World J Surg
DOI 10.1007/s00268-013-2283-3

World Journal of Surgery

Preparing for Prospective Clinical Trials: A National Initiative of an Excellence Registry for Consecutive Pancreatic Cancer Resections

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Abstract

Background Despite significant improvements in perioperative mortality as well as response rates to multimodality treatment, results after surgical resection of pancreatic adenocarcinoma with respect to long-term outcomes remain disappointing. Patient recruitment for prospective international trials on adjuvant and neoadjuvant regimens is challenging for various reasons. We set out to assess the preconditions and potential to perform perioperative trials for pancreatic cancer within a well-established Austrian nationwide network of surgical and medical oncologists (Austrian Breast & Colorectal Cancer Study Group).

Methods From 2005 to 2010 five high-volume centers and one medium-volume center completed standardized data entry forms with 33 parameters (history and patient related data, preoperative clinical staging and work-up, surgical details and intraoperative findings, postoperative complications, reinterventions, reoperations, 30-day mortality, histology, and timing of multimodality treatment). Outside of the study group, in Austria pancreatic resections are performed in three "high-volume" centers (>10 pancreatic resections per year), three "medium-volume" centers (5–10 pancreatic resections per year), and the rest in various low-volume centers (<5 pancreatic resections per year) in Austria. Nationwide data for prevalence of and surgical resections for pancreatic adenocarcinoma were contributed by the National Cancer Registry of Statistics of Austria and the Austrian Health Institute.

Results In total, 492 consecutive patients underwent pancreatic resection for ductal adenocarcinoma. All postoperative complications leading to hospital readmission were treated at the primary surgical department and documented in the database. Overall morbidity and pancreatic fistula rate were 45.5 % and 10.1 %, respectively. Within the entire cohort there were 9.8 % radiological reinterventions and 10.4 % reoperations. Length of stay was 16 days in median (0–209); 12 of 492 patients died within 30 days after operation, resulting in a 30-day mortality rate of 2.4 %. Seven of the total 19 deaths (36.8 %) occurred after 30 days, during hospitalization at the surgical department, resulting in a hospital mortality rate of 3.9 % (19/492). With a standardized histopathological protocol, there were 70 % (21/30) R0 resections, 30 % (9/30) R1 resections, and no R2 resections in Vienna and 62.7 % (32/51) R0 resections, 35.3 % (18/51) R1 resections, and 2 % (1/51) R2 resections in Salzburg. Resection margin status with nonstandardized protocols was classified as R0 in 82 %

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Published online: 12 October 2013

(339/411), R1 in 16 % (16/411), and R2 in 1.2 % (5/411). Perioperative chemotherapy was administered in 81.1 % of patients (8.3 % neoadjuvant; 68.5 % adjuvant; 4.3 % palliative); chemoradiotherapy (1.6 % neoadjuvant; 3 % adjuvant; 0.2 % palliative), in 4.9 % of patients. The six centers that contributed to this registry initiative provided surgical treatment to 40 % of all Austrian patients, resulting in a median annual recruitment of 85 (51–104) patients for the entire ABCSG-group and a median of 11.8 (0–38) surgeries for each individual department.

Conclusions Surgical quality data of the ABCSG core pancreatic group are in line with international standards. With continuing centralization the essential potential to perform prospective clinical trials for pancreatic adenocarcinoma is given in Austria. Several protocol proposals aiming at surgical and multimodality research questions are currently being discussed.

