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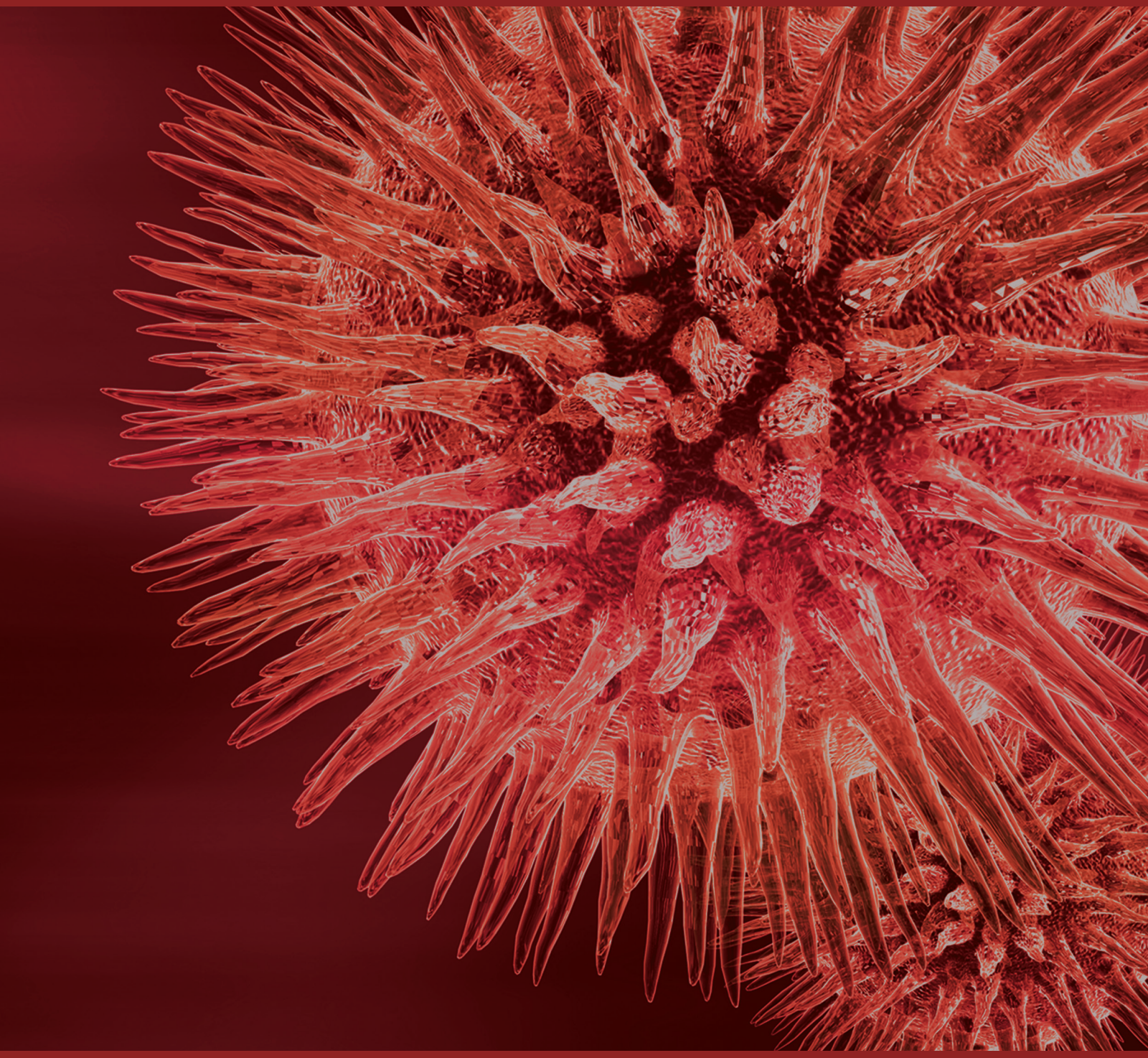
Innovations in Pancreatic Surgery

Guest Editors: Masahiko Hirota, Juhani Sand, Ralf Segersvärd, and Roberto Cirocchi



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Editorial

Innovations in Pancreatic Surgery

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New knowledge about the nature of pancreatic diseases and the ability to perform more complex pancreatic surgical procedures have changed the indication for surgical treatment and permitted an introduction of organ-preserving surgical techniques. The rapid development in technological innovations has improved surgeons' techniques, and accumulation of surgeons' experiences improved the outcome after pancreatic surgery.

Pancreatic cancer is one of the most devastating diseases known to mankind with the worst 5-year survival rate among neoplasms. Many surgeons created their own devices to improve the prognosis of such dismal disease, for example, no-touch approach, artery-first approach, or extensive intraoperative peritoneal lavage. By their endeavor, some lines of hope are being reported in several academic meetings.

On the other hand, recent progress in diagnostic imaging procedures enables us to find various pancreatic lesions. Among them, slow growing tumors, such as intraductal papillary mucinous neoplasm (IPMN), mucinous and serous cystic neoplasms, solid pseudopapillary tumor, and pancreatic neuroendocrine tumor, are included. The presence of these rather low malignant tumors facilitated us to devise organ-preserving minimally invasive surgery, such as laparoscopic or robotically assisted pancreatectomy. Indeed, minimally invasive surgery has become widely accepted as a superior alternative to conventional open surgery for selected patients within the field of pancreatology.

The first paper of this special issue addresses current and future intraoperative imaging modalities and their potential for improved tumor demarcation during pancreatic surgery.

The second paper presents a new surgical technique of proximal subtotal pancreatectomy with splenic artery and vein resection; the so-called pancreaticoduodenectomy with splenic artery resection (PD-SAR). PD-SAR with preoperative chemoradiotherapy seems to be a promising surgical strategy for pancreatic ductal adenocarcinoma of head and/or body with invasion of the splenic artery, with regard to the balance between operative radicality and postoperative QOL.

The third paper is on the Finnish binding (purse-string) pancreaticojejunal anastomosis (FBPJ), which was shown to reduce the risk for postoperative pancreatic fistula (POPF) after PD. In this paper, the efficacy of FBPJ after left pancreatectomy is discussed showing that FBPJ was not technically achievable in 72% of the cases and did not reduce the risk for POPF compared to the conventional hand-sewn closure. Therefore, FBPJ cannot be recommended for the routine closure of the pancreatic remnant after left pancreatectomy.

The fourth paper describes paraduodenal pancreatitis (PP) which was proposed as a synonym for duodenal dystrophy (DD) and groove pancreatitis. Although conventional PD is the main surgical option for treatment of PP today, early diagnosis makes pancreas-preserving duodenal resection (PPDR) the treatment of choice for PP. Efficacy of PPDR provides proof that PP is an entity of the duodenum and not of paraduodenal origin.

The fifth paper addresses the efficacy of combined endoscopic lithotomy (EL) plus extracorporeal shock wave lithotripsy (ESWL) and additional electrohydraulic lithotripsy (EHL) on pancreatic lithiasis. Combined EL plus ESWL therapy is regarded as the first treatment option. However, in cases where the combined therapy was not successful for stone clearance, SpyGlass guided EHL or X-ray guided EHL was effective.

The sixth paper is a systematic review of randomized controlled trials (RCTs) dealing with surgical techniques in distal pancreatectomy. Management of the pancreatic remnant after distal pancreatectomy is still a matter of debate. New well designed and carefully conducted RCTs must be performed to establish the optimal strategy for pancreatic remnant management after distal pancreatectomy.

The seventh paper presents the state of the art of pancreatic robotic surgery. With the current lack of evidence of any oncologic advantages, the cosmetic benefits offered by robotic surgery are not enough to justify its extensive use in cancer patients. In contrast, the safety of this procedure can justify the use of the robotic technique in patient with benign/low grade malignant tumors of the pancreas.

The eighth paper describes the role of morphological and histological features of pancreatic stump in POPF occurrence after PD. Pancreatic texture, assessed by the surgeon, is a significant determining factor for pancreatic fistula and high grade pancreatic fistula and corresponds to pancreatic fibrosis grade. Moreover, careful consideration should be given to the larger pancreatic stumps, small Wirsung duct, wide pancreatic remnant mobilization, and duct decentralization on the stump anteroposterior axis. These morphological features also influence anastomosis failure.

Finally, the last paper discusses the efficacy of splanchnicectomy to relieve pain in pancreatic cancer. Transhiatal bilateral splanchnicectomy achieves a certain denervation of splanchnic nerves, but it requires a laparotomy. Unilateral thoracoscopic splanchnicectomy is a minimally invasive procedure to cause definite denervation. Bilateral thoracoscopic splanchnicectomy is recommended for unsatisfactory cases or recurrent pain occurring after an initial unilateral splanchnicectomy.

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Review Article

Current and Future Intraoperative Imaging Strategies to Increase Radical Resection Rates in Pancreatic Cancer Surgery

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Prognosis of patients with pancreatic cancer is poor. Even the small minority that undergoes resection with curative intent has low 5-year survival rates. This may partly be explained by the high number of irradical resections, which results in local recurrence and impaired overall survival. Currently, ultrasonography is used during surgery for resectability assessment and frozen-section analysis is used for assessment of resection margins in order to decrease the number of irradical resections. The introduction of minimal invasive techniques in pancreatic surgery has deprived surgeons from direct tactile information. To improve intraoperative assessment of pancreatic tumor extension, enhanced or novel intraoperative imaging technologies accurately visualizing and delineating cancer cells are necessary. Emerging modalities are intraoperative near-infrared fluorescence imaging and freehand nuclear imaging using tumor-specific targeted contrast agents. In this review, we performed a meta-analysis of the literature on laparoscopic ultrasonography and we summarized and discussed current and future intraoperative imaging modalities and their potential for improved tumor demarcation during pancreatic surgery.

1. Introduction

Surgery is the cornerstone of curative intended treatment of pancreatic cancer [1]. However, resection of pancreatic cancer is only suitable for a minority of patients [2, 3]. Pancreatic cancer surgery is only conducted when there is a reasonable chance of complete removal of all cancer cells (radical resection), as irradical resection does not improve survival but elicit procedure-related morbidity and mortality [4]. Consequently, pancreatic cancer is known for its high mortality and low 5-year survival of only 6% [5].

Despite recent advances in preoperative imaging modalities, such as computed tomography (CT) and magnetic resonance imaging (MRI), the preoperative assessment of resectability is limited due to difficult differentiation of necrosis, fibrosis, and edematous tissue from malignant tumor cells, especially after neoadjuvant therapy [6–9]. The combination of endoscopic ultrasonography (EUS) and laparoscopic ultrasonography improves resectability assessment [10, 11]. However, microscopic involvement of resection margins (R1 resection) is reported up to 75% of cases, which results in local recurrences and decreased overall survival [12–17]. Therefore, intraoperative imaging strategies accurately visualizing pancreatic cancer cells are highly necessary.

Preoperative imaging of pancreatic cancer using CT, MRI, single-photon emission CT (SPECT), positron emission tomography (PET), and EUS enhances surgical planning, but translating these results to the operating room is difficult due to altered body positioning, tissue manipulation by the surgeon, and lack of sensitivity for subcentimeter lesions. When laparotomy is performed, careful palpation and inspection can yield more information about tumor localization. Minimal-invasive techniques have become important in daily clinical practice but limit tactile feedback.

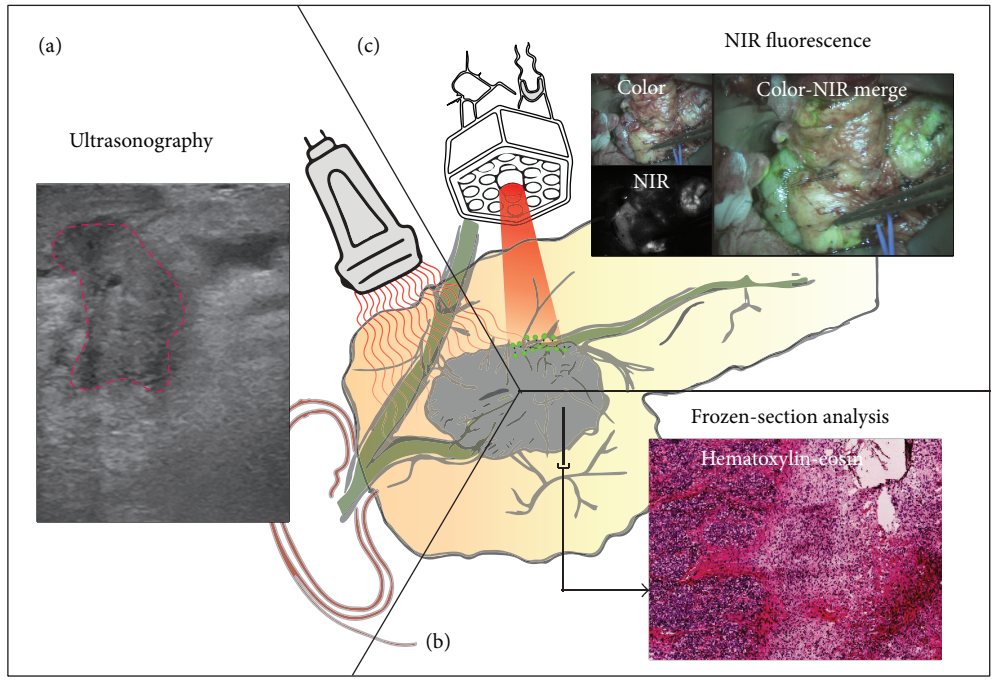


Figure 1: Schematic overview of current and future intraoperative imaging modalities. (a) Ultrasonography showing a pancreatic tumor (demarcated with red line). (b) Intraoperative frozen section analysis and (c) optical imaging using near-infrared imaging.

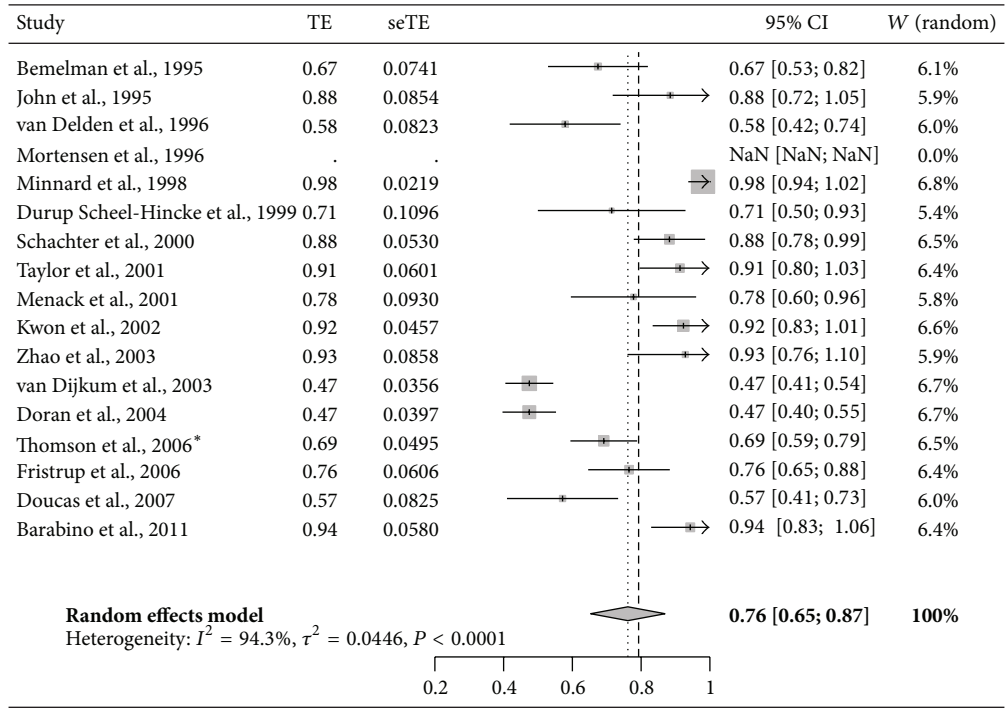
In conclusion, there is a dire need for imaging techniques accurately visualizing and delineating pancreatic cancer during surgery. This review discusses current techniques that are used to assess pancreatic tumor extension during surgery and evaluates the most promising future imaging techniques (Figure 1).

2. Current Strategies

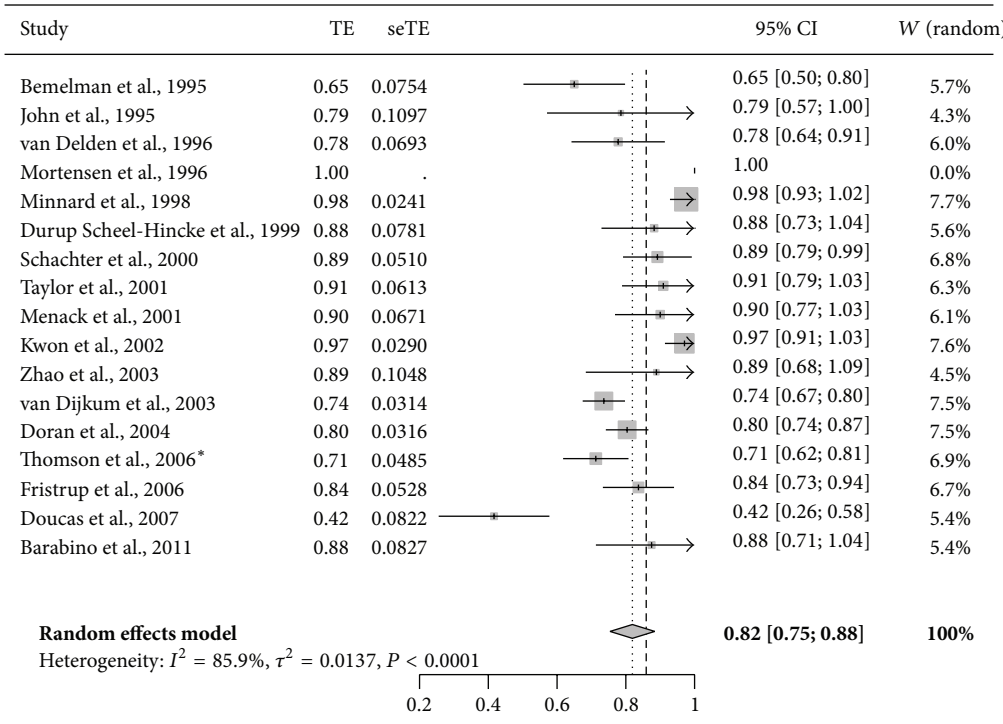
2.1. Ultrasonography during Surgery. Ultrasonography (US) is a safe and inexpensive modality that can be used for determination of resectability and identification of metastases (Figure 1(a)) [18–21]. Besides percutaneous application, US is also used during laparoscopy (laparoscopic ultrasonography, LUS) and open surgery (intraoperative ultrasonography, IOUS). Compared to palpation and visual inspection, US is less sensitive for surface evaluations but outperforms in examination of the interior of organs and helps to determine blood flow in vasculature [22]. Its user dependency is a limitation; substantial training and experience are required for generating and interpreting useful images during pancreatic cancer surgery. Furthermore, ultrasound waves are unable to penetrate through air or gas, hampering the visibility of structures and organs located behind hollow organs. But, by slight compression or by imaging from another side, this limitation can mostly be overcome.

Various studies have evaluated the role of LUS in predicting tumor resectability during staging laparoscopy [23–39]. The term "resectability" is used to indicate if radical resection (R_0) of the tumor is technically possible in the absence of vascular involvement and distance metastases. Staging laparoscopy combined with LUS is not always used to determine resectability, since it is debated whether this approach should be offered routinely, selectively, or not at all to those who appear resectable during their preoperative workup [38, 40]. We performed an extensive review of the literature and pooled the available data in a meta-analysis. We included seventeen studies published between 1995 and 2011. We excluded individual patients from the meta-analysis; if patients were diagnosed with unresectable pancreatic cancer during their preoperative workup, but underwent palliative surgery [27, 29, 34, 36, 38], patients did not undergo LUS, but only laparoscopy [34, 36, 37]; patients declined surgery [31, 37]; if patients were diagnosed with other pathology then pancreatic cancer [31, 32, 35, 37]. In two studies on selective use of LUS, it was not possible to extract the subpopulation of patients that received LUS assessment [41, 42]. Therefore, these studies were not included. In total, data on 1,255 patients undergoing LUS were available for the meta-analysis. A random effect model was chosen due to significant heterogeneity between studies. Pooled sensitivity of LUS for determining unresectable disease was 76% (95% CI = 65–87%) and negative predictive value, the proportion of patients correctly diagnosed with resectable disease, was 82% (95% CI = 75–88%) (Figure 2). The variance between studies may partly be explained by a difference in *a priori* probability, potentially as a result of patient selection by different preoperative imaging modalities. Furthermore, different criteria for unresectability were used.

We were unable to find any study on the use of IOUS in determining resectability, except some outdated literature, which reported success with IOUS in visualizing nonpalpable pancreatic masses [43].



(a)



(b)

Figure 2: Forest plot of pooled data on (a) sensitivity and (b) negative predictive value of laparoscopic ultrasonography in predicting unresectability of pancreatic cancer, which is preoperatively considered to be resectable. *Thomson et al. included 152 patients, 61% had pancreatic adenocarcinoma, 12% presumed pancreatic cancer, 11% ampullary cancer, 5% cholangiocarcinoma, and 11% had other diagnoses. No data solely describing pancreatic cancer patients was available.

Besides assessing localization and characteristics of the primary tumor, US can also be used for the detection of previously unnoticed metastases. Sensitivity of laparoscopy combined with LUS reached 100% in detecting hepatic and peritoneal metastases in a study of 26 patients with pancreatic cancer compared with percutaneous US, CT, or EUS [44].

US is a useful intraoperative imaging technique and provides valuable information about size, localization, and characteristics of lesions. By intraoperative suspicion of unresectability, LUS can aid in avoiding futile resections, and even more when combined with pretherapeutic EUS [10, 11, 36, 45]. However, little literature exists about the value of US-guided surgery in reducing positive resection margins in pancreatic cancer surgery.

2.2. Intraoperative Frozen-Section Analysis. Intraoperative frozen-section analysis (IFSA) of the margins in the pancreatic neck is commonly performed and currently considered as the most important method for intraoperative assessment of the resection margin (Figure 1(b)). It is safe, fast and easy to perform; however, it requires significant processing and evaluating time [46]. Additional resection in case of positive resection margins seems logical, but several studies describe no significant survival benefit after reresection [47–49]. However, no standardized protocol for frozen sections of pancreatic cancer resection margins was described in the studies. The use of nonstandardized methods for histopathological analysis greatly influences the reporting of resection margin status [13, 17, 50]. This may explain the low sensitivity of only 33% in evaluating final resection margin status using IFSA [46]. Due to this inconsistent reporting, little is known on the relation between exact tumor location within the pancreas and margin involvement. When standardized protocols are used, IFSA can potentially be a good method for resection margin assessment. However, IFSA will not provide visual and real-time feedback.

