anesthesiologists (ASA) classification. Operation time, perioperative blood loss and post-operative hospital stay were recorded. Post-operative complications were divided into surgical and nonsurgical complications. Major surgical complications comprised pancreatic or biliary leakage, bleeding and intra-abdominal abscess. Minor surgical complications included delayed gastric emptying, cholangitis, chylous ascites, and wound infection and dehiscence. Nonsurgical complications such as pneumonia were defined as complications that occurred during hospital stay or within 30 days from surgery. Perioperative death was defined as deaths occurring during hospitalization and/or within 30 after surgery. Events related to survival were measured from the time of surgery. Hospital stay was defined as stay in our institution until discharge to the patients' own home.

TNM status (T: size of tumour, N: lymph node status and M: distant metastases) was classified according to the AJCC 2010 cancer manual [13]. The resection margin status (R-status) was evaluated according to the general recommendations by Verbeke et al, where R0 and R1 were defined as a resection margin of > 1 mm or ≤ 1 mm from the tumour respectively [14].

Events related to survival were measured from the time of surgery. Data are expressed as medians (interquartile range). Kaplan-Meier estimations were used to analyse the overall survival. Patients alive at the last follow-up were censored. Survival analysis was performed using IBM SPSS version 20 for Mac (IBM Corporation, New York).

Operative technique

After thorough exploration and intraoperative ultrasound, a wide Kocher's manoeuvre was performed. All procedures were performed as "artery first" [15] in which the superior mesenteric artery (SMA) was dissected to rule out tumour invasion. This allowed the posterior resection margin to be freed from the SMA. This facilitated that the entire dissection could be performed before the PV/SMV was divided in order to keep the venous stasis ("clamp time") of the gut as short as possible. This technique also facilitated a "no-touch" approach to prevent dissemination of tumour cells into the portal circulation. The venous reconstruction was performed primarily with

an end-to-end anastomosis or by a bridging raft (donor vein or the patient's own umbilical vein), see **Figure 1**.

When pancreatico-duodenectomy (PD) was performed, reconstruction of the intestinal continuity was restored with all anastomoses on the same jejunal loop.

Apart from general thrombosis prophylaxis with low-molecular heparin from the evening before surgery, patients were not anticoagulated during surgery.

Trial registration: not relevant.

RESULTS

A total of 47 PV/SMV resections were performed in 22 (47%) men and 25 (53%) women. Of the 47 enrolled patients, 44 (93.7%) had ductal adenocarcinomas. For more tumour characteristics, see **Table 1**. Partial resection of the vein wall was never performed. Six vessels were reconstructed with interposition grafts from deceased donors and two by using the patient's own umbilical vein (Figure 1). The remaining 39 vessels (83%) could be reconstructed with an end-to-end anastomosis. The median clamp time was 11 min. (range 5-28 min.). This never resulted in visible oedema of the bowel (Table 1).

A total of 29 patients (62%) had a PD, 15 patients (32%) a total pancreatectomy (TP) and three patients (6%) a distal pancreatectomy (DP). Two of the three patients who had a DP had concomitant resection of the coeliac trunk; both patients had tumour invasion into the common hepatic artery without invasion of the coeliac trunk (confirmed by frozen section microscopy). In both cases, the arterial blood supply to the stomach could be preserved due to sufficient collateral perfusion via the gastroduodenal artery. All DP and TP patients underwent splenectomy. In addition, seven patients (14.9%) had multiple organ resections because of tumour invasion. Three patients with TP had a total gastrectomy with oesophagojejunostomy and one DP patient had a partial gastric resection. All patients with DP and two with TP underwent left-adrenalectomy. Four patients (two DP, one TP, and one PD) had an extended right hemicolectomy due to transverse colon invasion.

There were no perioperative deaths. The average hospital stay was 11.4 days (range 6-26) (**Table 2**). Three patients were re-operated: one on suspicion of PV thrombosis, which was not found; one because of late erosion bleeding after a dehiscent pancreatico-jejunostomy where angiographic coiling failed, and the last patient due to ischaemia of the transverse colon.