Introduction

Perioperative mortality of pancreatic resection has improved dramatically in recent decades. An analysis of a consecutive series of pancreatoduodenectomies at Johns Hopkins revealed a decrease in postoperative mortality from 30 % in the 1970s to 1 % in the 2000s [1]. In concordance, nationwide and regional surveys on outcome quality of pancreatic surgery in the United States found similar results. For example, in-hospital mortality dropped from 7.8 to 4.6 % in the past decade, and in a report from Europe (Netherlands) for the same time period, it decreased from 24.4 to 3.6 % [2, 3]. Surgical quality of pancreatic resection has been addressed by numerous studies and reviews since the 1990s. Continuing improvement in surgical technique, perioperative intensive care, management of complications, and a documented correlation between high case load and low perioperative mortality causing a trend to centralize pancreatic surgery, are believed to be underlying factors of this success [4–6]. In contrast to the significant decrease of perioperative mortality; however, no decisive improvement could be achieved with respect to oncologic outcome, especially overall survival. To date, the largest published phase III trial in pancreatic adenocarcinoma on adjuvant therapy following resection reporting 5-year survival is the ESPAC-1 trial, recruiting 289 patients with 8–21 % survival rates, depending on the assigned therapy [7]. Not only survival rates remained disappointing, there is also an obvious problem in patient recruitment to prospective clinical trials. The more recent ESPAC-3 trial included 1,088 patients, but 159 centers and a recruitment period of seven years were necessary [8]. There is clearly a need for large, interdisciplinary trials of new adjuvant or neoadjuvant regimens. Because of the high numbers of patients needed, these trials should optimally be conducted in an international multi-center setting; however, this has not yet been successfully established. A reasonable alternative could be to establish national study groups, comprising high-volume centers of pancreatic surgery in a given country. This might be easier in conducting studies due to shorter distances, similar legal requirements, and easier communication, but obviously limits the number of patients available for recruitment. Indeed, only a few nationwide groups have performed oncologic studies in pancreatic cancer. Within Europe, the Netherlands and France are pioneers, publishing relevant studies on oncologic survival and surgical technique in the field of pancreatic cancer [3, 9]. Basic requirements for such trials are comparable perioperative surgical results among centers in accordance with international quality criteria.

Especially in a small country like Austria, concentration of scientific resources is an absolute requirement to achieve essential results. The Austrian Breast and Colorectal Cancer Study Group (ABCSG) has established a nationwide network, enabling the group to conduct large oncologic trials, particularly in breast cancer [10–12]. Overall, more than 23,000 patients have been recruited to prospective randomized ABCSG trials so far. The obvious need for trials targeting pancreatic cancer led to the foundation of a Pancreas Task Force within the ABCSG. The initial initiative of this group was to start cooperation among the few departments specialized in pancreatic surgery in Austria. A Pancreas Registry was built up with the aim to assess perioperative surgical results and estimate possible patient recruitment for future Austrian studies in pancreatic adenocarcinoma.

Patients and methods

The new ABCSG registry consists of six center series of consecutive patients undergoing pancreatic resections for pancreatic adenocarcinoma from 2005 to 2010 ($n = 492$).

Five of six recruiting centers were high volume; one was medium volume according to common definitions [4, 6, 13]. In Austria, outside of our study group, pancreatic resections are performed in three high-volume centers (>10 pancreatic resections per year), three medium-volume centers (5–10 pancreatic resections per year), and, the rest, in low-volume centers (<5 pancreatic resections per year).

The present study was conducted according to the institutional review board regulations of the participating centers. Major points of investigation are reintervention and reoperation rates [14], 30-day mortality, resection margin status, center caseload, and data quality. At two centers prospectively maintained databases for all parameters have

already been implemented (Vienna 1993, Linz 2001), at two centers there were prospective databases, although some parameters were collected retrospectively (Innsbruck 1989, Salzburg 2007), and at the other centers (Graz, Wiener Neustadt) all data were collected retrospectively. All centers completed standardized Excel (Microsoft Inc.) spreadsheets with $n = 33$ parameters, including history and patient-related data (gender, age, diabetes, chronic pancreatitis, icterus), preoperative clinical staging, and work-up (computed tomography [CT] scan, magnetic resonance imaging scan [MRI], endoscopic ultrasound, endoscopic retrograde cholangiopancreatography [ERCP], biopsy, biliary drainage), surgical details and intraoperative findings (vascular resection, technique of anastomosis, diameter of pancreatic duct, quality of pancreatic tissue, stenting of pancreatic duct), postoperative complications, reinterventions, reoperations, 30-day mortality, histological work-up (pTNMLV), R classification according o the 7th Edition of the American Joint Cancer Commission (AJCC) Cancer Staging Manual, and timing of multimodality treatment (chemoradiotherapy, chemotherapy).

Data sets from all centers were collected and reviewed for completeness, and missing parameters were completed whenever possible. Finally, data sets were joined to form a single database, which was analyzed retrospectively.

Austrian Data for total annual incidence of and resections for pancreatic adenocarcinoma were contributed by the National Cancer Registry of Statistics Austria and the Austrian Health Institute (Gesundheit Österreich GmbH; DI Dr. Gerhard Fülöp).

Definitions

Complications that were evident in patient charts were classified retrospectively as proposed by Clavien and Dindo [15] and adapted for pancreatic surgery by DeOliveira et al. [16].