3. Future Strategies

3.1. Contrast-Enhanced Ultrasonography. Ultrasonography is very usable during pancreatic surgery; hence improvements such as contrast-enhanced US (CEUS) are currently being studied. CEUS uses intravenously administered microbubbles, which allow better determination of vessel infiltration and improved visualization of tumor margins during percutaneous imaging [51–54]. Furthermore, CEUS has already shown to help differentiate between chronic pancreatitis and ductal carcinoma [55]. Finally, CEUS can potentially help in identifying more hepatic metastases [56]. During open resection of colorectal liver metastases, the use of CEUS was of significant value in assessing adequate margins and detecting additional lesions. Preoperative CEUS results are encouraging; translation to the operation room is required to fully study the added value of CEUS during pancreatic cancer surgery.

3.2. Fluorescence-Guided Surgery. Fluorescence-guided surgery has emerged as a novel intraoperative modality to assist surgeons to visualize tumors, sentinel lymph nodes, and vital structures in real time (Figure 1(c)) [57]. Near-infrared (NIR) light (700–900 nanometers) can penetrate through several millimeters tissue, revealing targets below the tissue surface [58]. Consequently, NIR fluorescence imaging is currently a surface technique.

At present only two NIR fluorochromes are FDA approved and can be used in the clinical setting, namely, indocyanine green and methylene blue. Both fluorochromes are nonspecific and are mainly used for sentinel lymph node mapping, bile duct imaging, and ureter visualization [57]. Indocyanine green has been shown to accumulate around hepatic metastasis of pancreatic and colorectal cancers, probably due to retention of indocyanine green in compressed hepatocytes, which is shown by a fluorescent rim [59, 60]. In 16% of patients undergoing pancreatic resection without preclinical detected hepatic metastases, fluorescence imaging revealed micrometastases of at least 1.5 mm, which was confirmed by histopathological examination. By revealing undetected hepatic metastases, NIR fluorescence imaging can further decrease the rate of futile pancreatic resections. Furthermore, although its mechanism is unknown, we and others showed that methylene blue tends to accumulate in neuroendocrine tumors, including pancreatic insulinomas [61, 62]. However, due to the nonspecificity no tumor-specific targeting can be expected of ICG and MB, as was shown by our group in pancreatic carcinomas [63]. To obtain the full advantages of NIR fluorescence imaging for pancreatic cancer visualization, tumor specific NIR conjugated ligands need to be designed and tested.

The biological tumor makeup can be used to visualize pancreatic tumors. In the last decades, research on pancreas carcinoma proteomics gained more attention. An increasing number of differentially expressed proteins are identified (http://www.pancreasexpression.org/). Although very promising, these biomarker studies focus mainly on diagnosis or prevention and not necessarily on biomarkers which can be used to recognize malignant cells and to function as tumor-specific target. Potential biomarker for these approaches must possess additional characteristics, such as homogenic expression, upregulation of more than ten times compared to the surrounding tissue, and localization on the cellular membrane for better accessibility. Ideally, these biomarkers can also recognize precursor lesions at early stages and distinguish between pancreatic cancer and inflammation.

Until now, no membrane-bound biomarkers are validated in the clinic, but recent literature shows very promising results in preclinical studies. Various forms of CEA, integrins, BRCA1, and tumor-associated glycoprotein-17 (TAG-17) are overexpressed on pancreatic tumor cells while c-MET, EpCAM, and CXCR-4 are also used as pancreatic cancer stem cell markers [64, 65]. Biomarkers from the plasmin(ogen) cascade are frequently associated with early stage invasion and cell dissociation [66]. The urokinase receptor (uPAR) is highly upregulated on pancreatic tumors and is associated with tumor invasion and its soluble variant differentiates between pancreatic adenocarcinomas and chronic pancreatitis [67, 68].

Very promising preclinical results are already reported for pancreatic cancer specific molecular targets like CEA, MMPs, claudin-4, RGD, and cholecystokinin-2 receptor [69–73]. The focus within the field is currently shifting towards clinical translation and the first successful in-human results of tumor targeted probes have already been published, although this study is concerning ovarian cancer patients [74]. Real-time NIR fluorescence imaging using tumor-targeted probes has the potential to accurately visualize tumor and its demarcation and hence to increase radical resection rates. The next steps should be clinical translation of pancreatic cancer specific probes, improving commercially available NIR fluorescence imaging systems, and validation of the benefits for patients.

3.3. Nuclear Imaging. Besides fluorophores, ligands can also be conjugated to radiotracers, which are directed to tumor-specific biomarkers eliciting tumor specific signals and enhancing tumor visualization (Figure 1(d)). These radioactive ligands are used in the preoperative setting with PET and SPECT and intraoperative with radioimmunoguided surgery (RIGS). RIGS was first described in 1984 by Aitken et al., who developed a hand-held gamma detector that can be used intraoperatively, but the technique has become relatively redundant due to the variable sensitivity, the delay in imaging of nearly a week (due to clearance of unbound antibody from the body), and difficulties in handling and disposing the radioactive material [75–78]. A relatively new nuclear imaging technique is freehand SPECT (fSPECT), which was lately introduced as a three-dimensional (3D) imaging and navigation technique that provides real-time images designed for use in the operating room to facilitate detection and resection [79]. However, this technique shows promising results in lymphatic mapping in breast cancer and for the visualization of thyroid diseases but not yet for pancreatic cancer where no known literature exists [79, 80].

4. Discussion

The field of pancreatic cancer surgery is changing due to improvements in therapies and imaging modalities. These advances have not only led to better pancreatic cancer surgery but also to limitations. The introduction of laparoscopic techniques, for example, has resulted in less postoperative pain, shorter hospital stay, and lower morbidity [81, 82]. However, laparoscopy deprives the surgeon of tactile information, which is helpful during pancreatic cancer surgery. Another example is neoadjuvant therapy, after which a proportion of patients becomes eligible for curative-intended surgery [83]. However, preoperative imaging modalities, such as CT and MRI, drop in sensitivity and specificity in patients who received chemotherapy, for instance, because they cannot accurately distinguish between vascular involvement or vascular encasement only due to periarterial stranding and fibrosis [6–9].

Intraoperative imaging modalities, which can accurately depict pancreatic cancer, can overcome these limitations. Current available technologies, such as US, have their own limitations. US-guided surgery failed to decrease the rate of R_1 resections, possibly due to the fact that quality of obtained images is not high enough. The combination of different imaging modalities has proven to be a successful way to overcome separate limitations; PET/CT, for example, fuses anatomical and functional images in a single scan [84]. The combination of US with other techniques could increase functionality. A potential hybrid concept is fSPECT/US, which has already proven to be possible and easy to perform [80].

Molecular imaging is another promising research field where improvements may be expected. NIR fluorescence imaging offers visual guidance during surgery and can therefore potentially reduce the rate of positive resection margins. Fluorescence-guided laparoscopy during hepatopancreatobiliary surgery has already shown its potential to improve intraoperative identification and demarcation of tumors [85]. Remaining fluorescence signal in the resection wound can be an indication of irradical resection, which may make IFSA redundant. To date, no in-human trials have been done with pancreatic cancer specific contrast agents, but preclinical studies are very promising. A major restriction of NIR fluorescence imaging is its limited penetration depth; fluorescence signal is diminished within one centimeter tissue. This is an issue due to the retroperitoneal location of the pancreas. But again, fusing technologies could overcome this limitation. Radiolabeled NIR fluorescence probes may result in the best of two worlds: direct optical guidance and high penetration capacity of the radiotracer [86]. In addition, preoperative planning is possible with PET detection of the radiotracer [87]. Another improvement should be the development of novel probes that are highly specific for pancreatic cancer cells only and hence result in less background signal and lower false-positive rates. Improved fluorophores, which can easily be conjugated to different ligands, are already available, such as ZW800-1 and CW800 [88]. Furthermore, improved imaging systems should become commercially available, making NIR fluorescence imaging available to a broader range of hospitals. But before NIR fluorescence imaging or a hybrid approach can lead to change in patient management, large multicenter studies are necessary to show if these intraoperative imaging modalities are beneficial for patients.

5. Conclusion

To improve surgical outcome, reduce irradical resections, and improve patients' survival, novel intraoperative imaging strategies are necessary in pancreatic cancer surgery. Therefore, enhanced imaging technologies that can accurately visualize and delineate pancreatic cancer and its extension in real time are currently being developed and tested. Tumor-specific targeted probes for near-infrared fluorescence imaging are very promising, but research in the next years will have to determine if these modalities are truly of added value for our patients.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

Authors' Contribution

Henricus J. M. Handgraaf and Martin C. Boonstra contributed equally to this paper and share the first authorship.

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Clinical Study

A New Surgical Technique of Pancreaticoduodenectomy with Splenic Artery Resection for Ductal Adenocarcinoma of the Pancreatic Head and/or Body Invading Splenic Artery: Impact of the Balance between Surgical Radicality and QOL to Avoid Total Pancreatectomy

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For pancreatic ductal adenocarcinoma (PDAC) of the head and/or body invading the splenic artery (SA), we developed a new surgical technique of proximal subtotal pancreatectomy with splenic artery and vein resection, so-called pancreaticoduodenectomy with splenic artery resection (PD-SAR). We retrospectively reviewed a total of 84 patients with curative intent pancreaticoduodenectomy (PD) for PDAC of the head and/or body. These 84 patients were classified into the two groups: conventional PD ($n = 66$) and PD-SAR ($n = 18$). Most patients were treated by preoperative chemoradiotherapy (CRT). Postoperative MDCT clearly demonstrated enhancement of the remnant pancreas at 1 and 6 months in all patients examined. Overall survival rates were very similar between PD and PD-SAR (3-year OS: 23.7% versus 23.1%, $P = 0.538$), despite the fact that the tumor size and the percentages of UICC-T4 determined before treatment were higher in PD-SAR. Total daily insulin dose was significantly higher in PD-SAR than in PD at 1 month, while showing no significant differences between the two groups thereafter. PD-SAR with preoperative CRT seems to be promising surgical strategy for PDAC of head and/or body with invasion of the splenic artery, in regard to the balance between operative radicality and postoperative QOL.

1. Introduction

When pancreatic ductal adenocarcinoma (PDAC) of the head and/or body invades the origin of splenic artery (SA), we usually cannot be able to avoid total pancreatectomy (TP) because the blood supply of distal pancreas becomes scarce after dividing the origin of splenic artery. Prognosis of PDAC patients following TP, however, has not overcome that of pancreaticoduodenectomy (PD) [1–3]. Moreover, TP causes insulin dependent diabetes mellitus (DM) and exocrine insufficiency, leading to a poor quality of life (QOL). DM after TP means a complete lack of endogenous insulin and glucagon, leading to uncontrollable frequent and deep states of hypoglycemia with hyperglycemic episodes (brittle diabetes) [3]. Recently, favorable perioperative control of blood glucose levels for patients with TP has been reported by using an artificial endocrine pancreas during the perioperative term [4] or at an outpatient clinic by using continuous subcutaneous insulin infusion pumps [5]. Nevertheless, inevitable insulin therapy, presence of brittle DM, and malabsorption

after TP lead to poor QOL. Therefore, if the surgical margin status could be a microscopically negative (R0), TP should be avoided.

For the tumors with invasion of the SA, we had developed a new surgical technique of proximal subtotal pancreatectomy with splenic artery and vein resection, so-called pancreaticoduodenectomy with splenic artery resection (PD-SAR), usually in consideration of the balance between operative radicality and postoperative QOL. Blood flow to the pancreas tail can be obtained by the left gastroepiploic artery (LGEA) and/or posterior epiploic artery (PEA) even if we have to resect the left gastric artery (LGA) combined with total gastrectomy and splenectomy [6]. Previously, proximal subtotal pancreatectomy was performed by preserving SA to maintain blood supply of the pancreatic tail [7, 8]. Our procedure of PD-SAR was inspired by Sutherland et al. [9] and Warshaw [10] technique for distal pancreatectomy with preservation of the spleen which resects the SA and vein along with the pancreas but with careful preservation of the vascular collaterals in the splenic hilum.

The aim of the present study was to evaluate the significance of PD-SAR by examining surgical outcomes, RPV, and prognosis in comparison with those of conventional PD, paying special attention to postoperative pancreatic functions, total daily insulin dose, and nutritional status using TP as a control.

2. Patients and Methods

We retrospectively reviewed a total of 84 patients who had consecutively undergone curative intent pancreaticoduodenectomy (PD) for PDAC of the head and/or body at the Mie University Hospital between January 2008 when we experienced the first case with PD-SAR and December 2013. These 84 patients were classified into the two groups: conventional PD ($n = 66$) and PD-SAR ($n = 18$). Most patients were treated by preoperative chemoradiotherapy (CRT): gemcitabine-based CRT (G-CRT) (40 Gy radiation in 25 fractions with weekly intravenous infusion of gemcitabine 800 mg/m2 for 5 weeks including one-week break) [11, 12] or gemcitabine plus S1-based CRT (GS-CRT) (50.4 Gy radiation in 28 fractions with biweekly intravenous infusion of gemcitabine 600 mg/m2 for 8 weeks and oral S-1, active combination of tegafur, gimeracil, and oteracil, 60 mg/m2/day from day 1 to day 21 and from day 29 to day 49). We compared the two groups with respect to prognosis, postoperative pancreatic functions, and nutritional status.

2.1. Indication and Surgical Procedure of PD-SAR. We determined the indication for PD-SAR for PDAC patients as follows: pancreatic head and/or body tumor invading the proximal site of SA as well as gastroduodenal artery (GDA) according to preoperative multidetector computed tomography (MDCT) and intraoperative findings (Figures 1(a)–1(c)). MDCT was performed according to a defined pancreas protocol as four-phasic contrast-enhanced MDCT with thin slices at intervals of 1 mm [12]. We usually determined the indication of PD-SAR according to initial MDCT findings. After CRT, tumor abutment of SA was almost unchanged on MDCT even when the tumor size decreased. Therefore, indication of PD-SAR did not change before and after CRT. However, one patient who was scheduled to perform PD-SAR underwent conventional PD, because SA could be easily dissected from the tumor.

Since 2005, in our institution, surgical procedures of PD for PDAC of the head had been standardized for resection technique as anterior approach to the superior mesenteric artery [13, 14] according to the concepts of radical antegrade modular pancreatosplenectomy by Strasberg et al. [15] and no-touch isolation technique by Hirota et al. [16], and for pancreaticojejunostomy as pair-watch suturing technique [17].

Surgical procedures of PD-SAR are similar to those of PD except for combined resection of SA and vein, and total gastrectomy and splenectomy if necessary. As shown in Figure 1(d) indicating arterial anatomy around the pancreas and cutting sites of artery, the blood supply of the remnant pancreas is provided by the short gastric arteries (SGA), LGEA, and PEA. At surgery, adequacy of blood supply of the pancreatic tale and spleen is confirmed by the presence of arterial bleeding from the cut surface of the remnant pancreas and by color change of the spleen. If the spleen color becomes dark, splenectomy is performed with carefully preserving LGEA. When the tumor additionally invades the LGA, we perform combined resection of LGA followed by total gastrectomy and splenectomy if curative-intent resection is possible. In such case, the blood supply of the remnant pancreas is provided by PEA alone.

Figure 2(a) shows intraoperative findings after PD-SAR. As of reconstruction procedures, end-to-side pancreaticojejunostomy is performed using the pair-watch suturing technique (PWST) [17], and hepaticojejunostomy is performed by interrupted or continuous suture, followed by gastrojejunostomy and Braun's anastomosis (Figure 2(b)). The blood supply of the remnant pancreas is clearly demonstrated on postoperative MDCT (Figure 2(c)). Figure 2(d) shows the schema of reconstruction after PD-SAR with total gastrectomy and splenectomy, and Figure 2(e) clearly demonstrates enhancement of the remnant pancreas on postoperative MDCT. When the pancreatic duct is too small to perform duct-to-mucosa pancreaticojejunostomy because the remnant pancreas becomes very small, we perform dunking pancreaticojejunostomy.

The arterial supply of the remnant pancreas after PD-SAR is demonstrated in Figure 3. MDCT (Figure 3(a)) and 3D CT angiography (Figure 3(b)) after subtotal stomach preserving PD-SAR show that SA is clearly enhanced from SGAs anastomosing with LGA. Pre- (Figure 3(c)) and postoperative MDCTs (Figure 3(d)) in PD-SAR with total gastrectomy and splenectomy demonstrate that SA and the remnant pancreas are enhanced probably via PEA. As of feeding artery for PEA, our previous report demonstrated on postoperative angiography that the middle colic artery was the source of blood supply of PEA which fed SA [6].

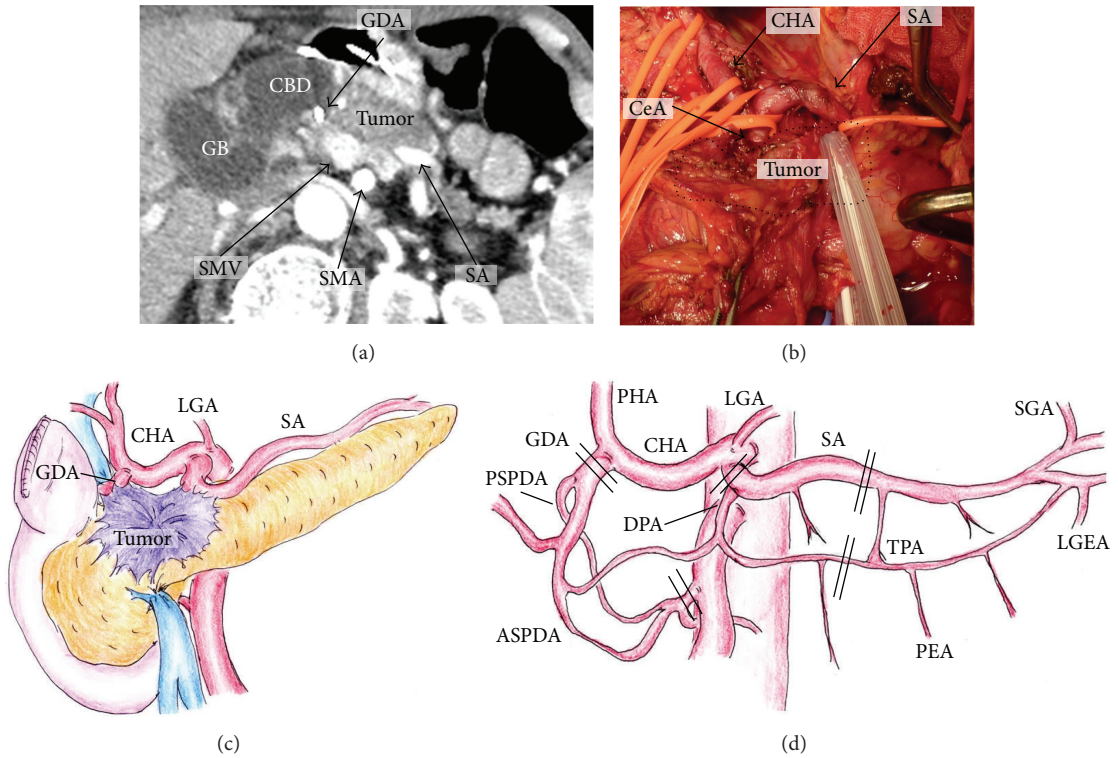


Figure 1: Indication of PD-SAR according to MDCT findings (a), intraoperative findings ((b) dotted circle indicates tumor border and schema of intraoperative findings) (c), and the arterial anatomy around the pancreas ((d) double line indicates cutting sites of artery). GB: gallbladder. CBD: common bile duct. SMV: superior mesenteric vein. SMA: superior mesenteric artery. SA: splenic artery. CeA: celiac artery. PHA: proper hepatic artery. LGA: left gastric artery. CHA: common hepatic artery. GDA: gastroduodenal artery. PSPDA: posterior superior pancreaticoduodenal artery. ASPDA: anterior superior pancreaticoduodenal artery. DPA: dorsal pancreatic artery. TPA: transverse pancreatic artery. SGA: short gastric artery. LGEA: left gastroepiploic artery. PEA: posterior epiploic artery.

2.2. Preoperative Characteristics, Surgical Outcomes, and Pathological Findings. We compared various factors in the patients between PD and PD-SAR, including (1) preoperative characteristics such as gender, age, size of tumor before treatment, International Union for Cancer Control (UICC)-T factor, resectability according to National Comprehensive Cancer Network guideline 2010 [18], cancer involvement of major vessels, and treatment before surgery and preoperative CA19-9 level, (2) surgical outcomes such as intraoperative blood loss, operation time, combined resection of major vessel or another organ, type of pancreaticojejunostomy anastomosis, intraoperative blood transfusion, degree of postoperative complications according to the Clavien-Dindo (C-D) classification [19], and duration of hospital stay (DHS), and (3) pathological findings of the resected specimen such as size of tumor, UICC-T factor, histological type, lymph node metastasis, degree of lymphatic invasion, venous invasion and intrapancreatic nerve invasion according to classification of pancreatic carcinoma of Japan Pancreatic Society [20], histological effect according to Evans' grading system for chemoradiation treatment effect [21], and surgical margin status (R0, R1, and R2).

2.3. Postoperative Chemotherapy and Follow-Up. From 6 weeks after operation, we made arrangement to start the adjuvant chemotherapy, consisting of gemcitabine at a dose of 800 mg/m2 biweekly or S1 60 mg/m2/day for 4 weeks followed by 2-week break for at least 6 months. All patients were evaluated as follows: physical examination every month; laboratory tests including CEA serum levels (normal < 5 ng/mL) and CA19-9 levels (normal < 37 U/mL) every 2 or 3 months; and MDCT every 3 months within 2 years, and thereafter every 6 months. All patients after PD, PD-SAR, and TP were given pancreatic enzyme, but the time of initiating and dosage of pancreatic enzyme supplementation were determined by each surgeon. The pancreatic enzyme supplementation was performed by pancreatin of 6 to 12 g/day or pancrelipase of 1800 or 3600 mg/day. The time of initiating and type of diabetes mellitus (DM) treatment were determined by each surgeon or DM specialist.