Fifteen patients (32%) died during the median 11.9-month observation period, the median survival was 25.2 months (confidence interval (CI): 19-31.4) (**Figure 2**). Five patients (11%) did not receive adjuvant chemotherapy, and the remaining 42 (89%) completed chemotherapy.

TABLE 1

Tumour characteristics and post-operative complications.

	n	%	Size, cm, median (range)
Pathology			
Histology			
Adenocarcinoma: papilla of Vater	1	2.1	
Adenocarcinoma: duodenum	1	2.1	
Adenocarcinoma: common bile duct	1	2.1	
Ductal adenocarcinoma: head	35	74.5	
Ductal adenocarcinoma: body	6	12.8	
Ductal adenocarcinoma: tail	3	6.4	
Tumour size			4.4 (0.5-35)
T1	0	0	
T2	6	12.8	
T3	39	83	
T4	2	4.3	
N0	9	19.1	
N1	38	80.9	
M0	46	97.9	
M1	1	2.1	
No vascular invasion	17	36.2	
Vascular invasion	30	63.8	
R0	43	91.5	
R1	4	8.5	
Complications			
Perioperative mortality	0	0	
Surgical complications	14	29.8	
Non-surgical complications	9	19.1	
Surgical complications			
Leak pancreatico-jejunostomy	2	4.3	
Leak hepatico-jejunostomy	2	4.3	
Intra-abdominal abscess	4	8.5	
Sepsis	3	6.4	
Bleeding	1	2.1	
Wound infection	3	6.4	
Delayed gastric emptying	5	10.6	
Wound dehiscence	2	4.3	
Non-surgical complications			
AMI/heart failure	3	6.4	
Pneumonia	4	8.5	
Pulmonary embolism	1	2.1	
Respiratory depression	1	2.1	
Kidney failure	4	8.5	

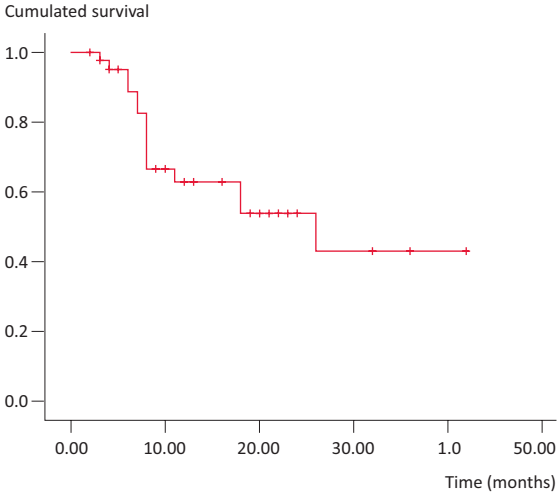
AMI = acute myocardial infarction.

DISCUSSION

It has been a common opinion that PV/SMV involvement is an expression of aggressive tumour biology resulting in undetectable synchronous micrometastases at diagnosis with resulting poor prognosis [16]. A meta-analysis from 2006 concluded that patients who underwent PV/SMV resection had a poor survival. This was explained by aggressive tumour biology since a high rate of N1 patients (67.4%) was observed. This resulted in a high risk of synchronous metastasis when the PV/SMV was in-

FIGURE 2

Kaplan-Meier plot of survival after PV/SMV resection.