Pancreatic fistula definitions varied significantly among the six centers and during the study period. The International Study Group Definition published in 2005 was applied in Vienna and Graz [17]. At least in Vienna, there was some variance according to the time point of amylase level measurement ranging between 3 and 5 days. In Linz and Wiener Neustadt the Pancreatic Surgery Group Definition published in 2003 was kept throughout the whole study period [18]; also, patients with intra-abdominal amylase-rich fluid collections after drain removal, who underwent percutaneous ultrasound or CT-guided drainage, were classified as having pancreatic fistula. In Innsbruck and Salzburg individual definitions were used, with any amylase-rich fluid retention or secretion being regarded as pancreatic fistula. Postoperative bleeding was defined according to the proposal of the ISGPS for "severe" hemorrhage published in 2007 [19].

Unplanned reintervention was defined as any unscheduled percutaneous procedure performed with an intention to treat within 30 days from resection or during hospitalization. This included ultrasound or CT-guided percutaneous drainage of intra-abdominal fluid retentions and angiographic interventions. Postoperative mortality was defined as death during hospitalisation or any death within 30 days after operation.

Up until 2005, all centers assessed resection margin status by 2-dimensional sampling of ductus choledochus and pancreaticus according to a local protocol with an R0 resection defined as no tumor cells reaching the resection margin. In two centers (Salzburg 2006; Vienna 2010) a standardized protocol including multicolor margin staining, axial slicing, and extensive tissue sampling as proposed by Verbeke et al. [20] and Esposito et al. [21] is implemented. According to this definition, R1 is a tumor within 1 mm of the resection margin. Data quality was assessed as completeness of documentation. Statistical analysis was only descriptive, and was performed with Excel (Microsoft Inc.).

Results

The median annual patient recruitment of each center was 11.8 (0–38) patients, resulting in a median annual patient recruitment of 85 patients for the entire ABCSG-group (Table 1).

Austrian nationwide data for incidence of pancreatic adenocarcinoma, annual number of resections, and percentage of cases managed in centers of the ABCSG-group are shown in Table 2. The study population ($n = 492$) consisted of 51 % female patients and 49 % male patients with a median age of 66 years (range: 34–88 years). All postoperative complications leading to readmission were treated at the primary surgical department and documented in the database (Table 3). Complications led to 9.8 % (48/492) reinterventions and 10.4 % (51/492) reoperations; length of hospital stay was 16 days in median (range: 0–209 days); 12 of 492 patients died within 30 days after operation, resulting in a 30-day mortality rate of 2.4 %. Seven of all 19 deaths (36.8 %) occurred after 30 days, during hospitalization at the surgical department, resulting in a hospital mortality rate of 3.9 % (19/492) (Table 4).

Within the participating centers there were variations in overall morbidity (17.1–76.1 %; median 39.1 ± 21.6 %); pancreatic fistula (1.3–17.4 %; median 5.1 ± 6.3 %); reintervention (0–25 %, median 6.8 ± 9.1), reoperation (2.6–20 %, median 9 ± 6.8); and mortality rates (0–6.8 %; median 3.1 ± 3 %).

Table 1 Patient recruitment of centers: annual, median, percentage of total ($n = 492$)

	2005	2006	2007	2008	2009	2010	Median	Total %
Vienna	15	21	31	26	38	30	28.0	33
Innsbruck	14	9	17	13	18	17	15.5	18
Graz	8	12	9	10	17	20	11.0	15
Linz	5	13	11	19	12	15	12.5	15
Salzburg	9	9	13	7	5	17	9.0	12
Wr. Neustadt	0	0	6	7	14	5	5.5	7
	51	64	87	82	104	104	85	100

Table 2 Austrian nationwide data for incidence of pancreatic adenocarcinoma, annual number of resections, and the percentage of cases managed in centers of the Austrian Breast and Colorectal Cancer Study Group (ABCSG) group

	Austria	Austria		ABCSG	
	Incidence *n*	Resections *n*	Resections %	Resections *n*	Resections %
2005	1,387	206	14.9	51	24.8
2006	1,417	256	18.1	64	25.0
2007	1,437	251	17.5	87	34.7
2008	1,483	234	15.8	82	35.0
2009	1,419	254	17.9	104	40.9
2010	1,526	287	18.8	104	36.2

Table 3 Grading of complications according to DeOliveira et al. [16]

	n	%
I	37	7.5
II	85	17.3
III a	30	5.9
III b	32	6.7
IV a	12	2.4
IV b	10	2.0
V	19	3.9

With standardized histopathological protocols, there were 70 % (21/30) R0, 30 % (9/30) R1, and no R2 resections in Vienna and 62.7 % (32/51) R0, 35.3 % (18/51) R1, and 2 % (1/51) R2 resections in Salzburg. Resection margin status with nonstandardized protocols was classified as R0 in 82 % (339/411), R1 in 16 % (16/411), and R2 in 1.2 % (5/411). Details of histopathologic grading and staging are shown in Table 5.