2.4. Measurement of the Remnant Pancreatic Volume. We measured the remnant pancreatic volume (RPV) by CT volumetry at 1 and 6 months after pancreatectomy. Serial

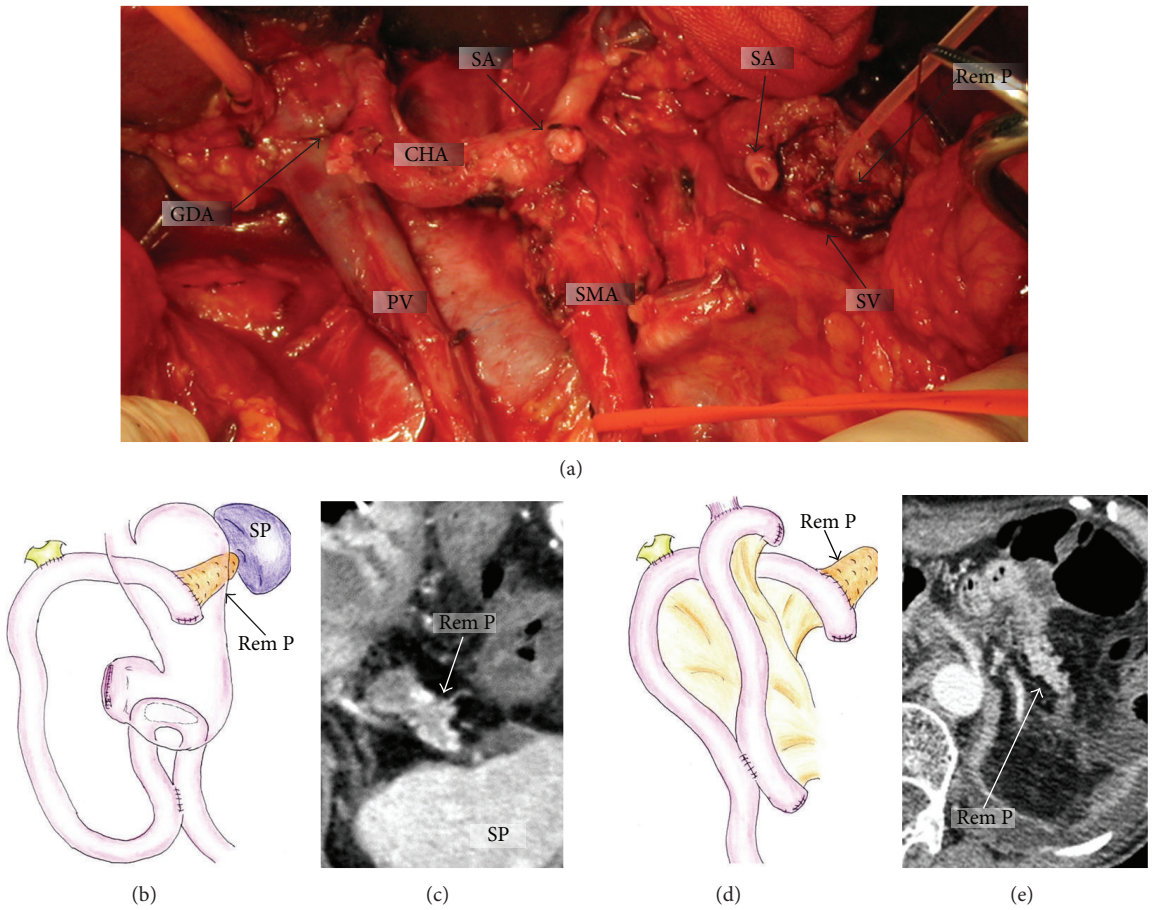


Figure 2: Intraoperative findings after PD-SAR (a) and schemas of reconstruction after PD-SAR and postoperative MDCT showing clear enhancement of the remnant pancreas (b)–(e). (b) and (c): schema of reconstruction after subtotal stomach preserving PD-SAR and postoperative MDCT. (d) and (e): schema of reconstruction after PD-SAR with total gastrectomy and splenectomy and postoperative MDCT. PV: portal vein. SMA: superior mesenteric artery. SA: splenic artery. CHA: common hepatic artery. GDA: gastroduodenal artery. SV: splenic vein. Rem P: remnant pancreatic parenchyma. SP: spleen.

transverse enhanced CT scan images were obtained at 1 and 1.25 mm interval. Each slice of the remnant pancreatic parenchyma was traced, and the corresponding area was calculated as the sum of pancreatic tissue area. Splenic vein and dilated pancreatic duct (3 mm or more) were excluded.

2.5. Prediction of Postoperative Pancreatic Functions Using Several Markers. Because exact methods for evaluation of pancreatic endocrine and exocrine functions are expensive and labor intensive, and, furthermore, insulino-acinar-ductal-incretin gut hormonal axis influences endo- and exocrine functions each other, which in turn makes it difficult to discriminate each other [22], there has been an increased need in clinical practice for a simple and widely available screening tool for detection of pancreatic functions. Lindkvist et al. [23] reported significance of nutritional markers such as albumin, prealbumin, magnesium, HbA1C, and cholesterol to predict the probability of pancreatic exocrine insufficiency. Furthermore, Yadav et al. [24] have recently suggested that decreased levels of serum amylase in type 2 DM are associated with decreased pancreatic function. To predict the remnant pancreatic functions in the present study, therefore, we examined type of DM treatment, total daily insulin dose, fasting blood sugar (FBS) level, HbA1c, serum amylase level, degree of body weight loss, serum albumin level, serum cholesterol level, and frequency of evacuation before and 1, 3, 6, and 12 months after pancreatectomy. In the present study, the patients were diagnosed as DM when either one of fasting blood sugar of 126 mg/dL or more or HbA1c of 6.5% or more was found or when DM treatment had been introduced preoperatively. As a control for PD and PD-SAR, we measured the same parameters in the 6 patients who underwent total pancreatectomy (TP) during the study period: PD-SAR was converted to TP in 2 and remaining 4 underwent resection of the remnant pancreatic head due to tumor occurrence (PDAC in 2 and intraductal papillary mucinous adenocarcinoma in 2) in the pancreatic head after distal pancreatectomy for PDAC in 1 and for intraductal papillary mucinous neoplasm in 3. The reason why the number of TP was very small as a control group was because

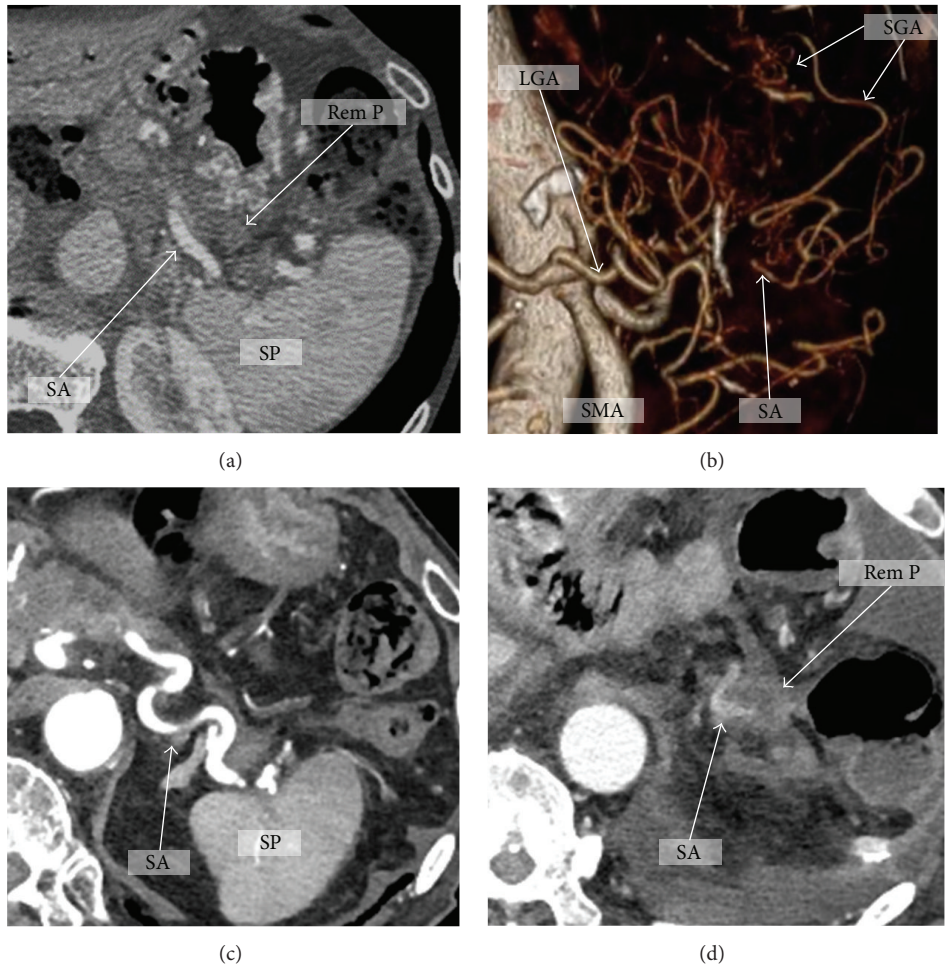


Figure 3: The arterial supply of the remnant pancreas after PD-SAR. MDCT (a) and 3D CT angiography (b) after subtotal stomach preserving PD-SAR showing SA clearly enhanced from SGAs anastomosing with LGA. Pre- (c) and postoperative MDCTs (d) in PD-SAR with total gastrectomy and splenectomy: SA and Rem P are enhanced even after PD-SAR with total gastrectomy and splenectomy, probably from PEA. LGA: left gastric artery. SGA: short gastric artery. SMA: superior mesenteric artery. SA: splenic artery. SP: spleen. Rem P: remnant pancreas. PEA: posterior epiploic artery.

we had been avoiding TP as much as possible by aggressively employing the procedure of PD-SAR.

2.6. Glucagon Stimulation Test. Because the blood supply of the remnant pancreas becomes scarce after PD-SAR, it is crucial to determine whether islets cells are functional or not. Oral glucose tolerance test (OGTT) provides a stimulus for the release of C-peptide from the islet cells which is equally as effective as intravenous glucagon injection test, that is, glucagon stimulation test (GST) [25]. OGTT after PD or PD-SAR is highly influenced by the types of gastrointestinal reconstruction, while GST is not. Therefore, GST was performed in the morning after an overnight fast: serum levels of C-peptide immunoreactivity (CPR) were measured in blood sample taken before (pre-CPR) and 10 minutes (post-CPR) after 1 mg of glucagon was intravenously injected. Δ CPR was calculated as (post-CPR-pre-CPR).

2.7. Statistical Analyses. All continuous values were presented as mean ± SD according to results of Fisher's distribution. Continuous variables were compared using Student's t-test, and categorical variables were compared using Pearson's chi-squared test.

In all patients, the date of the initial treatment was chosen as the starting point for the measurement of survival time. Recurrence-free survival time was defined as the time from the date of initial treatment to the date of first relapse or death. Overall and recurrence-free survival was calculated using the Kaplan-Meier method and was compared between the groups using the log rank test. The day of final follow-up was January 31, 2014, and there was no loss of follow-up. All statistical

Table 1: Comparison of preoperative characteristics between PD and PD-SAR.

Variable	PD ($n = 66$)	PD-SAR ($n = 18$)	P value
Gender			
Male	43	6	**0.029**
Female	23	12	
Age (years)	66.5 ± 9.6	67.6 ± 9.2	0.718
Tumor size before treatment (mm)	30.8 ± 8.7	37.8 ± 10.9	**0.030**
UICC-T3	40 (61.7%)	6 (33.3%)	**0.060**
UICC-T4	26 (39.3%)	12 (66.7%)	
Resectability			0.124
R	6	1	
BR	49	10	
UR	11	7	
Cancer involvement of major vessels			
SMV/PV	59 (89.4%)	16 (88.9%)	0.713
SMA	20 (30.3%)	5 (27.8%)	0.934
HA	8 (12.1%)	8 (44.4%)	**0.006**
CeA	6 (9.0%)	6 (33.3%)	**0.026**
SA	0 (0%)	18 (100%)	<**0.001**
Ao/IVC	2 (3.0%)	1 (5.6%)	0.838
Treatment before surgery			
G-CRT	35 (53.0%)	11 (61.1%)	0.917
GS-CRT	24 (36.4%)	5 (27.8%)	
CTA	3	1	
Non	4	1	
CA19-9 levels (U/mL)			
Before preoperative treatment	620.7 ± 1710.5	681.9 ± 1803.3	0.878
After preoperative treatment	87.7 ± 77.2	155.6 ± 335.0	0.216

UICC: International Union for Cancer Control; R: resectable; BR: borderline resectable; UR: unresectable; SMV: superior mesenteric vein; PV: portal vein; SMA: superior mesenteric artery; HA: hepatic artery; CeA: celiac artery; SA: splenic artery; Ao: aorta; IVC: inferior vena cava; G-CRT: gemcitabine-based chemoradiotherapy; GS-CRT: gemcitabine plus S1-based chemoradiotherapy; CTA: chemotherapy alone; Non: no treatment before surgery.

Table 2: Comparison of surgical outcomes between PD and PD-SAR.

	PD ($n = 66$)	PD-SAR ($n = 18$)	P value
Blood loss (g)	1967 ± 1874	1605 ± 1215	0.340
Operation time (min)	587 ± 118	607 ± 127	0.429
Combined resection			
SMV/PV	58 (87.9%)	18 (100%)	0.271
Colon	7 (10.6%)	0	0.336
Total gastrectomy	1 (1.5%)	2 (11.1%)	0.219
HA	3 (4.5%)	1 (5.6%)	0.656
SA	0 (0%)	18 (100%)	<**0.001**
Type of P-J anastomosis			
PWST	65 (98.5%)	12 (61.1%)	<**0.001**
Dunking	1 (1.5%)	6 (38.9%)	
Blood transfusion (mL)	400 ± 420	320 ± 406	0.660
Postoperative complication			
C-D grade ≥ III	13 (19.7%)	3 (16.7%)	0.790
DHS (days)	40.2 ± 17.9	38.2 ± 13.5	0.980

P-J: pancreaticojejunostomy; PWST: pair-watch suturing technique (16); C-D: Clavien-Dindo classification (18); DHS: duration of hospital stay.

analyses were performed using SPSS version 21 (SPSS Inc., Chicago, IL) software. A P value < 0.05 was considered as being statistically significant.

3. Result

3.1. Preoperative Characteristics. The patients' background and preoperative clinical findings in the two groups are listed in Table 1. The mean size of tumor before treatment and the percentages of UICC-T4 and involvement of hepatic artery (HA), celiac artery (CeA), and splenic artery (SA) were markedly higher in PD-SAR than in PD, although the status of resectability according to NCCN guideline showed no difference between two groups. The rate of female was significantly higher in PD-SAR than in PD ($P = 0.029$), while there was no difference in the mean age of patients between two groups. Basically, our institutional policy to treat UICC-T3 and T4 PDAC patients, especially BR and UR, is to undergo CRT before surgery, as we previously reported [11, 12]. Among the total of 84 patients, we performed CRT before surgery in 75 patients (89.3%), chemotherapy alone in 4 (4.8%), and no treatment before surgery in 5 (5.9%). Among 18 patients with PD-SAR, 16 (88.9%) underwent preoperative CRT, and the remaining 2 who did not receive CRT had multiple (two) tumors in the head and body, of which body tumor invaded SA. Between the two groups, however, there were no differences in the type of preoperative treatment. Serum CA19-9 levels before and after preoperative treatment did not differ between the two groups.

3.2. Surgical Outcomes. Between PD and PD-SAR, there were no significant differences in surgical outcomes including blood loss, operation time, blood transfusion, degree of postoperative complications, and DHS, except for the rates of combined resection of SA and dunking pancreaticojejunostomy (Table 2).

3.3. Pathological Findings of Resected Specimen. As shown in Table 3, pathological tumor size was larger in PD-SAR than in PD, although there was no statistical difference in the two groups ($P = 0.098$). Pathological T classification

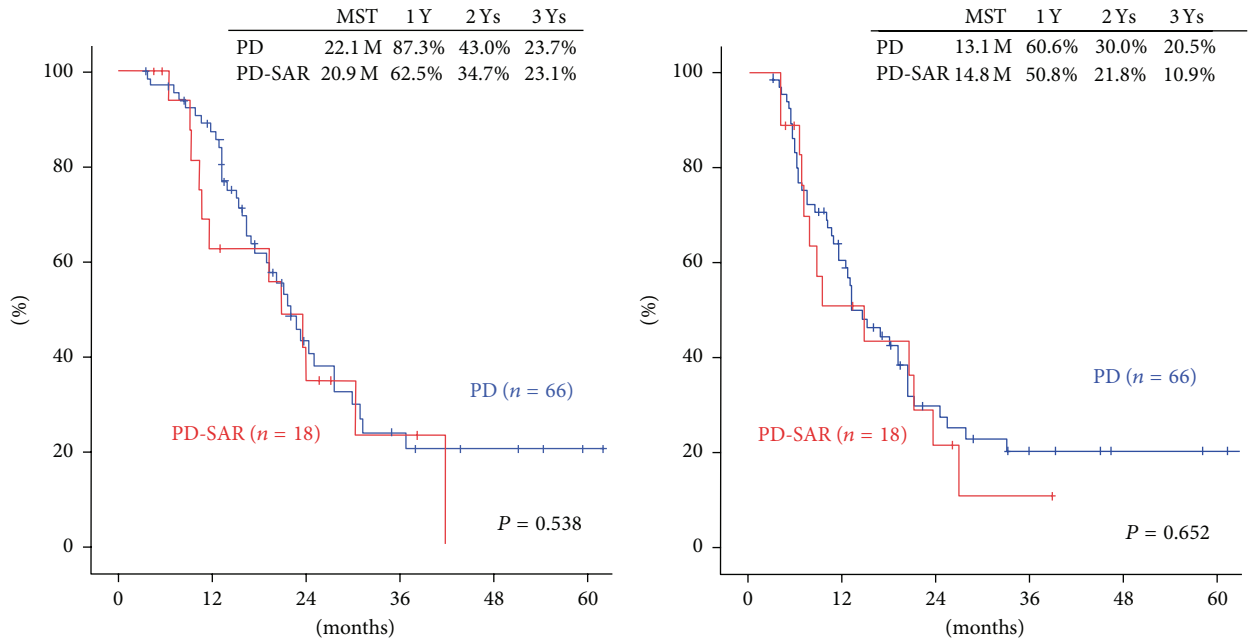
Table 3: Comparison of pathological findings of resected specimen between PD and PD-SAR.

	PD ($n = 66$)	PD-SAR ($n = 18$)	P value
Tumor size (mm)	26.3 ± 10.2	31.6 ± 10.9	0.098
UICC-T1	8	1	0.869
UICC-T2	12	3	
UICC-T3	36	11	
UICC-T4	10	3	
UICC-stage			
IA/IB/IIA/IIB/III/IV	5/4/22/24/10/1/0	1/2/7/5/2/0/1	0.529
JPS-stage			
I/II/III/IVa/IVb	5/7/30/24/0	1/2/8/6/1	0.435
Histological type			
Well	30	11	0.108
Moderate	29	4	
Poor	7	2	
Other	0	1	
Lymph node metastasis			
Positive	27	4	0.117
Negative	39	14	
Degree of lymphatic invasion*			
ly0	17	5	0.754
1–3	44	10	
Degree of venous invasion*			
v0	42	9	0.358
1–3	19	6	
Degree of intrapancreatic nerve invasion*			
ne0	17	4	1.000
1–3	44	11	
Histological effect of CRT (Evans' criteria)			
I	10	3	0.083
IIa	22	10	
IIb	21	3	
III, IV	6	0	
Status of surgical margin			
R0	56	14	0.150
R1	9	2	
R2	1	2	

UICC: International Union for Cancer Control; JPS: Japan Pancreatic Society; ly: degree of lymphatic invasion; v: degree of venous invasion; ne: degree of intrapancreatic nerve invasion; R0: negative surgical margin; R1: positive microscopic margin; R2: positive gross margin. *Excluding 8 cases in which histological assessment could not be determined.

did not differ between the two groups, although preoperative T classification was significantly different. As of histological effect of CRT, the incidence of grade IIb or more was higher in PD than in PD-SAR: 27/59 (45.8%) versus 3/16 (18.8%) ($P = 0.083$). The remaining factors such as UICC-stage, JPS-stage, histological type, lymph node metastasis, degrees of lymphatic, venous and intrapancreatic nerve invasions, and status of surgical margin showed no significant differences between the two groups. As of surgical margin, there were no patients with pancreatic cut margin positive in both groups, and the sites of R1 were unexceptionally dissected margins around SMA and/or HA and/or CeA in both groups. The causes of R2 in 2 cases with PD-SAR were macroscopic positive dissected margin around the common hepatic artery and solitary liver metastasis which was palliatively resected by partial hepatectomy, respectively. The cause of R2 in 1 case with PD was solitary liver metastasis which was palliatively resected by partial hepatectomy.

3.4. Overall Survival and Recurrence-Free Survival Rates. Median survival time (MST) and overall survival rates (OS) were almost similar between PD and PD-SAR: MST: 22.1 months versus 20.9 months and 3-year OS: 23.7% versus 23.1% ($P = 0.538$). Recurrence-free MST and recurrence-free



(a) Overall survival

(b) Recurrence-free survival

Figure 4: Comparisons of overall survival (OS) and recurrence-free survival (RFS) rates after pancreatectomy between PD and PD-SAR. (a) Overall survival. There were no significant differences in survival rates of two groups ($P = 0.538$). (b) Recurrence-free survival. There were no significant differences in survival rates of two groups ($P = 0.652$). MST: median survival time.

rates (RFS) were also similar between PD and PD-SAR: MST: 13.1 months versus 14.8 months and 3-year RFS: 20.5% versus 10.9% ($P = 0.652$) (Figure 4).

3.5. Sites of Tumor Recurrence. Recurrence after operation occurred in 44 patients (66.7%) in PD and in 11 (68.8%) in PD-SAR, showing no significant difference. Although there were no significant differences in distant metastases between the two groups, the rate of local recurrence in the remnant pancreas was significantly higher in PD-SAR than in PD: 3/18 (18.8%) versus 2/66 (3.0%) ($P = 0.030$). The rate of recurrence in the remnant pancreas alone showed no significant difference: PD-SAR: 1/18 (6.3%) versus 0/66 (0%) ($P = 0.483$) (Table 4).

Table 4: Comparison of tumor recurrent sites between PD and PD-SAR.