PV = portal vein; SMV = superior mesenteric vein.

volved. The study, therefore, concluded that PV/SMV resections could not be recommended. Recent studies, however, are leaning more towards the view that venous involvement is rather an expression of tumour size and anatomical localization than of aggressive tumour biology [9, 10, 17]. Immunohistochemical studies of the presence of tumour cells in the regional lymph nodes and in the bone marrow have been shown to correlate with disease-free survival [18, 19]. A recent study found a good correlation between the detection of micro-metastases in lymph nodes and bone marrow and overall survival. There was, however, no correlation between the anatomical relation of tumour and the portomesenteric veins and the presence of micro-metastases. It was, therefore, concluded that tumour location resulted in perivascular growth and infiltration, and patients who had PV/SMV resections did not have a prognosis different from that of patients who did not, provided an R0 resection was achieved [9]. This is partly confirmed by our study. Although 80.9% of our patients had local lymph node metastases (N1), the survival was 25.1 months, which is far more than expected compared with the median 13-month survival in Siriwardana & Siriwardena's 2006 meta-analysis with an N1 rate of 67.4% [16].

When the perioperative evaluation of vein involvement was compared with the final histologic examination, 30 of our patients (63.8%) had invasion of the vascular wall, whereas 17 (36.2%) did not have histological evidence of tumour invasion. It is widely accepted that the perioperative distinction between inflammatory adhesions and true tumour infiltration is difficult or even impossible [8]. The consequence of PV/SMV resection in patients without invasion of the veins was investigated in a recent French study of 78 consecutive patients who routinely underwent PV/SMV resection when a PD or TP was performed. The study showed that patients without venous invasion had a significantly better survival than a matched control group of patients without venous infiltration [20].

We did not perform wedge resections, since this procedure has shown poor results with a high frequency of tumour-positive resection margins compared with complete resections [4, 17].

Several studies have shown that if an R0 resection is achieved, long-term survival of patients who have a PV/SMV resection is not different from that of patients without vascular resection [9, 10, 16].

PV/SMV resection can usually be performed with a low mortality and morbidity. Studies from high-volume centres have shown that mortality varies between 1.2 and 6.3% [10, 16].

A mortality rate of zero in our series was noteworthy given that several patients underwent multiple organ resections. Operating time was shorter and the amount of bleeding was lower than previously described [8, 10, 17]. The median hospital stay was 11.4 days which concurs with previously published studies [8, 17]. The total rate of complications was 48.9%, of which 29.8% were surgical complications. This also corresponds well with previous studies [10, 16].

In the present study, the median survival was 25.2

TABLE 2

Patient characteristics and intra-operative data.

Patients	
Male, n (%)	22 (46.8)
Female, n (%)	25 (53.2)
Age, years, average (range)	63.7 (40-84)
ASA score, n (%)	
1	7 (14.9)
2	22 (46.8)
3	16 (34)
4	2 (4.3)
Hospital stay, days (range)	11.4 (6-26)
Operation	
PD, n (%)	29 (61.7)
TP, n (%)	15 (31.9)
DP, n (%)	3 (6.4)
Operation time, min. (range)	288 (175-489)
Blood loss, ml (range)	536 (200-1,600)
Clamp time, min. (range)	11 (5-28)
Reoperation, n (%)	3 (6)

ASA = American Society of Anesthesiologists; DP = distal pancreatectomy; PD = pancreatico-duodenectomy; TP = total pancreatectomy.

months. This is higher than the survival established in a recent meta-analysis in which the median survival was 13-22 months [10]. The rather large tumour size in our material could explain the high number of patients with lymph node metastases (80.9%), but this did not seem to have a negative impact on median survival. The favourable survival could instead be owed to a high degree of free resection margins (91.5% R0) resulting in a better clearance of tumour and positive lymph nodes when using novel artery first techniques. The relatively high number of total pancreatectomies (31.9%) may also have contributed to this.

However, the high median survival should be interpreted with caution since the median observation time was 11.9 months, which is relatively short. Nevertheless, the results are encouraging.

CONCLUSION

We found that resection of the PV/SMV is a safe procedure without increased perioperative morbidity and mortality in accordance with the findings in other high-volume centres. The median survival was far better than expected, especially since our material had a high number of patients with lymph node metastases.

Surgery for locally advanced pancreatic cancer is a highly specialised task that should only be handled in a high-volume centre [4].

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