Resections for ductal adenocarcinoma were performed as pylorus-preserving pancreaticoduodenectomy in 52.4 % of all patients. In 23.8 % of patients a classic Kausch-Whipple procedure was done; 17.3 % underwent distal pancreatectomy; and in 6.5 % a total pancreatectomy was needed. There were 17.1 % portal vein resectons and 1.2 % arterial resections. In 98.4 % of patients (369/375) a pancreaticojejunostomy was the favored reconstruction method following pancreaticoduodenectomy (Table 6). Pancreatic duct diameter and tissue quality was systematically assessed in one third of patients.

Table 4 Complications, reinterventions, reoperations, and 30-day mortality

	n	%
No complications	268	54.5
Pancreatic fistula	39	7.9
Bleeding	17	3.5
Pancreatic fistula and bleeding	11	2.2
Intra-abdominal abscess/retention	18	3.7
Other infectious complications	63	12.8
Other complications	65	13.2
Biliary fistula	8	1.6
Liver failure	3	0.6
Sonography-guided drainage	13	2.6
CT-guided drainage	26	5.1
Angiography	9	1.8
Reoperation	51	10.4
No reoperation	441	89.6
30-day mortality	12	2.4
No 30-day mortality	480	97.6
In-hospital mortality	19	3.9
No in-hospital mortality	473	96.1

Table 5 Histopathological findings

	n	%
G1	27	5.5
G2	276	56.1
G3	168	34.1
G4	3	0.6
No info	18	3.7
T1	25	5.1
T2	57	11.6
T3	391	79.5
T4	18	3.7
Tis	1	0.2
N0	138	28.0
N1	349	70.9
N2	2	0.4
NX	3	0.6
Total LN	Min	0.0
	Max	59.0
	Median	13.0
	Mean	14.7
Positive LN	Min	0.0
	Max	19.0
	Median	2.0
	Mean	2.9
LN ratio	Min	0.029
	Max	1.000
	Median	0.250
	Mean	0.284
M0	459	93.3
M1	32	6.5
MX	1	0.2

LN lymph nodes

Table 6 Surgical details and intraoperative findings

	n	%
Pylorus-preserving pancreaticoduodenectomy	258	52.4
Distal pancreatectomy	85	17.3
Kausch-Whipple procedure	117	23.8
Total pancreatectomy	32	6.5
Pancreaticojejunostomy	369	98.4
Pancreaticogastrostomy	6	1.6
Pancreatic duct diameter >3 mm	106	21.5
Pancreatic duct diameter <3 mm	53	10.8
No info	333	67.7
Fibrotic pancreatic tissue	97	19.7
Smooth pancreatic tissue	87	17.7
No info	308	62.6
No vascular resection	402	81.7
Portal vein resection	84	17.1
Arterial resection	6	1.2
Stenting of pancreatic anastomosis	172	35.0
No stenting of pancreatic anastomosis	235	47.8
No info	85	17.3

Table 7 Staging and preoperative work-up

	n	%
CT	473	96.1
No CT	9	1.8
No info	10	2.0
MRI	202	41.1
No MRI	221	44.9
No info	69	14.0
Endoscopic ultrasound	171	34.8
No endoscopic ultrasound	261	53.0
No info	60	12.2
Needle biopsy positive	118	24.0
Needle biopsy negative	119	24.2
Biopsy not conclusive	7	1.4
Biopsy not done	177	36.0
No info	71	14.4
ERCP	226	45.9
No ERCP	225	45.7
No info	41	8.3
Preoperative biliary drainage	203	41.3
No preoperative biliary drainage	255	51.8
No info	34	6.9

MRI magnetic resonance imaging; *ERCP* endoscopic retrograde cholangiopancreatography

Overall morbidity was 45.5 %, and the incidence of pancreatic fistula was 10.1 % (50/492) (Tables 3 and 4). Details of preoperative clinical staging and work-up are given in Table 7.