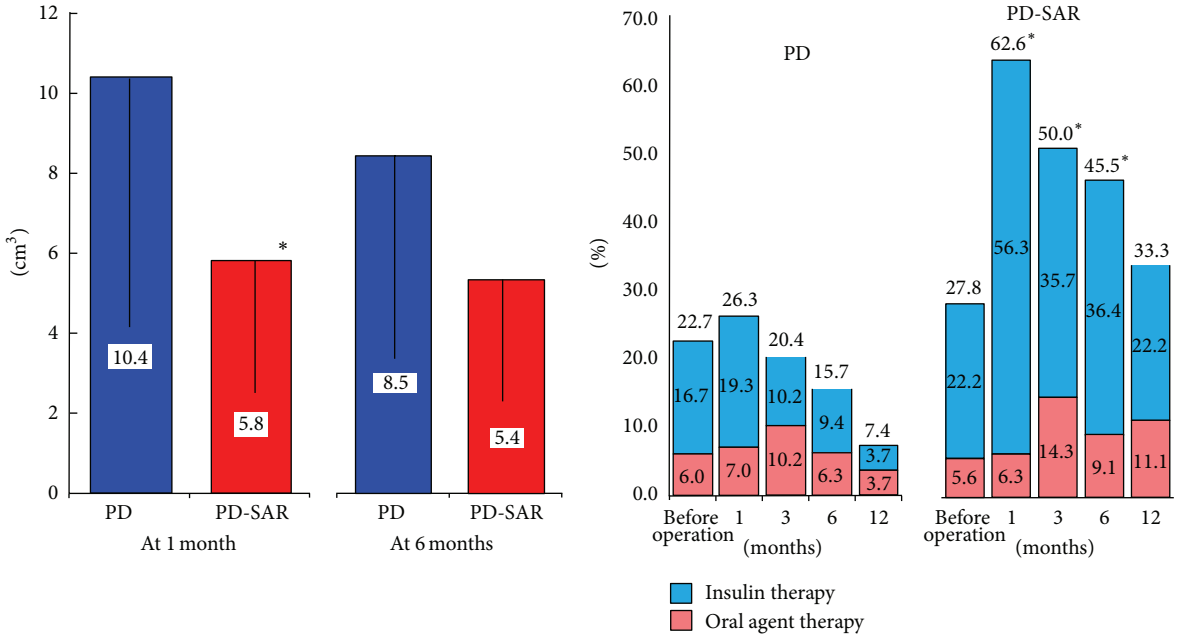
	PD ($n = 66$)	PD-SAR ($n = 18$)	P value
Recurrence	44 (66.7%)	11 (68.8%)	0.873
Local			
Remnant pancreas*	2 (3.0%)	3 (18.8%)	**0.109**
Remnant pancreas alone	0 (0%)	1 (6.3%)	0.483
Others	4 (6.1%)	2 (12.5%)	0.825
Metastasis			
Liver	15 (22.7%)	3 (18.6%)	0.817
Lung	10 (15.2%)	2 (12.5%)	0.957
Lymph node	2 (3.0%)	1 (6.3%)	0.838
Dissemination	9 (13.6%)	3 (18.6%)	0.957

*Recurrence of remnant pancreas associated with metastasis of other organs.

3.6. RPV and Type of DM Treatment. In PD and PD-SAR, the parenchyma of the remnant pancreas could be clearly enhanced in all patients. The RPV was significantly smaller in PD-SAR than in PD at 1 month after operation ($5.8 \pm 3.8\ cm^3$ versus $10.4 \pm 6.0\ cm^3$, $P = 0.029$) but showed no significant difference at 6 months ($5.4 \pm 3.7\ cm^3$ versus $8.5 \pm 5.9\ cm^3$, $P = 0.199$) (Figure 5(a)).

The percentage of patients who preoperatively required DM treatment was very similar between PD-SAR and PD: 27.8% (5/18) versus 22.7% (15/66). Postoperatively, however, the percentage became significantly higher in PD-SAR than in PD except for that of 12 months: 62.6% (10/16) versus 26.3% (15/57) at 1 month ($P = 0.012$), 50.0% (7/14) versus 20.4% (10/49) at 3 months ($P = 0.027$), 45.5% (5/11) versus 15.7% (5/32) at 6 months ($P = 0.043$), and 33.3% (3/9) versus 7.4% (2/27) at 12 months ($P = 0.137$). Additionally, the percentage of patients who postoperatively required insulin therapy was significantly higher in PD-SAR than in PD except for that of 12 months ($P = 0.082$) (Figure 5(b)).

3.7. Prediction of Postoperative Pancreatic Functions Using Several Markers. Total daily insulin dose (units) was significantly higher in PD-SAR than in PD at 1 month: 11.1 ± 13.1 versus 2.7 ± 6.7 ($P = 0.026$), while showing no significant



(a) Remnant pancreas volume

(b) Type of DM treatment

FIGURE 5: Comparisons of remnant pancreas volume (a) and type of postoperative DM treatment (b) between PD and PD-SAR. $^{*}P < 0.05$ versus PD.

differences between the two groups at 3, 6, and 12 months. As compared to TP, however, the dose in PD-SAR was significantly lower at 1, 3, and 6 months: 11.1 ± 13.1 versus 20.3 ± 5.4 ($P = 0.024$), 7.6 ± 13.3 versus 17.3 ± 3.1 ($P = 0.025$), and 10.1 ± 16.3 versus 26.3 ± 10.4 ($P = 0.021$) (Figure 6(a)). Fasting blood sugar, HbA1c, and serum amylase levels did not differ significantly among the three groups except for HbA1c levels at 12 months, showing significantly higher levels in PD-SAR than in PD: 7.8 ± 0.7% versus 5.6 ± 0.8% ($P < 0.001$) (Figures 6(b), 6(c), and 6(d)). No patients with PD and PD-SAR had experienced hypoglycemic attacks after discharge, while all patients with TP had experienced hypoglycemic attack after discharge. Degree of body weight loss and serum albumin and cholesterol levels did not differ significantly among the three groups (Figures 7(a), 7(b), and 7(c)). The degree of body weight loss seemed to be milder after TP than after PD-SAR, because in 6 patients in TP group including 2 with intraductal papillary mucinous adenocarcinoma body weight loss was minimal. Frequency of evacuation did not differ between PD-SAR and PD before and after operation, while it was significantly less in PD-SAR than in TP at 3 and 6 months: 2.5 ± 2.3 versus 5.8 ± 2.9 ($P = 0.024$) and 2.2 ± 1.2 versus 4.8 ± 3.0 ($P = 0.011$) (Figure 7(d)).

3.8. Glucagon Stimulation Test (GST). GST could be performed in 14 patients with PD and 5 with PD-SAR at 1 to 4 months after operation (median: 85 days). As a result, pre- and post-CPR levels (ng/dL) did not significantly differ between PD and PD-SAR: 0.79 ± 0.39 versus 0.60 ± 0.21 ($P = 0.381$) and 1.17 ± 0.51 versus 0.98 ± 0.72 ($P = 0.692$). Additionally, ⊿CPR (ng/dL) showed no significant difference between the two groups: 0.39 ± 0.26 versus 0.38 ± 0.52 ($P = 0.968$) (Figure 8).

4. Discussion

For justification of PD-SAR procedure, sustained blood supply to the remnant pancreas is mandatory. Postoperative MDCT clearly demonstrated enhancement of the remnant pancreas at 1 and 6 months in all patients examined. Although we fortunately had not experienced any postoperative complications regarding lack of blood supply of the pancreatic parenchyma, it would be much better if the method to enhance blood supply of the remnant pancreas can be performed preoperatively. Hirano et al. [26] reported the usefulness of preoperative coil embolization of the common hepatic artery to enlarge the collateral pathways and prevent ischemia-related complications in patients who underwent distal pancreatectomy with en bloc celiac axis resection. Therefore, it might be also useful for PD-SAR patients to undergo preoperative coil embolization of the root of splenic artery for enhancing blood supply of the remnant pancreas. Furthermore, our present method to confirm blood supply of the remnant pancreas and spleen by macroscopic findings is unreliable and not objective, and therefore much more secure methods such as color Doppler ultrasound and indocyanine green fluorescence angiography [27] should be introduced in the future. Secondary point is, whether or not enough, surgical margin can be obtained by PD-SAR. As a result, there were no patients with pancreatic cut margin positive in both

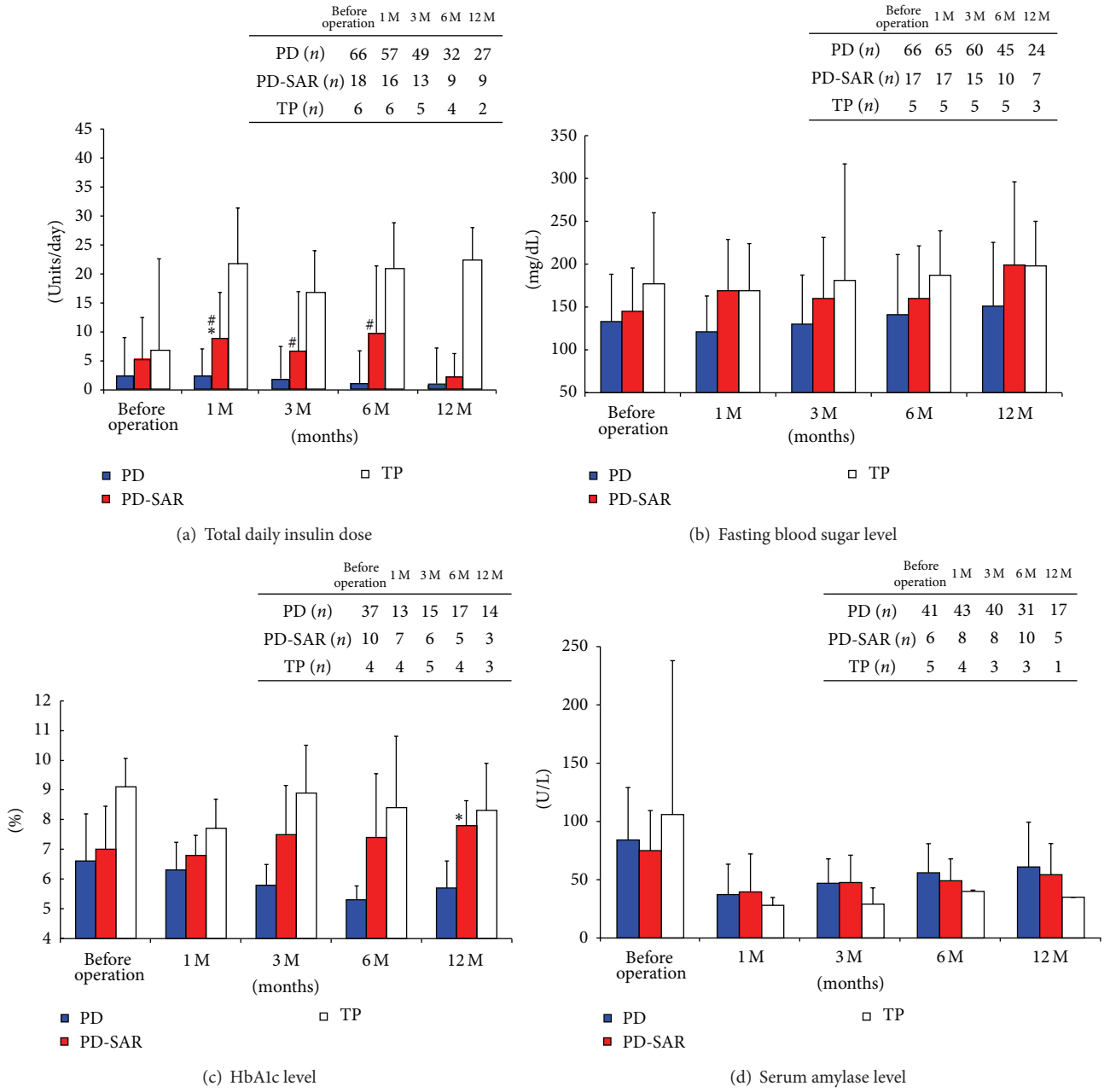
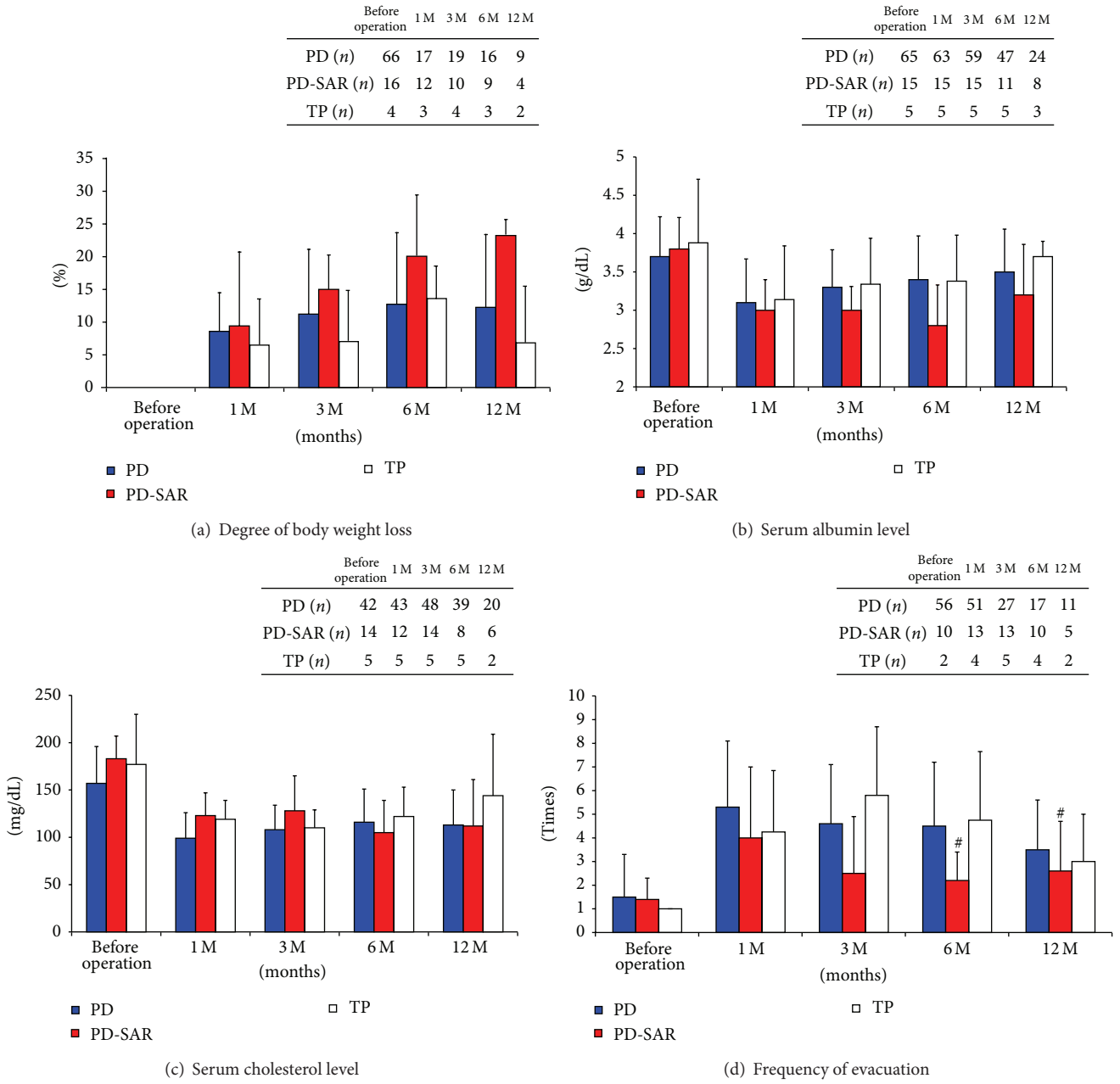


FIGURE 6: Markers for prediction of pancreatic functions before and after PD, PD-SAR, and TP. $^{*}P < 0.05$ versus PD. $^{\#}P < 0.05$ versus TP.

PD and PD-SAR and the sites of R1 were unexceptionally dissected margins around SMA and/or HA and/or CeA in both groups, although almost 90% of the patients in both groups had preoperative CRT. Additionally, surgical outcomes such as degree of postoperative complications and DHS did not differ between the two groups.

As of prognosis after PD-SAR, both OS and RFS were very similar to that after PD, despite the fact that the tumor size and the percentages of UICC-T4 and involvement of HA, CeA, and SA determined before treatment were significantly higher in PD-SAR. In contrast, there became no significant differences in pathological findings of the resected specimen including tumor size, T classification, lymph node metastasis, and degrees of lymphatic, venous, and intrapancreatic nerve invasions between the two groups. This was considered because preoperative CRT was effective to destruct tumor cells as shown in histological effect of CRT: the incidence of grade IIb or more (tumor destruction more than 50%) was higher in PD (45.8%) than in PD-SAR (18.8%) and incidence of grade IIa or more (tumor destruction more than 10%) was similar to each other (PD: 83.1% versus PD-SAR: 81.3%). In the present study, it was considered that preoperative CRT might enhance prognosis after PD-SAR. As shown in Table 3, the incidence of pathological T4, which



(a) Degree of body weight loss

(b) Serum albumin level

(c) Serum cholesterol level

(d) Frequency of evacuation

Figure 7: Nutritional markers for prediction of pancreatic functions and frequency of evacuation before and after PD, PD-SAR, and TP. $^{*}P < 0.05$ versus PD. $^{\#}P < 0.05$ versus TP.

means involvement of SMA and/or CeA, was 15.2% (10/66) in PD and 16.7% (3/18) in PD-SAR, which were markedly lower than 39.3% in PD and 66.7% in PD-SAR determined by MDCT before treatment (Table 1). Pathological diagnosis of arterial involvement of SMA and/or CeA was determined by presence of nerve plexus involvement in the dissected margin of SMA and/or CeA because combined resection of SMA and/or CeA was not performed. On the other hand, arterial involvement of SMA and/or CeA determined by MDCT depended on imaging findings such as tumor abutment and/or encasement. Mochizuki et al. [28] examined MDCT findings of extrapancreatic nerve plexus invasion around SMA by "point-by-point" correlation with en bloc pathological specimens to assess their diagnostic accuracy in 37 patients with PDAC including 16 with combined resection of SMA. As a result, diagnostic accuracy of nerve plexus invasion around SMA reached 94.6%. In the present study, histological effect of CRT showed that the incidence of grade IIb or more was 45.8% in PD and 18.8% in PD-SAR. Taken these facts together, it was likely assumed that preoperative CRT reduced incidence of pathological arterial involvement.

When we compared mode of tumor recurrence between PD and PD-SAR, the rate of local recurrence in the remnant pancreas was significantly higher in PD-SAR (18.8%) than in

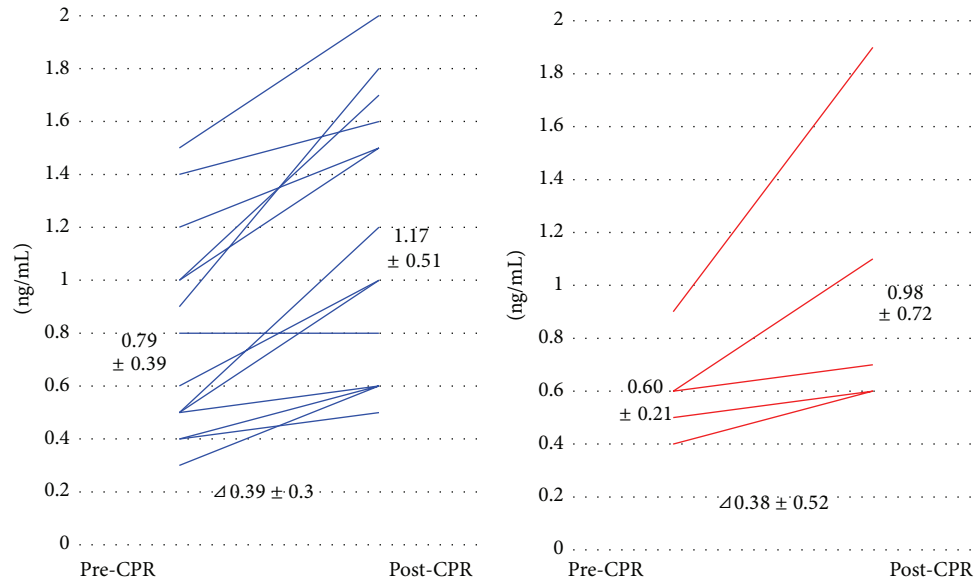


Figure 8: Glucagon stimulating test. CPR: serum levels of C-peptide immunoreactivity.

PD (3.0%). Among 3 patients with local recurrence of the remnant pancreas, 2 had distant metastasis simultaneously and died at 5 and 8 months after PD-SAR, respectively, and 1 had local recurrence of the remnant pancreas alone and died at 18 months. These results suggested that local recurrence of the remnant pancreas after PD-SAR might not affect long-term survival, although further study to accumulate number of cases is required. According to the study of Schmidt et al. [29], on the oncologic benefit of conversion of PD to TP to achieve an R0 resection in PDAC patients with an isolated positive cut margin of the pancreas, 28 patients underwent PD with an isolated positive cut margin without additional resection, while 33 patients had conversion to TP for isolated cut margin involvement to achieve R0 resection. As a result, patients undergoing TP versus PD had a greater MST (18 versus 10 months, $P = 0.04$). Therefore, they concluded that conversion of PD to TP to achieve an R0 resection was associated with a survival benefit. In PD-SAR, however, we made the pancreatic cut line as distal as possible to achieve a negative cut margin, and fortunately all patients except for 2 could obtain negative pancreatic margin and avoid TP. As a result, both OS and RFS were very similar to that after PD.

To the best of our knowledge, there have been no previous reports to examine the postoperative changes of the RPV after PD, although a few studies [30, 31] measured it at one point of time. We examined RPV at 1 and 6 months after pancreatectomy. As a result, RPV was significantly smaller in PD-SAR than in PD at 1 month but showed no significant difference at 6 months. Comparing RPV between 1 and 6 months after PD, it decreased from 10.4 ± 6.0 to 8.5 ± 5.9 ($P = 0.079$), while after PD-SAR it did not change from 5.8 ± 3.8 to 5.4 ± 3.7. These results demonstrated that small remnant pancreas after PD-SAR kept the volume almost unchanged until 6 months, indicating the significance of PD-SAR.

Because RPV after PD-SAR becomes almost half of PD, it was predicted that insulin therapy becomes a big problem after PD-SAR. However, total daily insulin dose was significantly higher in PD-SAR than in PD at 1 month alone, while showing no significant differences between the two groups thereafter. As compared to TP, however, the dose in PD-SAR was significantly lower, and no patients after PD-SAR had experienced hypoglycemic attacks, while all patients after TP had experienced it. Recently, Barbier et al. [3] reported short- and long-term outcomes of 56 patients with TP. In their study, 40% of the patients had a loss of consciousness owing to hypoglycemia and all patients had experienced a median of 10 hypoglycemic episodes per month. Furthermore, 5 deaths were related to TP (two postoperative deaths, one hypoglycemia, one ketoacidosis, and one anastomotic ulcer). They conclude that endocrine and exocrine insufficiency after TP impacts on the long-term QOL. Ourpresent studies on the prediction of postoperative pancreatic functions using several makers revealed no significant differences between PD and PD-SAR except for HbA1c levels at 12 months, and these results suggested that PD-SAR maintained long-term QOL. Finally, we performed GST in selected patients with PD and PD-SAR to confirm insulin secretion ability from the remnant pancreas. Pre- and post-CPR levels and ⊿CPR did not significantly differ between the two groups, revealing enough insulin secretion ability from the remnant pancreas after PD-SAR. In the present study, we did not examine the measurement of future RPV before surgery. It is considered that preoperative measurement of future RPV is useful to predict postoperative pancreatic functions and development

of fatty liver (nonalcoholic fatty liver disease: NAFLD) after PD, as we reported that the RPV less than 10 mL at 1 month is a strong predictor of NAFLD after PD [32].

Recently, it has been recognized that TP with islet cell autotransplantation is an effective surgery for end stage of chronic pancreatitis [33]. However, the possibility of infusion of occult carcinoma cells in the islet preparation restricts the use of this procedure to treat PDAC. In 2001, Liu et al. [34] reported the first successful case of islet cell autotransplantation combined with TP for treatment of PDAC. At 1-year follow-up, HbA1c was 6.2% although the patient remained insulin dependent (18 U/d). The pre- and post-CPR levels (ng/dL) in GST were 0.66 and 0.84, respectively, which were comparable to our data after PD-SAR: 0.60 ± 0.21 and 0.98 ± 0.72. Although islet cell autotransplantation combined with TP for PDAC seems to be feasible, our PD-SAR to avoid TP has broad utility to treat PDAC in terms of oncological safety, simplicity, and low cost.

In conclusion, PD-SAR with preoperative CRT seems to be promising surgical strategy for PDAC of head and/or body with invasion of the splenic artery, in regard to the balance between operative radicality and postoperative QOL.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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Clinical Study

Is Roux-Y Binding Pancreaticojejunal Anastomosis Feasible for Patients Undergoing Left Pancreatectomy? Results from a Prospective Randomized Trial

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Background. After pancreaticoduodenectomy, the Finnish binding pancreaticojejunal anastomosis (FBPJ) seems to reduce the risk for pancreatic fistula (POPF). Our aim was to investigate whether FBPJ is feasible and prevents the risk for POPF even after left pancreatectomy (LP). *Patients and Methods*. 47 consecutive patients underwent LP. 27 patients were recruited on the basis of CT and, of these, 16 patients were randomized on the basis of findings during surgery (transection line must be left of portal vein, as 2-3 cm pancreatic mobilization is required for FBPJ) to receive either Roux-Y FBPJ or hand-sewn closure of the pancreatic remnant. *Results*. Only 34% (16/47) of the patients met the randomization criteria. Clinically significant POPF rate was higher in FBPJ group (60%) compared to thand-sewn closure group (13%; $P < 0.05$). POPF rate in FBPJ group was higher even when compared to all patients with hand-sewn closure (60% versus 37%; $P < 0.05$). Overall, FBPJ was technically feasible for only 28% of patients. *Conclusion*. FBPJ cannot be recommended for the routine closure of the pancreatic remnant after LP, as it was not technically achievable in 72% of the cases. Moreover, the technique does not seem to reduce the risk for POPF compared to the hand-sewn closure.

1. Introduction

Left pancreatectomy (LP) is used to treat benign and malignant lesions in the body and tail of the pancreas or after abdominal trauma. The postoperative morbidity rate remains high, 30–50% [1, 2], and this is mainly due to pancreatic fistula (POPF) resulting from leakage of pancreatic enzymes from the transsection line of the pancreas. In addition to being the most common and clinically relevant complication, POPF is often associated with other complications such as intra-abdominal abscess, delayed gastric emptying (DGE), postpancreatectomy haemorrhage (PPH), wound infection, respiratory complications, and sepsis [1]. The risk for POPF after distal pancreatectomy remains an unsolved problem despite efforts to improve the surgical resection and closure techniques of the pancreatic remnant. These include hand-sewn suture techniques, stapled closure techniques, pancreatic transsection using various energy devices, pancreaticoenteric anastomosis techniques, application of meshes, sealing with fibrin sealants, pancreatic stent placement, and administration on octreotide [3–9]. A recent retrospective cost analysis showed that patients with pancreatic fistula double the cost and dramatically increase health care resource utilization [2, 10].

Previously we have shown that after pancreaticoduodenectomy the novel Finnish binding (purse-string) pancreaticojejunal anastomosis (FBPJ) technique reduces the risk for POPF [11]. The aim of this study was to investigate whether FBPJ is a feasible technique after distal pancreatectomy and whether it prevents the risk for POPF after distal pancreatectomy.

2. Patients and Methods

A prospective, randomized trial was designed to include patients with the type of distal pancreatic resection that is technically possible with FBPJ (RPT arm). In addition, all

pancreatic distal resections were included in the prospective follow-up (PFU arm).

2.1. Surgical Technique. In FBPJ, the pancreatic remnant was inserted 2-3 cm inside the jejunal limb with the aid of seven peripancreatic sutures (4-0 Maxon, Covidien, USA) after which the purse-string suture (4-0 PDS, Ethicon, USA) was tightened and a roux-Y entero-enteroanastomosis was performed (Figure 1). In the hand-sewn closure group, the main pancreatic duct was closed by suturing, followed by oversewing the pancreatic stump with 4-0 Maxon. A Penrose drain was placed near the anastomosis in all patients. A schematic drawing of the FBPJ is shown in Figure 1.

2.2. Recruitment Criteria for the RPT Arm. FBPJ is technically achievable only when the transection line of pancreas is clearly to the left of the portal vein because the pancreatic remnant needs to be mobilized 2-3 cm to be able to insert it into the jejunal limb. All patients were studied preoperatively by contrast-enhanced computer tomography scan (CT). Patients eligible for randomization according to the location of tumour in the CT analysis were recruited for the study. The rest of the patients were included in the prospective follow-up.

2.3. Randomization Criteria for the RPT Arm. After removing the distal pancreas, the patients still considered eligible for the FBPJ (i.e., transection line to the left of the portal vein) were randomized to receive either FBPJ or traditional hand-sewn closure of the pancreatic stump.

2.4. Patient Care and Follow-Up. Perioperatively all patients received a single-dose antibiotic prophylaxis IV (ceftriaxone 2 g, Rocephalin, Roche, Finland, and metronidazole 500 mg, metronidazole, Brown, Germany) and routine antithrombotic (enoxaparin 40 mg, Klexane, Sanofi-Aventis, France, or tinzaparin 4500 IU, Innohep, LEO Pharma, France) prophylaxis s.c. Postoperatively the patients were monitored by the standard pancreatic resection protocol of Tampere University Hospital. Abdominal drain output was recorded daily and the amylase concentration was measured from it on the third postoperative day, and thereafter if the drain still remained in place. The drain was removed when the drain amylase output was less than three times the serum upper limit. The urine trypsinogen strip test was used to detect postoperative pancreatitis and was measured daily during the first postoperative week [12]. Patient demographics (age, sex, BMI, and comorbidities) were compared and postoperative complications (fistulas, bleeding, abscesses, and wound infections) and mortality were defined and compared between the groups. POPF was classified into three grades (A, B, and C) depending on the clinical impact according to the ISGPF classification [13].

2.5. Power Analysis. For the RPT arm, population size was estimated on the basis of the results from our earlier study of FBPJ after pancreaticoduodenectomy [11], where the rate of clinically relevant (grades B-C) POPF was reduced by 50% compared to our historical controls. If the patients with hand-sewn closure had twice as much clinically relevant POPF compared to FBPJ (30% versus 15%), we would need 26 patients in each group to be able to show a statistically significant difference with power $\pi = 0.80$ (α 0.05). We estimated that about one-third of the patients would not meet the recruitment criteria based on CT and that about 10% of the recruited patients would not meet the randomization criteria according to findings during surgery. Thus for 52 randomized patients we would need 58 recruited patients, and for those we would need a population of 78 distal pancreatectomies. We planned to run the interim analysis when 29 patients had been recruited and estimated that about 40 distal pancreatectomies would be needed to achieve this recruited population.

The interim analysis was run in August, 2013. A total of 47 consecutive patients (16 M/31 F) had undergone distal pancreatectomy with the remaining pancreatic head in Tampere University Hospital between October 2009 and July 2013. We were prepared to increase our series but this proved unnecessary after analysing the results of these 47 patients.

The study protocol was approved by the Ethics Committee of Tampere University Hospital. The study was registered with clinical.trials.com NCT02113046.

Statistical analysis was performed using Fisher's exact test, Mann-Whitney U-test, and logistic regression test. $P < 0.05$ was considered statistically significant.

3. Results

Out of the 47 caudal resections, 27 met the recruitment criteria, but only 16 of these met the randomization criteria in the operation (as described in Section 2, the transsection line or the pancreas needed to be clearly to the left of the portal vein for the patient to be randomized). Patients were randomized into FBPJ or hand-sewn group. Out of the 8/16 patients randomised for FBPJ, in two patients, FBPJ was still technically impossible to accomplish and they received a hand-sewn closure. In addition, one had after all an advanced disease, and distal pancreatectomy was not performed. 8/16 were randomized for hand-sewn closure. Thus, of the recruited patients, five received a FBPJ and ten a hand-sewn closure in the RPT arm and 11 in the non-RPT arm. More 20 patients received a hand-sewn closure in the prospective follow-up arm. Thus a total of 41 patients had a hand-sewn closure. The flow chart is shown in Figure 2.

Patients were well comparable for age, sex, and comorbidities. Patient demographics are shown in Table 1. Indications for surgery were malignant tumours in 28 patients, benign tumors in 14 patients, chronic pancreatitis in 1 patient, and pancreatic pseudocyst in 3 patients. The final histopathological diagnoses are shown in Table 2.

The main endpoints of the study were the feasibility of FBPJ in LP patients and the POPF rate. POPF was significantly higher in the FBPJ group, in which 3/5 patients (60%) developed a grade B POPF compared to the hand-sewn group, where 1/8 patients (13%) developed a grade B fistula ($P < 0.05$). In the FBPJ group two patients

Table 1: Patient demographics and postoperative complications in the groups (FBPJ: randomized binding pancreaticojejunal group, hand-sewn rand.: randomized hand-sewn group, and hand-sewn all: all patients with hand-sewn anastomosis).

	FBPJ		Hand-sewn rand.		Hand-sewn all	
n	5		8		41	
Age (median and range)	67	(55–74)	60	(26–80)	66	(26–85)
Gender M/F	1/4		2/6		15/26	
BMI (mean)	28.2		27.2		26	
Smoking	1	(20%)	0		7	(17%)
Alcohol abuse (audit > 6)	0		1	(12.5%)	5	(12.1%)
Diabetes	0		2	(25%)	5	(12.1%)
Cardiac disease	0		1	(12.5%)	3	(7.3%)
Hypertension	2	(40%)	2	(25%)	20	(48.7)
Wound infection	0		0		4	(9.7%)
PPH	0		0		0	
Abscess	3	(60%)	0		9	(21.9)
Pancreatitis (CT verified)	0		1	(12.5%)	2	(4.9%)
Trypsinogen strip test positive	1	(20%)	1	(12.5%)	10	(24.3%)
Length of stay (days)	10	(7–15)	7	(6–9)	7	(6–32)
Readmission	1	(20%)	1	(12.5%)	4	10%
Operative time (mins, median, and range)	170	(136–300)	162	(115–200)	170	(90–305)
Blood loss (mL, median, and range)	750	(300–2350)	750	(300–1300)	750	(100–3600)
Mortality	0		0		0	

Table 2: Final histopathologic diagnoses (FBPJ: randomised binding pancreaticojejunal group, hand-sewn rand.: randomised hand-sewn group, and hand-sewn all: all patients with hand-sewn anastomosis).

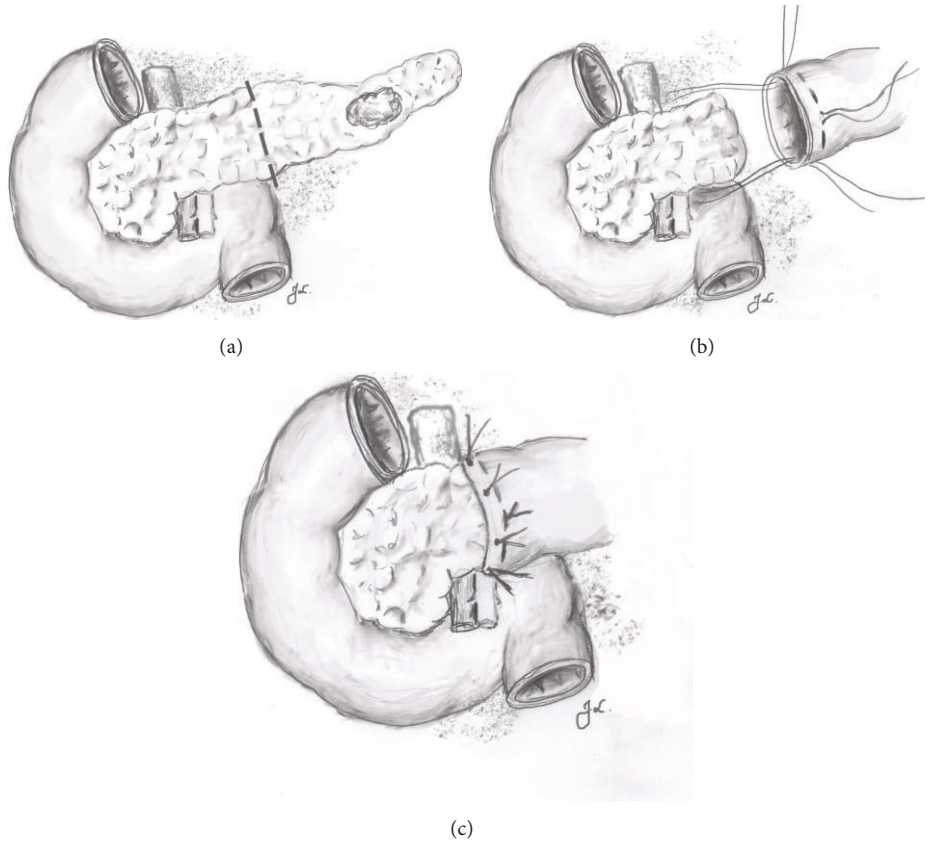
	FBPJ		Hand-sewn rand.		Hand-sewn all	
n	5		8		41	
Adenocarcinoma	2	(40%)	4	(50%)	13	(32%)
Neuroendocrine tumour	3	(60%)	2	(25%)	9	(22%)
Intraductal papillary mucinous neoplasm					4	(10%)
Pseudocyst			1	(12.5%)	3	(7%)
Mucinous cystic neoplasm					2	(5%)
Chr. pancreatitis					1	(2%)
Haemangioma			1	(12.5%)		
Nesidioblastoma					1	(2%)
Kidney ca metastases					1	(2%)
Serous cystadenoma					5	(12%)
None					1	(2%)

had an operatively placed drain removed and needed an interventional radiology placed drain due to subsequent abscess. The third patient had a high amylase output from the operatively placed drain, which was kept in place and removed five weeks postoperatively. In the hand-sewn group the patient who developed a grade B fistula was discharged with the drain but was readmitted and the CT showed pancreatitis and collection of fluid. The operatively placed drain was removed after six weeks, after which no additional drainage was needed. Fistula rates are shown in Figure 2.

The fistula rate in the FBPJ group was significantly higher, not only compared to the RPT hand-sewn group (POPF gr B 60% versus 13%; $P < 0.05$) but also compared to all hand-sewn closures (POPF gr B 60% versus 37%; $P < 0.05$).

In addition to the high fistula rate, only 13/47 (27%) of patients were eligible for FBPJ according to our interim analysis, so we decided to discontinue the study at this point.

30-day mortality was zero. There was no postoperative haemorrhage. No reoperation was needed in either group. Among the prospective follow-up hand-sewn patients, four patients had a wound infection, one patient had a lymphatic leak, and two patients had pancreatitis. Urine trypsinogen strip test was positive on two or more days in one patient in FBPJ (20%) and in ten patients in all hand-sewn groups (24%; NS) suggesting postoperative pancreatitis. Blood loss during surgery, length of hospital stay, and readmission rate to hospital were comparable between the groups. All these characteristics are shown in Table 1.



(a) (b) (c)

Figure 1: Schematic drawing of the binding (purse-string) pancreaticojejunal anastomosis (FBPJ) after left pancreatectomy. The transsection line needs to be clearly to the left of the portal vein (a). The pancreatic remnant is mobilized 2-3 cm and it is inserted inside the jejunal loop with the aid of anchoring sutures (b). The purse string applied in the jejunum is tightened to secure the anastomosis (c).

4. Discussion

POPF remains the most common complication after distal pancreatectomy with an incidence between 20 and 40% [3, 14, 15] and many surgical techniques for resection and closure of the pancreatic remnant have been studied without major success [3–5, 7, 9, 14, 16–19]. We have previously shown that the novel FBPJ technique reduces the risk for pancreatic fistula after pancreaticoduodenectomy [11], and within this study we investigated whether the FBPJ technique was feasible even for LP. We concluded that FBPJ cannot be recommended for a routine for pancreatic remnant closure after LP, as it is not technically achievable in most of the cases and does not seem to reduce the risk for POPF compared to the hand-sewn closure.

Stapler and suture closure are the two most common strategies for managing the pancreatic remnant. In the DISPACT trial [3], which included 450 patients, two groups of patients were randomized to either stapler or hand-sewn closure of the pancreatic remnant with no difference found in POPF incidence. The meta-analysis likewise revealed no significant differences between suture and stapler closure [4]. Several other methods have also been tried [16]. Recently the use of saline-coupled radiofrequency dissector in stump closure reduced the POPF rate, but further prospective studies are needed [5]. Pancreaticojejunostomies (PJ) have also been performed to reduce the fistula rate and the findings have been encouraging [6, 8]. In 2007 Wagner et al. [6] found a zero POPF rate Roux-en-Y end-to-side PJ after suture closure versus 20% in suture closure only. In their study, POPF was not classified into three grades according to the ISGPF definition and the number of patients was only 23 versus 20 in either group. In 2013 Meniconi et al. [8] reported a retrospective analysis where the fistula rate was also zero in PJ and 29% in the hand-sewn group. In the PJ group the main pancreatic duct was closed, after which the pancreatic remnant was invaginated into a jejunal loop. This was a nonrandomized retrospective study on a small group of patients (24 versus 12). We have shown previously that after pancreaticoduodenectomy the novel FBPJ technique reduces the risk for pancreatic fistula [11].

In this study we wanted to investigate whether FBPJ can also be used in distal pancreatectomy and whether it reduces the risk of pancreatic fistulae. FBPJ is technically achievable only when the transsection line of the pancreas is clearly to the left of the portal vein because the pancreatic remnant needs to be mobilized 2-3 cm before it can be inserted inside the jejunal loop. This is the reason why only 27 out of 47 patients who received an LP resection were recruited. We estimated the suitable patients based on the location

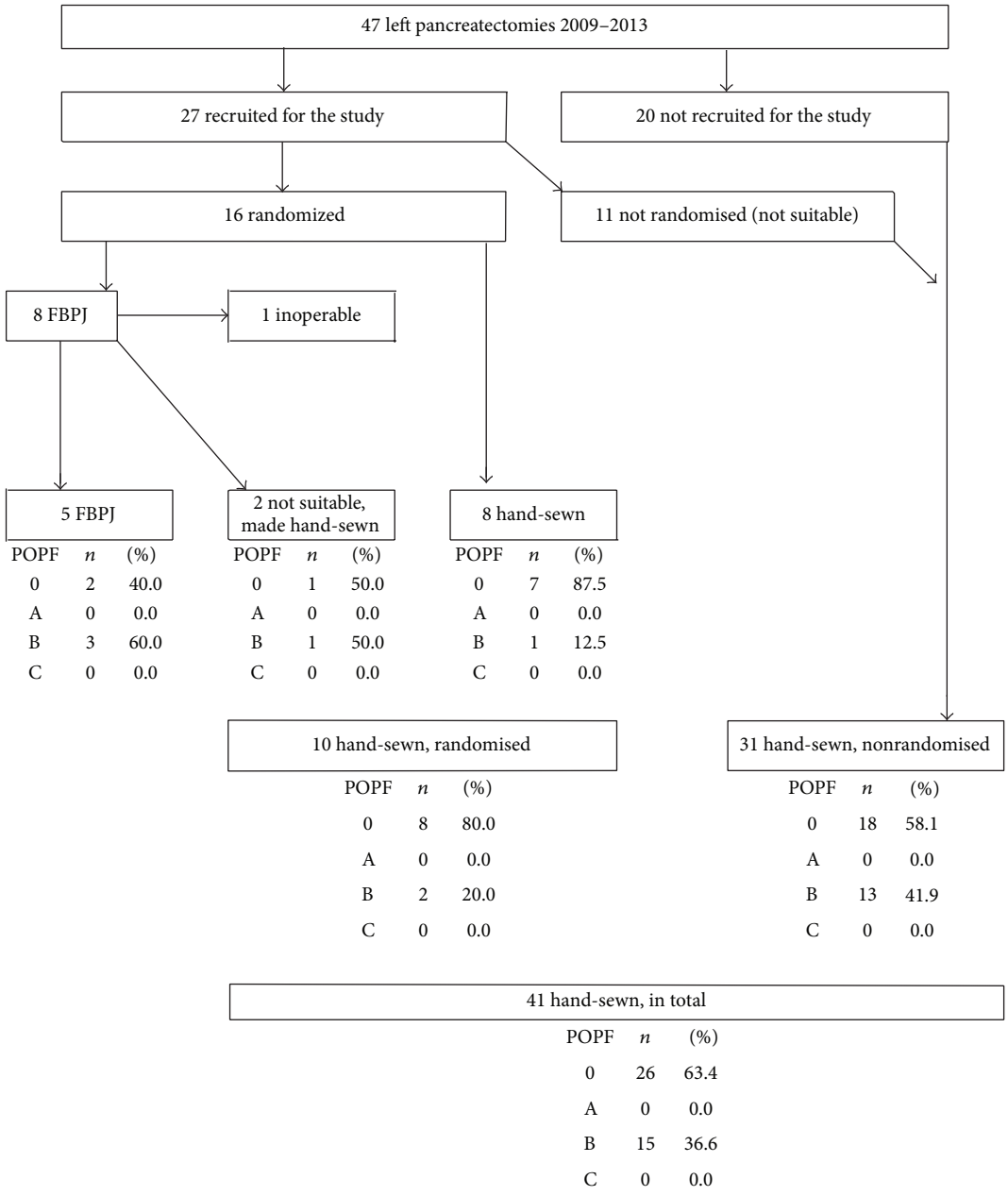


Figure 2: Flow chart of the study patients and POPF rate in each group. Out of 47 consecutive patients, 27 were recruited and only 16 of these met the randomization criteria. Finally, only 5 patients received a FBPJ (POPF 60%) and 8 patients a hand-sewn closure (POPF 12.5%) from the randomized patients. The POPF rate was 36.6% in all hand-sewn closure patients.

of the tumour preoperatively with the help of contrast-enhanced CT scan. Randomization was done intraoperatively and only 16 patients out of the total 46 met the randomization criteria, and of these one had an inoperable tumour and in two the FBPJ was impossible to perform. In most of the distal pancreatectomies it is not technically possible to mobilize the pancreatic remnant 2-3 cm in order to insert it inside the jejunal loop. The FBPJ would therefore have been technically feasible for only 28% (13/47) of patients. In the other studies where PJ was performed with good results [6, 8] the pancreatic remnant was invaginated instead of being inserted inside the jejunal loop. The anastomosis was made by capsule-to-seromuscular single layer sutures when the pancreatic remnant did not need to be mobilized as in our FBPJ technique. This may explain why it was possible to perform PJ on all patients in those studies.