Perioperative chemotherapy was administered in 81.1 % of patients (8.3 % neoadjuvant; 68.5 % adjuvant, 4.3 % palliative).

Only 4.9 % of patients received chemoradiotherapy (1.6 % neoajuvant; 3 % adjuvant; 0.2 % palliative) (Table 8). Eleven of 33 parameters (33.3 %) were not completely documented in all patients.

Discussion

The strong impact of volume on perioperative morbidity and mortality in the field of pancreatic surgery is well documented. Surgical expertise of large single centers is an obvious prognostic factor in pancreatic cancer management and outcome [1, 22]. Even in the United States, however, only 39 % of pancreatectomies are performed in

Table 8 Timing of multimodality treatment

	n	%
No chemotherapy	78	15.9
Neoadjuvant chemotherapy	41	8.3
Adjuvant chemotherapy	337	68.5
Palliative chemotherapy	21	4.3
No info	15	3.0
No chemoradiotherapy	452	91.9
Neoadjuvant chemoradiotherapy	8	1.6
Adjuvant chemoradiotherapy	15	3.0
Palliative chemoradiotherapy	1	0.2
No info	16	3.3

high-volume centers [2], and even within these centers, mortality rates can range between 0.7 and 7.7 % [23], as shown by a large nationwide U.S. study. Meanwhile, in smaller countries like the Netherlands the rate of patients operated in high-volume or at least medium-volume centers reaches 91 %, with documented significant improvements in postoperative mortality [6]. There are also emerging data on the impact of centralization on survival after resection of pancreatic adenocarcinoma [3].

In 2010, the prevalence of newly diagnosed pancreatic adenocarcinoma in Austria was $n = 1{,}526$, with 18.8 % of the Austrian patients undergoing resection proving previously published observations [24]. Some 30–40 % of patients have locally advanced, borderline resectable tumors. These patients have shown tumor response and increased R0 resection rates following neoadjuvant chemotherapy and chemoradiotherapy [25–29]. Multinational trials have been complicated by obvious problems with patient recruitment [7, 8]. There is clearly a need for large interdisciplinary conducted trials on new adjuvant or neoadjuvant treatment options. Conducting national trials may be an alternative because of shorter distances, similar legal requirements, and better communication.

The six members of the ABCSG-based core pancreatic group can report on the outcomes of around 40 % of Austrian pancreatectomy patients. Data sets have been completed fully except for minor issues; however, there still may remain some bias due to retrospective data acquisition and somewhat heterogeneous definitions for pancreatic fistula and resection margins. For further investigations, and particularly for the planned prospective randomized trials, these definitions need to be standardized, both according to the current literature and in a friendly harmonization process that has already begun.

Although there are variations within the participating centers, overall rates of postoperative morbidity (45.5 %); reinterventions (9.8 %); reoperations (10.4 %), and 30-day (2.4 %) and in-hospital mortality (3.9 %) have been found comparable to previously published national reports [2, 6, 9] and are an important prerequisite for future studies.

Differences in individual quality data may be explained by retrospective data acquisition in four of the six centers, historically differing definitions of pancreatic fistula, and a variance in complication management strategies and patient risk profiles.

Since 2011, pancreatic surgery in Austria is theoretically restricted to centers performing more than 10 resections per year. To date this law appears not to have been fully enforced everywhere in the country. Nevertheless, further centralization comparable to other examples such as in The Netherlands is needed and is to be expected.

In general, over the last 5 years, resection rates in Austria have increased. Within the core ABCSG-group, there is the potential to recruit approximately 75 patients per year, assuming a dropout rate of 25 %. Additional recruitment should be possible through collaboration and networking with other Austrian hospitals.

More importantly, the referral to high-volume centers can provide more accurate initial staging [30, 31], thereby theoretically identifying an estimated potential 460–600 patients in Austria per year who suffer from borderline or resectable tumors and could potentially profit from neoadjuvant multimodality treatment in the setting of a clinical trial.

Conclusions

Surgical quality data of the ABCSG core pancreatic group are in line with international standards. With continuing centralization the essential potential to perform prospective clinical trials for pancreatic adenocarcinoma is given in Austria. Several protocol proposals aiming at surgical and multimodality research questions are currently being discussed.

Acknowledgements The authors thank Gerhard Fülöp (Austrian Health Institute) for contributing absolute numbers of annual pancreatic resections in Austria.

Conflict of interest The authors declare no conflict of interest

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