FBPJ did not decrease the number of pancreatic fistulae in this small study. On the contrary, it seemed to increase the cases of POPF. In addition, FBPJ anastomosis is feasible in only a minority of patients, which is why we discontinued the study after performing the interim analysis. The number of patients who received FBPJ was small, but, as most patients

did not seem to be eligible for this kind of anastomosis, it was challenging to achieve a large enough patient population in the FBPJ group to show the differences in the fistula forming.

In conclusion, the FBPJ technique, which reduces the POPF rate after pancreaticoduodenectomy, is suitable only for selected patients with LP and thus it cannot be recommended for routine use in the closure of the pancreatic remnant. In addition, according to this study it does not seem to reduce the risk of POPF.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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Clinical Study

Pancreas-Preserving Approach to "Paraduodenal Pancreatitis" Treatment: Why, When, and How? Experience of Treatment of 62 Patients with Duodenal Dystrophy

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Background. The term "paraduodenal pancreatitis" (PP) was proposed as a synonym for duodenal dystrophy (DD) and groove pancreatitis, but it is still unclear what organ PP originates from and how to treat it properly. *Objective*. To assess the results of different types of treatment for PP. *Method*. Prospective analysis of 62 cases of PP (2004–2013) with histopathology of 40 specimens was performed; clinical presentation was assessed and the results of treatment were recorded. *Results*. Preoperative diagnosis was correct in all the cases except one (1.9%). Patients presented with abdominal pain (100%), weight loss (76%), vomiting (30%), and jaundice (18%). CT, MRI, and endoUS were the most useful diagnostic modalities. Ten patients were treated conservatively, 24 underwent pancreaticoduodenectomies (PD), pancreatico- and cystoenterostomies (8), Nakao procedures (5), duodenum-preserving pancreatic head resections (5), and 10 pancreas-preserving duodenal resections (PPDR) without mortality. Full pain control was achieved after PPRDs in 83%, after PDs in 85%, and after PPPH resections and draining procedures in 18% of cases. Diabetes mellitus developed thrice after PD. *Conclusions*. PD is the main surgical option for PP treatment at present; early diagnosis makes PPDR the treatment of choice for PP; efficacy of PPDR for DD treatment provides proof that so-called PP is an entity of duodenal, but not "paraduodenal," origin.

1. Introduction

Cystic dystrophy of the duodenal wall, or duodenal dystrophy (DD), is a relatively rare disease which is essentially a chronic inflammation of ectopic (aberrant, heterotopic) pancreatic tissue in the duodenal wall. This entity was first described in 1970 by French authors Potet and Duclert [1], and "duodenal dystrophy" as a term for this condition was also proposed by these authors.

Despite genetic predisposition, heterotopic pancreatic tissue in any abnormal location is usually diagnosed in adults presenting with complications. Chronic pancreatitis developing in the intraduodenal ectopic pancreas is characterized by fibrotic thickening and infiltration of the duodenal wall (typically, its vertical branch) with cyst formation in its muscle and/or submucosal layers. Initially, only ectopic pancreatic tissue may be involved, but progressing ectopic pancreatitis may result in the compression of the main pancreatic or accessory pancreatic duct and subsequent obstructive pancreatitis in the orthotopic (main) pancreas [1–7]. There is still uncertainty with the terminology for this condition, and it is rooted in an uncertain localization of the

primary lesion. For example, "groove pancreatitis" and DD are considered synonyms by some authors [5], whereas others believe that DD is one of the causes of "groove pancreatitis" (groove pancreatitis is a form of focal chronic pancreatitis in the pancreatic tissue between the duodenal wall and the intrapancreatic portion of the common bile duct (CBD) [8]). DD is classified into cystic or solid types according to predominating component (fibrotic thickening or cyst formation) [6, 7, 9–12]. Against the background of chronic inflammation in the orthotopic pancreas, it is difficult to confirm DD of the solid type, and, hence, cystic variant is found much more often, so the diagnosis of DD generally implies its cystic form. Cysts of the ectopic pancreas can be either postnecrotic or represented by a cystically dilated bile duct with preserved or desquamated epithelium [6–8]. More often (but not necessarily), the disease occurs against the backdrop of regular alcohol consumption. In 15 retrospective reports, 79.68% (251 out of 305) patients with duodenal dystrophy were alcohol abusers [13].

Duodenal dystrophy is typically manifested by recurrent episodes of acute pancreatitis, recurrent or chronic abdominal pain in the epigastrium, left, or right upper quadrant, weight loss, and nausea and vomiting caused by the duodenal stenosis. As the pathological process in the orthotopic pancreas progresses, the clinical picture is becoming more similar to that of chronic pancreatitis [4, 5]. Pancreatic ectopy within the gastric wall (25–60%) and duodenum (25–35%) is the most common gastrointestinal heterotopia [13, 14]. Nevertheless, DD is found relatively infrequently [9–12]. The instrumental semiotics of DD is well studied: the diagnosis is based on CT or MRI imaging and endosonography [10–15]. The conservative treatment is based on the use of regular or long-lasting somatostatin analogues [16–18] and can be complemented with endoscopic manipulations [19, 20]. If the above approaches fail, surgical procedures are considered, and pancreaticoduodenectomy (PD) remains the method of choice [21–33]. When DD is complicated by obstructive jaundice, duodenal stenosis, and chronic orthotopic pancreatitis with its typical complications, as well as in cases of suspected tumor [34, 35], the conservative treatment [36, 37] is either *a priori* ineffective or not indicated.

The aim of this prospective study was to analyze the clinical and demographic characteristics of patients and methods of DD diagnosis and treatment.

In 2004, Adsay and Zamboni [5] suggested a term "paraduodenal pancreatitis" for the duodenal dystrophy, and it has become widespread. However, we refrained from such renaming based on our own data definitely indicating the localization of the pathology in the duodenum but not in the "paraduodenal" area (see Sections 3 and 4).

2. Patients and Methods

Sixty-two patients with DD were evaluated, treated, and followed up by the authors at the Moscow hospitals mentioned in authors affiliations during 2004–2013. All patients were symptomatic and demonstrated characteristic signs of DD on CT, MRI, and endosonography. By January 2013, 52 patients had undergone surgical treatment. The histological diagnosis of the cystic type of DD was based on the detection of pancreatic tissue isolated from the orthotopic gland and/or cystic masses in the duodenal wall with elements of transformed pancreatic tissue. When the duodenum was not available for histological examination, the diagnosis was based on the CT, MRI, or endosonographic findings on the ground of the pathognomonic signs: significant (>10 mm) thickening of the duodenal wall, cystic masses of variable size within the duodenal wall [10–13, 32], demarcation of pathological changes within the duodenal wall from the orthotopic pancreas, and medial displacement of the gastroduodenal artery from the pathological mass.

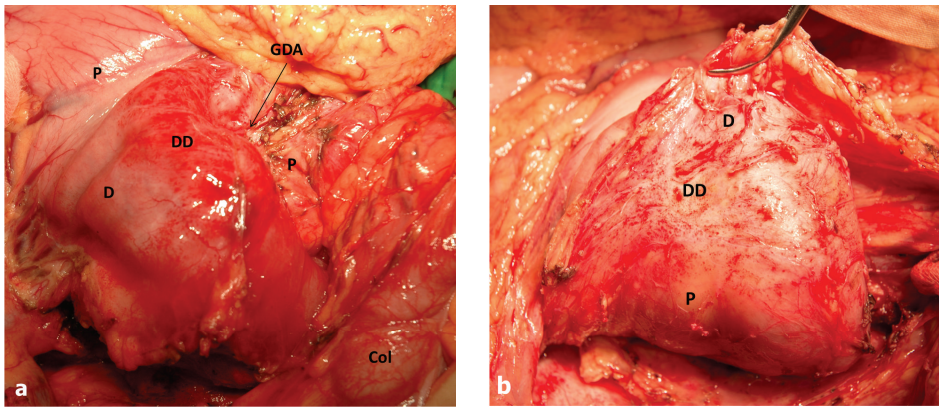
Clinical characteristics, pathological findings, data of various imaging techniques, and intraoperative, postoperative, and follow-up data were recorded for all patients. Clinical data included patient's age, gender, alcohol consumption, date of diagnosis, symptoms (weight loss or weight gain, vomiting, abdominal pain, jaundice, and steatorrhea), and enzyme therapy. Laboratory tests included C-reactive protein, fibrinogen, ESR, creatinine, electrolytes, bilirubin, AP, GGTP, ALT, and AST. Imaging data were evaluated by an attending surgeon jointly with a radiologist and gastroenterologist.

2.1. Procedures. The description of standard *pylorus preserving pancreaticodudenectomy* can be found elsewhere. As draining procedures we used pancreaticojejuno or cystopancreaticojejunostomy. As duodenum-preserving operations, the subtotal pancreatic head resection under the names of Bern [38] or Frey procedure [39] was used, which means the same amount of resected pancreatic tissue after modifications described by Frey and Mayer in 2003 [39].

Total pancreatic head resection with segmental duodenectomy including minor and major papilla (*Nakao procedure*) was performed by conserving the right gastric artery and the anterior inferior pancreaticoduodenal artery. Five to seven cm of the first portion, the third portion, and the anal side of the second portion of the duodenum is preserved with good arterial circulation. Reconstruction of the alimentary tract is then performed with pancreatogastrostomy, end to end duodenoduodenostomy, and end to side choledochoduodenostomy [40].

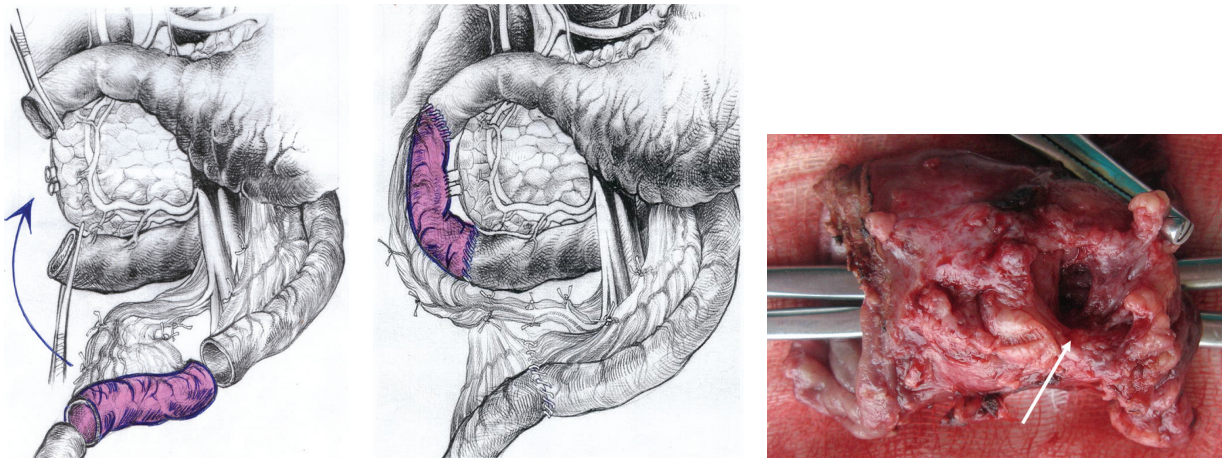
Pancreas-preserving operations for duodenal dystrophy begin through the midline incision with exploration and an extensive Kocher's maneuver well to the left. After detection of the inflammatory mass in the second part of the duodenum (Figures 1(a) and 1(b)), cholecystectomy is performed and the papilla is stented through the cystic duct stump with a Dogliotti probe as a landmark.

When the length of affected zone is short its *resection with duodenoduodenostomy* is possible but the probability of tension is a limitation of such a method. If the length of inflammatory area is not spread beyond the second duodenal portion the surgeon can choose its *resection with intestinal interposition for reconstruction* (Figures 2(a), 2(b), and 2(c)). In spite of moderately changed or unchanged pancreas, very often at surgery the duodenum and pancreatic head look inseparable due to prominent fibrosis around the duodenum



(a) (b)

Figure 1: Isolated form of the duodenal dystrophy (DD). Male, 57 y.o. Itraoperative photo. (a) Front view. Kocher's maneuver is completed. Deformation, hyperemia, and thickening of the medial duodenal wall with infiltrated fibrotic tissues around the duodenum (D). The gastroduodenal artery (GDA) is shifted forward and medially, lying in the groove between the unchanged pancreatic head (P) and affected duodenal wall. (b) Back view. Extensive Kocher's maneuver is completed. The duodenum and pancreatic head (P) look like inseparable monolith due to prominent fibrosis around the second portion of the duodenum (D). Col—transverse colon, Py—pylorus.



(a) (b) (c)

Figure 2: Duodenal dystrophy with moderate chronic orthotopic pancreatitis. Patient, 32 y.o. Scheme of the pancreas-preserving resection of the second portion of the duodenum. (a) The second part of the duodenum, including the main papilla, is removed and the segment of the proximal jejunum supplied by the artery and vein is cut out and prepared for transposition between the 1st and 3rd portions of the duodenum; (b) the shifted segment is interposed between the 1st and the 3rd parts of the duodenum. Jejuno-jejuno- and duodeno-jejuno-anastomoses are performed. The bile and the pancreatic ducts were implanted in the neoduodenum 4 cm below the proximal duodeno-jejuno-anastomosis; (c) the resected specimen of the second part of the duodenum. A large scarry-sided cyst in the medial duodenal wall is shown (arrow). Forceps were introduced into the duodenum to show the absence of communication between the cystic and duodenal lumen.

(Figures 1 and 3) and this is the main difference between the corresponding procedures for familial adenomatous polyposis. The duodenum is transected 2-3 cm below the pylorus and 3 cm below the main papilla. The second portion of the duodenum is detached from the pancreas by division of the short vessels by ultrasound scissors up to major papilla. Usually, during this detachment at the level of the major papilla, intramural duodenal cyst(s) is(are) opened and its(their) form(s) and location can be different: some of them are placed along one side of papilla vateri and some are surrounding it (Figure 3). Following the transection of the common bile and the main pancreatic ducts and detachment of the duodenum from the pancreatic head, the whole of its second part, including the main papilla, is removed (Figure 2(a)). In the case of direct duodeno-duodenal anastomosis it forms by end-to-end-technique. In case of jejunal pouch method, a 10 cm segment of the proximal jejunum, supplied by the artery and vein, 50 centimeters below the Treitz ligament, is cut out and passed through the mesocolon (Figure 2(a)). The shifted segment is interposed between the first and the third parts of the duodenum and jejuno-jejuno- and distal duodeno-jejuno-anastomoses are performed (Figure 2(b)).

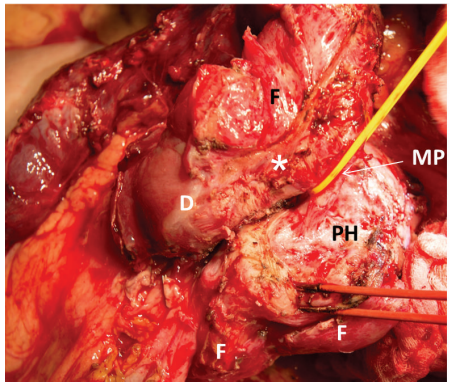


Figure 3: Isolated form of the duodenal dystrophy (DD). Male, 57 y.o. Intraoperative photo. Front view. Kocher's maneuver is completed. The first, third, and fourth portions of the duodenum (D) are detached from the pancreas head (PH) without its injury. The duodenal cyst located around the major papilla (MP) was opened and the papilla was taken by yellow tape. The fibrosis (F) was marked and medial cystic wall was left on the pancreas head (PH) in order not to damage it. There is no pancreatic tissue attached to the duodenal wall (∗).

When the inflammation and scarring are not so pronounced, it is possible to remove all the cystic walls without injury of the pancreas (Figure 2(c)); if the fibrosis is marked it is better to leave medial cystic wall on the pancreas in order not to damage it (Figure 3). The latter is safe with regard to possible relapse because the cysts have no epithelium due to long-term inflammation. Frozen section of the removed duodenum is mandatory to exclude cancer.

If inflammation and fibrosis of the duodenal wall expand beyond the second duodenal portion, the *subtotal duodenectomy* is preferable (Figures 4(a)–4(c)). Duodenum is transected 2-3 cm below the pylorus. The ligament of Trietz is incised, and the proximal jejunum is transected with the gastrointestinal stapler or by cautery and detached from its short mesentery. The freed jejunum is transferred to the right, behind the superior mesenteric vessels, and the third and fourth portions of the duodenum are detached from the pancreas by division of the short vessels between suture ligatures or by ultrasound scissors up to the level of the major papilla (Figure 5).

The proximal jejunum, mobilized by division of one or two jejunal branches but preserving the arcades, is passed either behind or in front of the superior mesenteric vessels for an end-to-end (Figure 4(b)) or Roux-en-Y anastomosis with the duodenum (Figure 4(c)). If cyst spreads up to stomach wall or there is a peptic duodenal or gastric ulcer the procedure can be added by distal gastrectomy with subsequent Roux-en-Y gastroenterostomy.

The papilla has no landmarks except the Dogliotti probe which helps to identify it around "fibrotic fields." The common bile duct and the bounded to its inferior aspect pancreatic duct are transected. If narrow the pancreatic duct can be intubated with a 1.3 mm stent the procedures are completed by reconstruction of bile and pancreatic ducts, which are sutured together and implanted in the duodenum 3 cm below direct duodenal anastomosis or in the neoduodenum 4 cm below the duodenojejunostomys (Figures 2 and 4). All the bowel anastomoses are made using a single layer continuous 4/0 absorbable suture. The choledocho-pancreaticojejunostomy is carried out with a single layer of interrupted 5/0 absorbable sutures by duct-to-mucosa technique (Figure 6). We used drainage of the common bile duct through the cystic duct stump and drainage of the upper right abdominal quadrant.

The *conservative treatment* included abstaining from alcohol, administration of analgesics, proton pump inhibitors, somatostatin analogues, nutritive support (parenteral and/or tube feeding), additional endoscopic procedures, or ultrasound-guided punctures and biopsies. Surgery was performed after failure of conservative therapy or occurrence of complications.

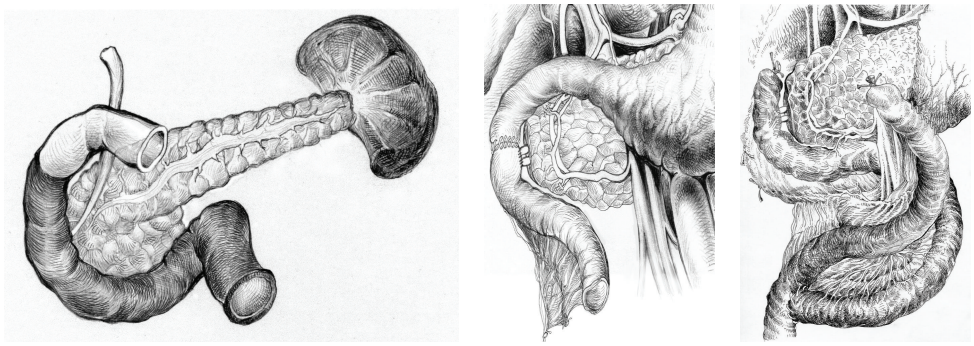
The results of treatment were followed up for a period of 12 to 58 months (median 19 months). Body weight and body mass index were measured at baseline, at presentation, and 12 months after surgery, that is, when most notable body weight changes are observed. At later terms, body weight variations were insignificant in all patients. Preoperative weight loss was recorded from patients' medical histories. The amount of pure alcohol consumed was calculated based on patient's information and might have been underestimated. All patients received pancreatin microgranules (Creon) at doses eliminating diarrhea.

The prevalence of pancreatic ectopy within the duodenal wall was estimated from macro- and microscopic findings of 100 sequential autopsies after nonabdominal deaths at the Moscow City Clinical Hospital No. 12.

2.2. Statistical Analysis. Statistica software (data analysis software system, version 8.0 StatSoft, Inc. 2001; MedCalc version 11.6.0.0) was used for the statistical analysis. Descriptive statistics were applied with absolute and relative frequencies. Fisher exact test was used for the comparison of the efficacy of the treatment methods. Two-sided P values were always computed, and an effect at $P < 0.05$ was considered statistically significant. The distributions of age at operation, alcohol abuse, weight, and BMI are described as medians with interquartile ranges. The numbers of the complications in the groups are expressed as integers without percentage in case of small sample size. Data values are presented on a continuous scale, but distributions different from normal (e.g., patient age) were compared using the Kruskal-Wallis test. One-way analysis of variance was used to test the difference between the means for several groups. Prior to the ANOVA test, Levene's test for equality of variances was performed. The results are presented in an ANOVA graph and associated P values if the means for at least two of the groups differ significantly.

3. Results

Ectopic pancreatic tissue in the medial duodenal wall was found in three of 100 pancreaticoduodenal specimens from subjects who died of nonabdominal diseases and in none



(a) (b) (c)

Figure 4: Duodenal dystrophy with moderate chronic orthotopic pancreatitis. Patient, 43 y.o. Scheme of the pancreas-preserving subtotal duodenectomy: (a) The parts of the duodenum to be removed are shown in black; (b) completion of the procedure by replantation of pancreatic and common bile ducts into the jejunum 1–1.5 cm below the duodenojejunoanastomosis; (c) patient 49 y.o. Variant of the completion of the pancreas-preserving subtotal duodenectomy with distal gastrectomy by Roux-en-Y reconstruction in case of stomach involvement or peptic ulcer.

Table 1: Characteristics of patients with duodenal dystrophy.

	Procedure					
	PD + Nakao $n = 29$	DPPHR $n = 5$	PPDR $n = 10$	Draining procedures $n = 8$	Conservative treatment $n = 10$	All $n = 62$
Age	45 (39–55)	40 (39–45)	48 (44–51)	48 (45–52)	44 (37–51)	46 (39–52)
Alcohol consumption before disease onset (mL)	72 (70–72)	72 (72-72)	68.5 (54–74)	66 (60–72.75)	72 (63–75)	72 (60–72)
Body mass before disease onset	82 (78–88)	84 (83–85)	84 (81–86)	86 (82–89)	89 (81–92)	84 (80–89)
Body mass at presentation	72 (68–78)	69 (68–73)	67 (65–71)	70 (69–74)	71 (68–72)	70 (67–75)
Body mass after surgery	78 (75–80)	73 (71–74)	80 (78–83)	72 (70–73)	71 (69–73)	75 (71–79)

The values are presented as medians with interquartile ranges (in brackets). PD: pancreaticoduodenectomy, Nakao: Nakao procedure, DPPHR: duodenum-preserving pancreatic head resection, PPDR: pancreas-preserving duodenal resections.

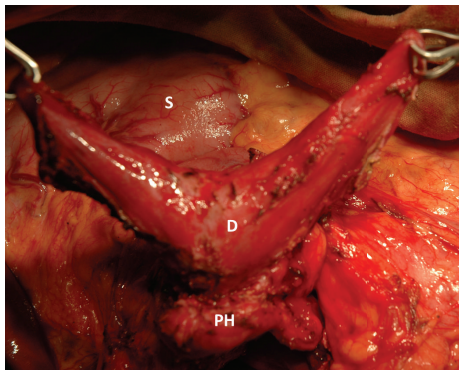


Figure 5: Isolated form of the duodenal dystrophy. Male, 57 y.o. Intraoperative photo. Side view. Kocher's maneuver is completed. Duodenum (D) was transected at the level of ligament of Trietz and 3 cm below the pylorus. The first, third, and fourth portions of the duodenum are detached from the pancreas by division of the short vessels by ultrasound scissors up to the level of the major papilla. S—stomach.

of these cases where the ectopic pancreas was associated with the orthotopic gland. Minor duodenal papilla was not found in two cases, and in one case it was located in the vicinity of the ectopic gland. No alterations were found in the heterotopic tissue, in the orthotopic gland, and in the surrounding tissues.

Duodenal dystrophy was diagnosed in 41 (12.7%) of 323 patients undergoing surgery for chronic pancreatitis in HPB department of Vishnevsky Institute of Surgery in 2005–2011, one of the study sites.

Our series included 59 males and 3 females aged 28 to 73 years (mean age 45.3 years); 57 patients (92%) regularly consumed alcohol (Table 1). Disease duration prior to the diagnosis was 1 to 168 months. Preoperatively, pancreatitis was diagnosed in all patients, with the exception of two women with no history of alcohol consumption and with a suspected cystic tumor of the pancreatic head. All patients were symptomatic at presentation. Weight loss was found in 57 (90%) patients (on average 15.1 kg, range 4 to 30 kg),

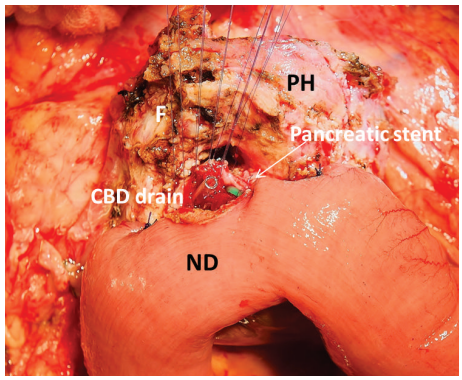


Figure 6: Isolated form of the duodenal dystrophy (DD). Male, 57 y.o. Itraoperative photo. Front view. The subtotal duodenectomy is performed: the first, third and fourth portions of the duodenum are detached from the pancreas head (PH) and removed. Jejunum transferred from below is becoming the neoduodenum (ND). The posterior wall of the choledocho-pancreatico-jejunostomy is sutured by duct to mucosa technique. The tip of the common bile drain duct and stent in the narrow pancreatic duct are visible. Marked fibrotic massif (F) surrounds the pancreatic head (PH) and will be used to cover the front wall of the anastomosis.

Table 2: Prevalence of symptoms at presentation.

Abdominal pain	62 (100%)
Jaundice	10 (16%)
Vomiting/duodenal obstruction	20 (32%)
Weight loss	56 (90%)
Tumor suspicion	2 (3.2%)

Table 3: Methods used for duodenal dystrophy diagnostics.

Transabdominal ultrasound	100%
MDCT	100%
MRI + MRCP	42%
Endoscopic ultrasound	66%

MDCT: multidetector computed tomography, MRI: magnet-resonance imaging, MRCP: magnet-resonance cholangiopancreatography.

vomiting was reported by 12 (20%), and jaundice was present in 8 (11%) patients. Cholestasis without jaundice was found in 10 (16%) patients. Nine (14.5%) patients had acute pancreatitis within 3 or less months before diagnosis. Forty (64%) patients had one symptom of the disease, and 21 (33.5%) patients had two or more symptoms (Table 2).

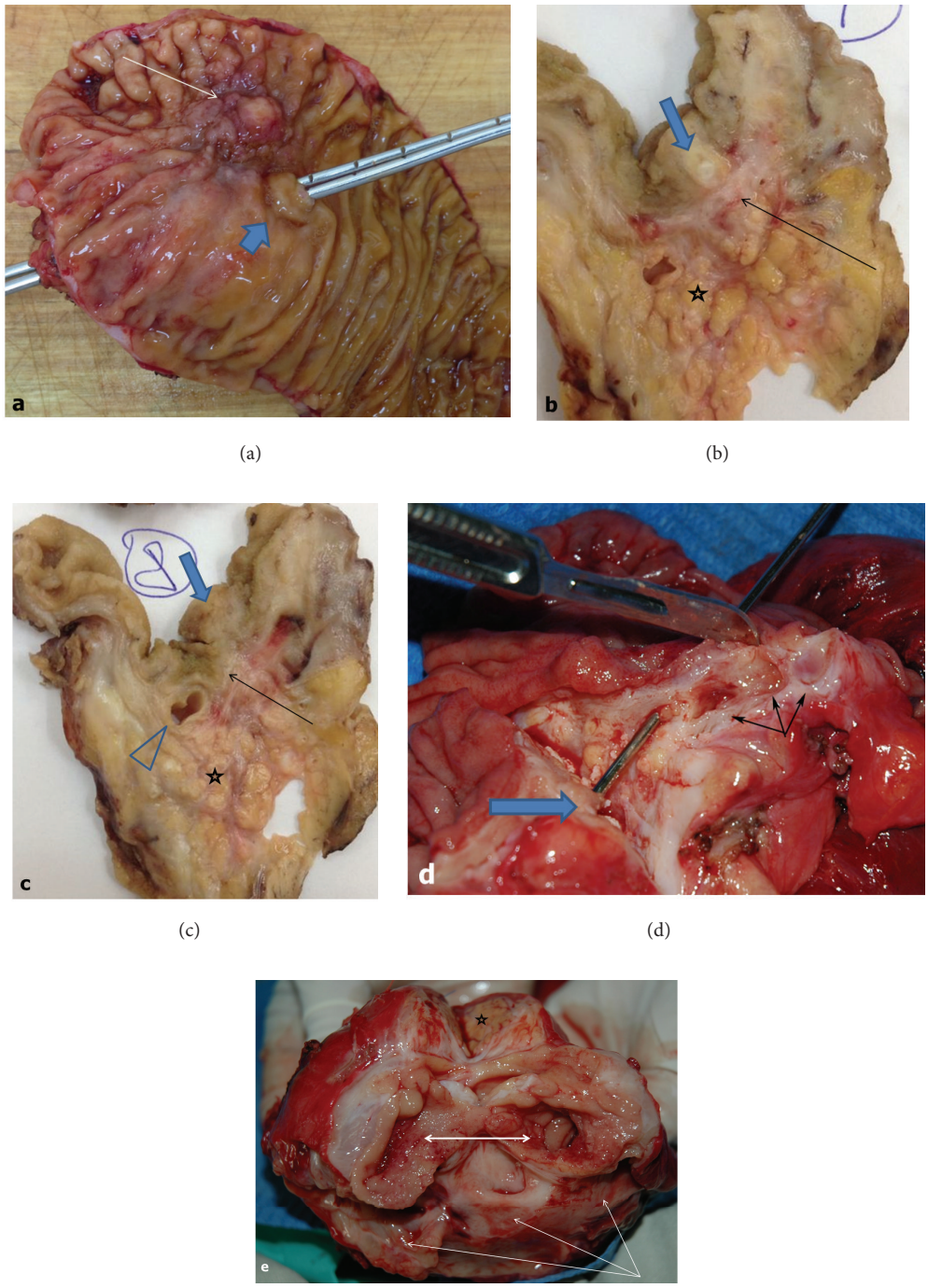
In 39 cases, the diagnosis was confirmed by histopathology of the removed pancreaticoduodenal or duodenal specimens. Typically, the ectopic tissue was found in the muscle layer and, when the size of the mass was large enough, also in the submucosal layer of the duodenum in close proximity to and often involving the major duodenal papilla (60 cases) (Figures 7, 8, and 9). The minor duodenal papilla was not detectable in the majority of cases, but clearly discernible outside the pathological lesion in 5 cases. Cysts could be lined with secretory pancreatic epithelium or composed of fibrotic tissue with polymorphic cell infiltration (Figures 9 and 10). When duodenum-preserving pancreatic head resection or draining procedures were performed, pathohistological examination of pancreatic tissue only was possible. A severe chronic "orthotopic" pancreatitis with massive fibrosis and the presence of pseudocysts and/or stones was found in 50 (80.6%) patients; changes in the orthotopic pancreas were moderate in 10 (16%) patients and mild in two cases (3.2%).

3.1. Imaging and Endoscopy. The use of various procedures is given in Table 3. Abdominal ultrasound and computed tomography with intravenous contrast as well as esophagogastroduodenoscopy were performed in all patients. Only in two cases, duodenal dystrophy was suspected based on transabdominal ultrasound findings. In all cases, intrinsic contour bulge of the medial duodenal wall into the lumen was found (Figure 11), and it was associated with significant duodenal stenosis in 21 (33.6%) patients. In three patients (4.8%), the duodenal portion downstream stenosis could not be reached by the endoscope. In 20 (32%) patients, the following conditions were also found: erosive esophagitis in 11 (17.6%) patients, erosive and ulcerative duodenitis in 7 (11.2%), and erosive gastritis in 12 (19.2%) patients. X-ray examination of the stomach showed evidence of severe stenosis with stomach dilation in 8 (12.8%) patients (Figure 12).

MRI and MRCP were performed in 26 (41.6%) patients. The main CT and MRI findings in DD patients included thickening, infiltration, and cystic structures in the duodenal wall (Figures 13(a)–13(e)). Endoscopic ultrasound (EUS) was performed in 40 (64%) patients, and the main signs of DD were duodenal wall thickening and presence of hypoechoic cavities (100%) in the muscular and/or submucosal layer of the duodenal wall (Figures 14(a)–14(d)) [32]. The sensitivity of CT, MRI, and EUS was 95%, 84%, and 94%, and specificity was 94%, 86%, and 98%, respectively.

Signs of chronic pancreatitis in the orthotopic gland, such as calcificates, tissue heterogeneity, cysts, enlarged pancreatic head, MPD, and common bile duct dilation, were found in 50 (80.6%) patients. Cystic lesions in the head of the pancreas were found in 16 (26%) patients and the diagnosis of them was "duodenal dystrophy associated with chronic pancreatitis of the orthotopic gland."

3.2. Patients and Procedures. Before surgery, all patients were observed by the gastroenterologist and received treatment for chronic pancreatitis. Before PD, four patients were subjected to ultrasound guided cholecystostomy for obstructive jaundice, and one patient underwent EUS-assisted transduodenal stenting of the duodenal wall cyst. Surgery was proposed to all patients. Ten patients refused for various reasons and continued conservative therapy under supervision of a gastroenterologist. Only 3 of 10 patients demonstrated improvement on conservative therapy and dietary restrictions, but pain episodes were not completely controlled in all patients. Indications for 52 patients who had undergone surgery are presented in Table 2. The type of proposed interventions changed as the surgeons were becoming aware that DD constituted a separate pathological entity which

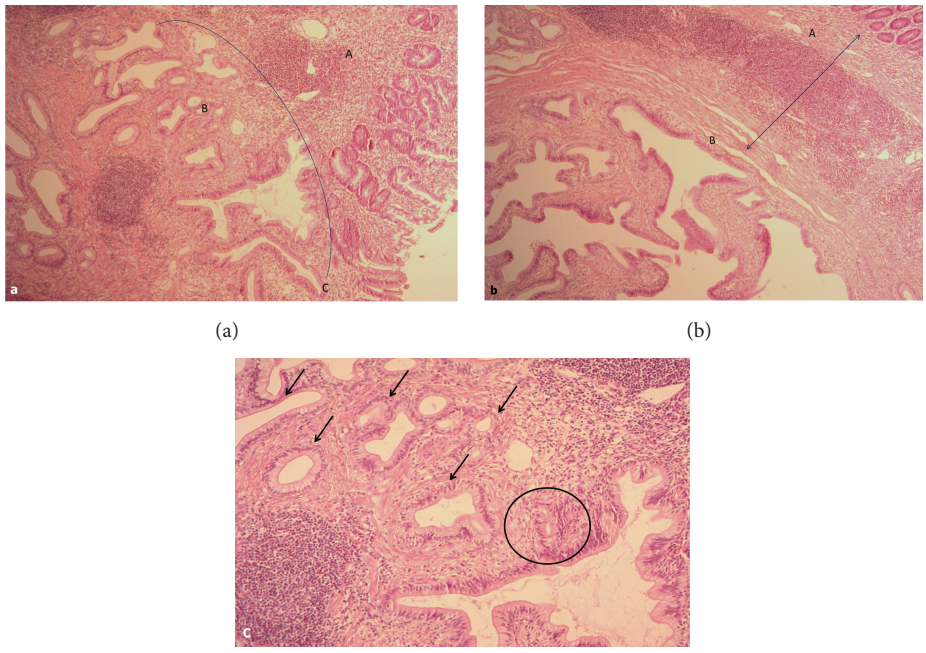


(a) (b)

(c) (d)

(e)

Figure 7: Removed pancreaticoduodenal specimen. (a) Patient 53 y.o. Duodenal dystrophy with chronic orthotopic pancreatitis. Ectopic pancreas within the medial wall of the duodenum (arrow) 1 cm from the main duodenal papilla (wide arrow) with a probe passed through the common bile duct and pancreatic duct; (b) and (c) macrophotograph. Section through the ectopic pancreas. The duodenal wall (arrow) separates the ectopic gland (wide arrow) and the head of the orthotopic pancreas (asterisk) with severe chronic inflammation. The ampulla of Vater (arrowhead) is 0.5 cm from the heterotopic gland; (d) patient 43 y.o. Duodenal dystrophy with moderate chronic pancreatitis in the main pancreas. The probe is passed through the ampulla of Vater. Septated cysts 0.5–1.5 cm in diameter (triple arrow) in the duodenal wall are isolated from the head of pancreas; (e) patient 34 y.o. Duodenal dystrophy with moderate chronic pancreatitis in the main pancreas (asterisk). The second portion of the duodenum is transversely dissected (two-headed arrow). The cyst up to 5 cm in diameter is spread along the whole duodenal wall (triple arrow).



(a) (b)

(c)

Figure 8: Microphotograph. Patient 53 y.o. Duodenal dystrophy with chronic orthotopic pancreatitis. (a) Ectopic pancreatic tissue (B) in the duodenal wall (A) is presented by acinar-ductal transformation and reaches duodenal mucosa lamina propria (C). Hematoxylin-eosin, ×50; (b) fibrosis and inflammatory infiltration in the ectopic pancreatic tissue in the duodenal wall (B) and at the periphery. Hematoxylin-eosin, ×50; (c) prominent atrophy of the acinar tissue with duct transformation (black arrows) and adenomatous hyperplasia of the epithelium (circle). Hematoxylin-eosin, ×100.

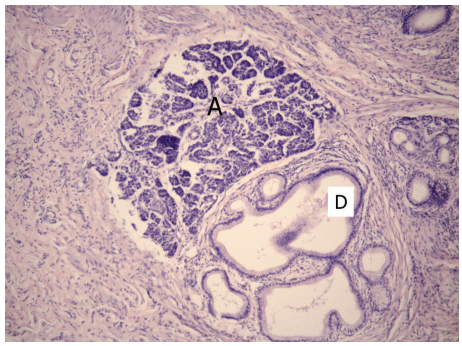


Figure 9: Microphotograph. Patient 47 y.o. Heterotopia of the pancreas tissue (acinuses—A and ducts—D) in the duodenal wall. Hematoxylin-eosin, ×100.

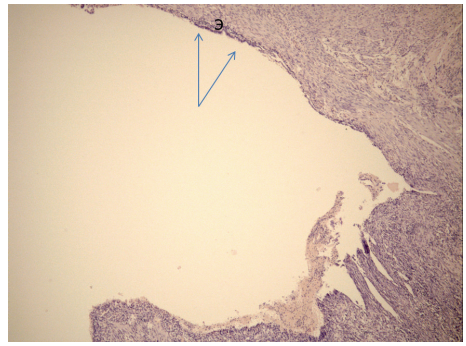


Figure 10: Microphotograph. Patient 61 y.o. Cyst in the duodenal wall formed by a dilated duct of the ectopic gland with islands of preserved epithelium (E and arrows). Hematoxylin-eosin, ×50.

must be eliminated to obviate symptoms. This explains the use of draining procedures and duodenum-preserving pancreatic head resections (DPPHR) at the beginning of this study. Internal drainage, that is, pancreaticojejunal and cysto pancreaticojejunal anastomoses, was performed in 8 cases. Patients presenting severe chronic pancreatitis of the orthotopic gland were subjected to PD (24 patients) or Nakao procedures (5 patients). DPPHR using Berne or Frey modifications was performed in 5 patients. Pancreas-preserving duodenal resection (PPDR) was performed in 10 patients without or with moderate changes in the orthotopic gland: distal gastrectomy for DD in the first portion of duodenum with an extension to the pylorus and antrum (1 patient); resection of the second part of the duodenum for cyst localized in the anterolateral wall of the second portion of the duodenum (2 patients); resection of the second duodenal portion with duodeno-duodeno anastomosis (2 patients); subtotal duodenectomy (3 patients), and resection of the vertical duodenal branch with jejunal interposition (2 patients). In two patients, subtotal duodenectomy was completed by end-to-end duodenojejunal anastomosis, and in one patient, with duodenal cyst spreading to the antrum,

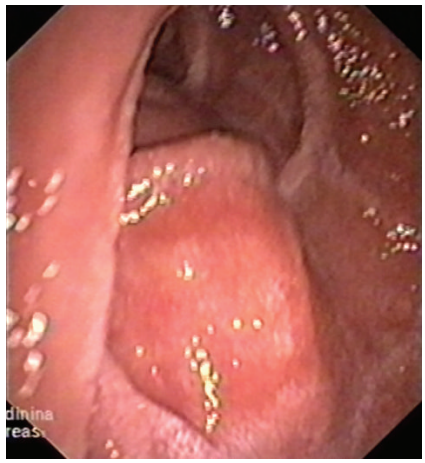


Figure 11: Duodenoscopy. Patient 47 y.o. Duodenal dystrophy. Cyst embedded in the medial wall of duodenum causing intrinsic contour bulge.

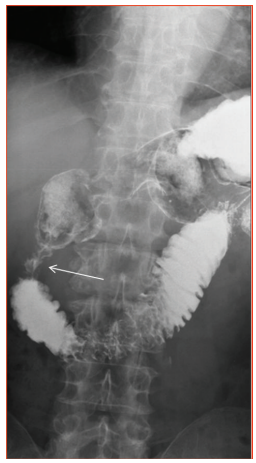


Figure 12: Stomach and duodenum X-ray with barium contrast. Patient 51 y.o. Duodenal dystrophy. Stenosed vertical branch of the duodenum (arrow).

subtotal duodenectomy was added by distal gastrectomy and completed as Roux-en-Y. One PPDR was performed for a patient who had no pain relief after previous gastroentero- and pancreatoenterostomy (Table 4).

There was no postoperative mortality. In one patient, intraoperative (PD) electrical injury of the ureter encased in the massive retroperitoneal fibrosis occurred. It required ureter stenting and ureteropelvic segment reconstruction which was successfully performed 3 months later. In one case, Nakao operation was converted into PD because of duodenal necrosis. Three episodes of bile leakage after duodenal resection were reported. It was prolonged in one case because of the leakage of the proximal duodenojejunal anastomosis. The complication was successfully treated by distal gastrectomy. Three cases of diabetes mellitus and three cases of steatorrhea were reported 12 months after PDs.

All patients were followed up. One 67-year-old woman died from the metastatic pancreatic cancer developed in the duodenal dystrophy five years after draining procedure. One patient died for an unknown reason 3.5 years after PD. About 80% of patients after PD and 90% patients after the pancreas-preserving duodenectomy reported resolution of symptoms. The duodenum-preserving pancreatic head resections and draining procedures appeared less effective. Six (20.6%) patients after PD, one (10%) after the pancreas-preserving duodenal resection, two (40%) after duodenum-preserving resection of the pancreatic head, and two (25%) patients after internal drainage reported diminished pain intensity, change in pain localization, and less often pain episodes, whereas 6 patients after draining procedures and one after DPPHR noticed no dynamics in symptoms (Tables 4 and 5).

Pain elimination and body weight gain is considered the most reliable objective criterion of the effectiveness of treatment option for chronic pancreatitis. Whipple procedures (PD + Nakao) and pancreas-preserving duodenal resections were significantly more efficient when compared to other treatment modalities for pain elimination and weight gain (Tables 4 and 5, Figure 15). No statistically significant difference was found between these two procedures and DPPHR with regard to pain management, probably due to a small series of pancreatic head resection: we do not use this method anymore for DD treatment, because no pain relief was achieved in 3 of 5 operated patients.

CT examination performed at different times after PD, Nakao operation, and duodenum-preserving pancreatic head resection did not reveal any significant changes in the pancreatic remnant. In all cases of pancreas-preserving duodenal resections, CT scans revealed either significant reduction or disappearance of inflammation in the orthotopic pancreas (Figures 16, 17, and 18). In all other cases, prominent signs of chronic pancreatitis persisted in the orthotopic and ectopic glands, sometimes with de novo formation or increased number of stones in the parenchyma of the main gland.

4. Discussion

To discuss the problem it is necessary to clarify the terms we use. Recently, Adsay and Zamboni [5], after studying of 21 pancreaticoduodenal specimens obtained from patients with chronic pancreatitis, in which chronic inflammation "predominantly involved the duodenal wall, extending to the adjacent pancreas and common bile duct," and "...predominant pathologic process contained acinar lobules as well as pancreatic-type ducts...," combined a number of pathological conditions previously described as cystic dystrophy in heterotopic pancreas or duodenal dystrophy [1, 4, 10, 41, 42], groove pancreatitis [43–46], pancreatic hamartoma of duodenum [47–50], paraduodenal wall cyst [8, 51–53], and myoadenomatosis [54, 55] under a new umbrella term "paraduodenal pancreatitis." According to these authors, all the above names describe a form of chronic pancreatitis involving the duodenal wall in close proximity to the minor duodenal papilla, that is, in a so called "groove" area—the parenchymal pancreatic tissue just in between the duodenal wall and the main biliary intrapancreatic tract [4, 41–44].

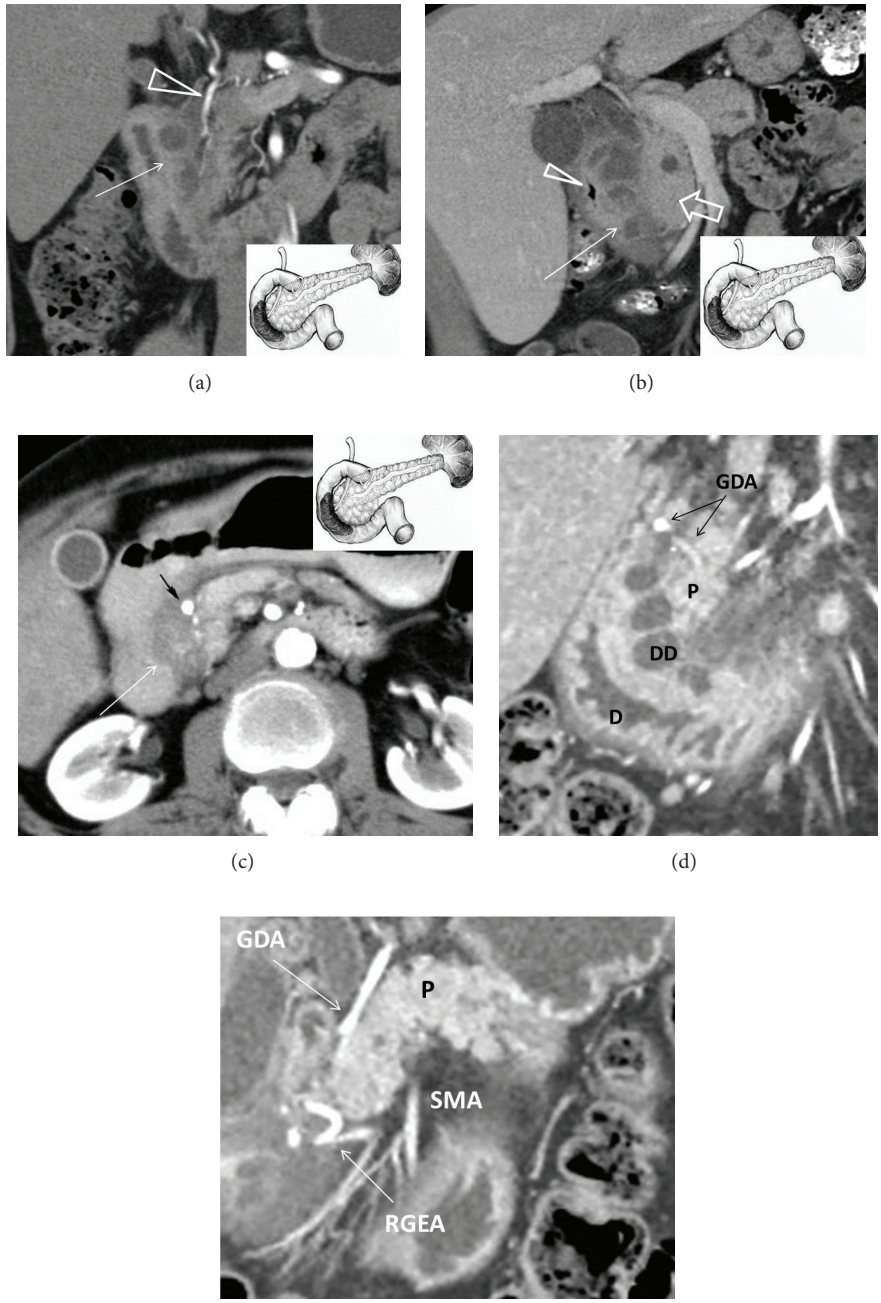


Figure 13: Duodenal dystrophy with moderate chronic orthotopic pancreatitis. Multidetector computed tomography. Frontal view. Patient, 32 y.o. (a) Arterial phase. Deformation and thickening of the medial wall of the duodenum with septated cyst (arrow). The gastroduodenal artery is shifted forward and to the left, lying in the groove between the pancreatic head and affected duodenal wall (arrowhead). The scheme of the lesion and the unaffected main pancreas is in the lower right corner; (b) patient 44 y.o. Venous phase. Deformed and thickened medial duodenal wall with multiple cysts (arrow), separated from moderately changed pancreatic head (thick arrow), is narrowing the duodenal lumen (arrowhead). The scheme of the lesion and the unaffected main pancreas is in the lower right corner; (c) patient 49 y.o. Arterial phase. Deformation and thickening of the medial wall of the duodenum with contrasted pancreatic tissue inside (arrow). The gastroduodenal artery is shifted forward and to the left, lying in the groove between the pancreatic head and affected duodenal wall (black arrow). The scheme of the lesion and the unaffected main pancreas is in the upper right corner. (d) Isolated form of the duodenal dystrophy. Multidetector computed tomography. (d) Male, 57 y.o. Arterial phase. Sagittal view. Deformation and thickening of the medial wall of the duodenum (D) with septated cysts (DD). The gastroduodenal artery (GDA) is shifted forward and to the left, lying in the groove between the unaffected pancreatic head (P) and duodenal wall. (e) Isolated form of the duodenal dystrophy with unchanged orthotopic pancreas. (a) Male 57 y.o. Arterial phase. Sagittal view. Septated cysts in the submucosa and muscularis of the diffusely thickened duodenal wall surround the major papilla.

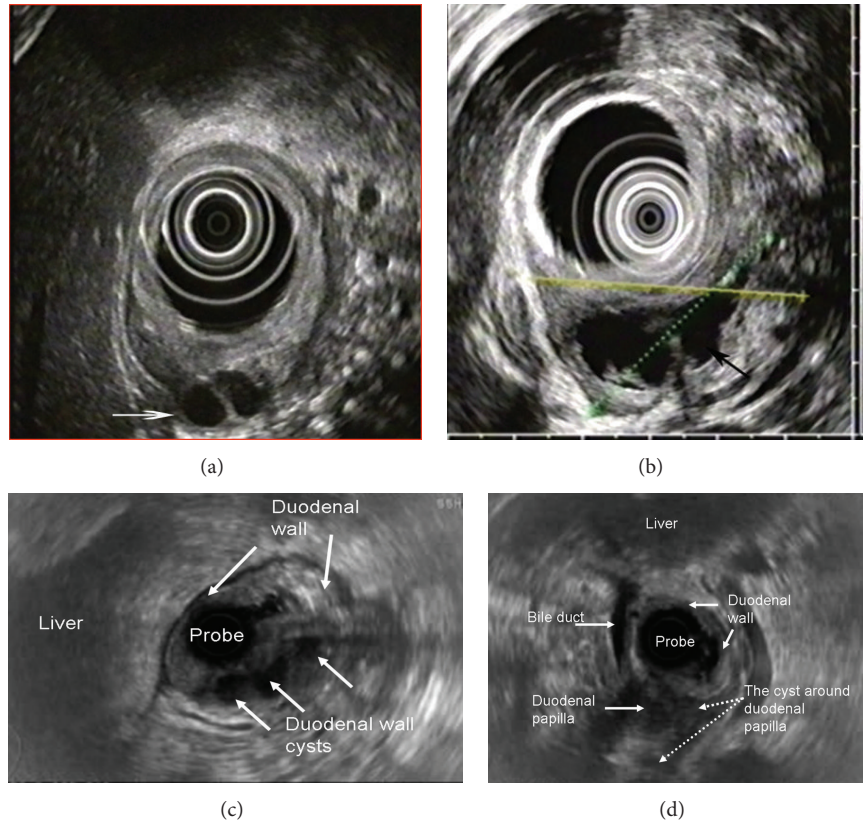


Figure 14: Endosonography. Duodenal dystrophy with moderate chronic orthotopic pancreatitis. (a) Patient 32 y.o. Ovoid septated cystic structure in the submucosa and muscularis of the diffusely thickened duodenal wall (arrow); (b) patient 43 y.o. Large septated multiloculated cyst in the submucosa and muscularis of the diffusely thickened duodenal wall (arrow). (c) Male 57 y.o. Isolated form of the duodenal dystrophy with unchanged orthotopic pancreas. Septated cystic structure (three arrows) in the submucosa and muscularis of the diffusely thickened duodenal wall (two arrows); (d) male, 57 y.o. Isolated form of the duodenal dystrophy with unchanged orthotopic pancreas. Septated cysts in the submucosa and muscularis of the diffusely thickened duodenal wall surround the major papilla.

Table 4: Results of surgery for duodenal dystrophy.

Procedure	Number	Morbidity	Full symptoms elimination	Steatorrhea	New diabetes mellitus
PD + Nakao	29	5 (17%)	23 (79%)	4 (14%)	3 (10%)
DPPHR	5	3	2	—	—
Internal drainage	8	2	2	1	1
Pancreas-preserving duodenal resections (PPDR)					
With direct duodeno-duodenoanastomosis	4	2	3	—	—
Subtotal duodenectomy	3	—	3	—	—
With intestinal interposition	2	1	2	—	—
Distal gastrectomy	1	—	1	—	—
All PPDRs	10	3	9	—	—

PD: pancreaticoduodenectomy, Nakao: Nakao procedure, DPPHR: duodenum-preserving pancreatic head resection.

Authors suggested the following pathogenetic mechanisms: for some reasons, mostly due to regular alcohol consumption and smoking, inflammation occurs in the "groove" pancreatic tissue that is clinically manifested in pain episodes resembling those in acute or chronic pancreatitis. During acute inflammatory phase, intramural areas of cystic degeneration are formed in the duodenal wall which can mimic one or more pseudocysts in the pancreatic head area adjacent to the duodenum. Eventually, owing to a typical localization of the "groove" pancreatic tissue in close proximity of the medial

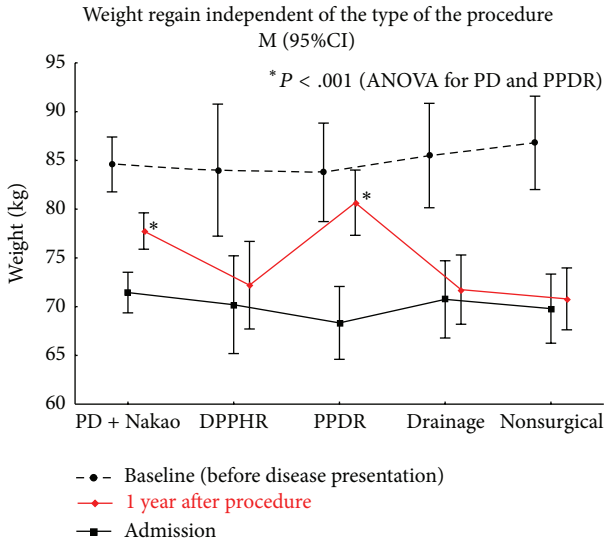


Figure 15: Body weight regain by the procedure performed for duodenal dystrophy. *Statistically significant difference.

Table 5: Efficacy of the PPDR and other treatment options for pain elimination in case of duodenal dystrophy.

Group	No pain	Have pain	Total N	P value
PPDR	9	1	10	
		vs		
DPPHR	2	3	5	0.076
PD + Nakao	23	6	29	0.652
Draining procedure	2	6	8	**0.012**
Consevative treatment	2	8	10	**0.005**

PD: pancreaticoduodenectomy, Nakao: Nakao procedure, DPPHR: duodenum-preserving pancreatic head resection, PPDR: Pancreas-preserving duodenal resections. Fisher's exact test two-sided (or two-tailed), P values < 0.05 mean a significant difference.

duodenal wall, the periampular area is becoming involved in the inflammation leading to the obstruction of the main pancreatic duct and development of chronic pancreatitis in the main (orthotopic) pancreas [5, 42, 43].

Initially, we had about the same view on such cases, and, as is clear from our series, tried to treat the disease performing surgeries that are commonly used for chronic pancreatitis, that is, draining procedure, duodenum-preserving pancreatic head resection, and Whipple procedure, more so that our patients usually had advanced diseases with fibrotic changes in the whole pancreas. With time, however, some cases accumulated, in which chronic pancreatitis involved the duodenal wall only with no or minor changes in the main (orthotopic) pancreas. In view of this, we suggested that this condition is an early stage of "paraduodenal pancreatitis," but at the same time it meant that lesion is of "duodenal," but not "paraduodenal," origin, as it was concluded in the first description of the entity and by some other authors, who used the term "duodenal dystrophy" [1, 4, 7, 30]. Pathohistological study confirmed that the site of the disease is a duodenal wall, and separation of the duodenal pancreatic tissue from the main pancreas suggested its ectopic origin. It happened that the historical term "duodenal dystrophy," not reflecting the nature of the disease, accurately demonstrates its localization. Based on histopathology findings and efficacy of pancreas-sparing duodenal resections, we consider duodenal dystrophy as a chronic inflammation of the ectopic pancreatic tissue in the duodenal wall. It can be either isolated [1, 4, 7, 30] or associated with severe inflammation and fibrosis in the main pancreas. It was precisely that circumstance that made us choose the term "duodenal dystrophy" and not "paraduodenal pancreatitis."

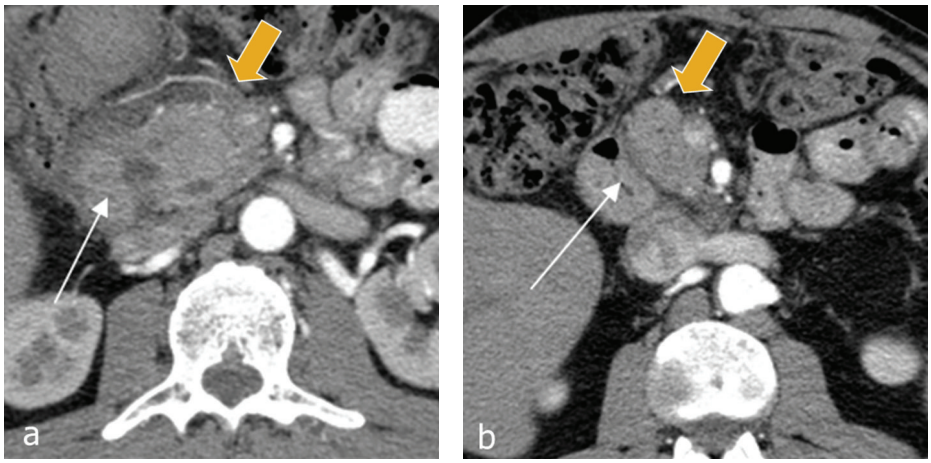
As for the term "paraduodenal pancreatitis," we think that it may be used only in cases of advanced inflammation and fibrosis of the main pancreas in presence of duodenal wall cysts, so far as, first, the term corresponds to the described condition and, second, dictates the only efficient surgical decision, that is, the Whipple procedure. Anyway, to escape confusion we prefer the definition "chronic pancreatitis associated with duodenal dystrophy" for such a combination.

Literature review confirmed our data suggesting that isolated involvement of the pancreatic tissue in the duodenum occurs in 25–30% of cases [4, 7, 30]. In the other 70–75% of cases inflammation and scarring involve the main pancreas with the progression of the disease initially located in the duodenum, and we followed up two such patients who preferred conservative treatment to surgery.

If the duodenum is only involved, resection of the main pancreas is an excessive and unnecessary option because of significant portion of the normally functioning pancreas is removed, draining procedures and head resections are inapplicable because of narrow pancreatic duct and almost unchanged parenchyma. Based on these considerations, we proposed to perform (and now consider an indication for) pancreas-preserving procedures instead of PDs in cases of isolated forms of duodenal dystrophy, when preoperative examination definitely showed preserved structure of the orthotopic pancreas without cysts, stones, and fibrosis. It makes it important to differentiate between duodenal dystrophy associated with chronic pancreatitis of the main pancreas and isolated duodenal dystrophy, so as Whipple procedure is the optimal treatment option for the former, while pancreas-preserving duodenal resection is the best surgical option for the latter.

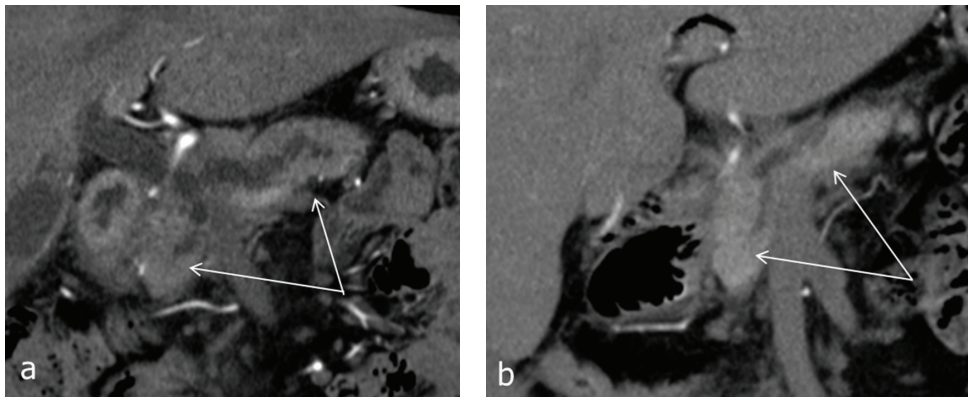
The duodenal dystrophy among patients with chronic pancreatitis was revealed in different studies in 2.7%–25% of cases [7, 9, 18, 19, 44, 56–59], although the histological verification of DD diagnosis was seldom presented. The prevalence of DD on the background of orthotopic pancreatitis may be underestimated due to dominating symptoms of classical chronic pancreatitis and insufficient awareness of radiologists and surgeons of DD semiotics or the very fact of its existence.

As of now, this study of 62 patients comprises one of the largest series of patients with cystic form of DD [2, 4, 7, 33]. Our patients presented with abdominal pain (100% patients) and weight loss (over 75%) was elsewhere reported. Their demographic characteristics (predominantly males, mean age 45 years) were also similar [2, 4, 7, 33–36, 57]. At the time of diagnosis, nearly all patients received treatment for



(a) (b)

Figure 16: Duodenal dystrophy with moderate chronic orthotopic pancreatitis. Patient, 32 y.o. Arterial phase of multidetector computed tomography before (a) and 6 months after (b) the pancreas-preserving resection of the second portion of the duodenum with the jejunal interposition. (a) There is a septated cystic structure (thin arrow) in the medial duodenal wall with prominent inflammation and fibrosis around the duodenum and pancreatic head (thick arrow). (b) Neoduodenum (thin arrow) and pancreatic head (thick arrow) without signs of inflammation or fibrosis.



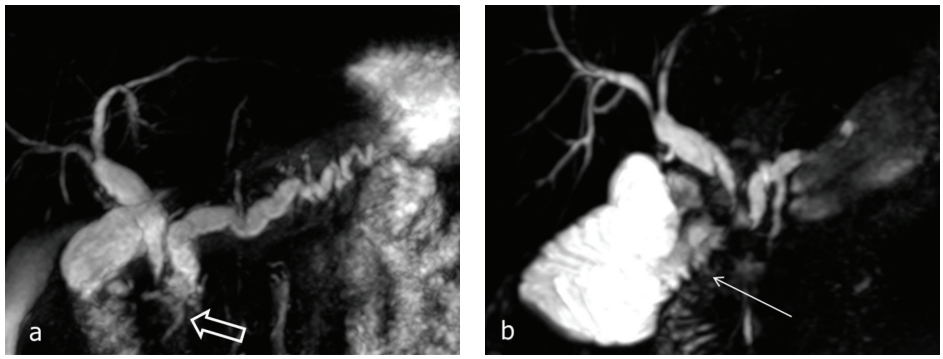
(a) (b)

Figure 17: Duodenal dystrophy with moderate chronic orthotopic pancreatitis. Patient, 35 y.o. Arterial phase of multidetector computed tomography before (a) and 6 months after (b) the pancreas-preserving resection of the second portion of the duodenum with the jejunal interposition. (a) Dilation of the pancreatic and bile ducts on the background of chronic inflammation and compression of pancreatic parenchyma (arrow). (b) Narrowing of the dilated pancreatic duct and reduction of inflammation in the pancreatic head and body (arrow).

chronic pancreatitis. In most cases, the disease affected men who regularly consumed alcohol (95% patients in our series versus 80% reported in the literature) [9, 57–59].

Computed tomography (CT), endoscopic ultrasound (EUS), and magnetic resonance imaging (MRI) appeared the most accurate methods for DD diagnostics in our study and elsewhere [9–13]. All the methods demonstrated equally high sensitivity and specificity. Transabdominal ultrasound examination is of limited value, as it usually does not allow differentiation DD from the pancreatic head cyst. Despite early reports on insufficient sensitivity of CT for DD diagnosis [12], now we have every reason to speak about typical CT semiotics of DD [10–13]. Given high diagnostic accuracy of these methods, we can rely on them even when no morphological data are available to confirm the diagnosis. The same approach is adopted by French authors who had reported the majority of DD cases [7].

Native CT and MRI can detect only overall increase of the pancreatic head in size, which is often associated with duodenal stenosis and gastric dilation. Following contrast enhancement, fibrotic thickening of the duodenal wall is detected as areas of lower density on CT scans or lower intensity on T2-weighted MRI pulse sequences. During the venous and late phases, contrast enhancement of the pathological focus is reduced, so the density of the pathological tissue on CT scan and signal intensity on MRI are higher as compared to those of the normal pancreatic parenchyma [20]. Some authors consider the mural fibrotic induration



(a) (b)

Figure 18: Duodenal dystrophy with moderate chronic orthotopic pancreatitis. Patient, 35 y.o. Magnetic resonance cholangiopancreatography; (a) a septated cyst is located in the medial wall of the second part of the duodenum (thick arrows) causing stenosis of the terminal parts of the common and the main pancreatic ducts with subsequent biliary and pancreatic hypertension; (b) 6 months after the pancreas-preserving resection of the second portion of the duodenum with the jejunal interposition (arrow). Narrowing of the pancreatic and common bile ducts after surgery.

viewed as a compact tissue layer between the duodenal lumen and pancreas the specific CT and MRI sign of DD [10]. In this area of thickened duodenal wall, one can see cysts localized in the space between the pancreatic head and vertical branch of the duodenum. These cysts are usually multiple (3 to 10), sized from 2 to 150 mm, and, unlike the pancreatic pseudocysts, they are multiloculated (more often two-chambered) and elongated (Figure 1). As the cysts are located within the duodenal wall, gradual increase in their size can lead to the shift of the gastroduodenal artery ventrally and to the left (centripetally), whereas the pancreatic head cyst displaces the artery dorsally and to the right. The solid type of duodenal dystrophy is visualized as a fibrotic thickening of the duodenal wall which is hardly differentiated from the pancreatic head. Thus, the diagnosis remains ambiguous without histological examination. For this reason, we avoided diagnosing fibrotic type of DD. In order to verify the diagnosis of DD and to personalize surgical strategy, we performed endoUS after CT scanning and/or MRI whenever possible followed by comprehensive data analysis.

Abstinence from alcohol is critical for successful treatment of DD. This is the only issue on the DD management that has been unanimously agreed on. Otherwise, expert opinions are controversial. Some authors reported successful use of somatostatin analogues [22, 39, 42, 50], whereas others [18, 19] observed no therapeutic effect of these agents. This can be due to short follow-up periods after octreotide therapy [36, 55] or lack of reports on long-term outcomes, for example, as in a large series of 105 patients, including 9 patients treated with octreotide, observed by Rebours et al. [7]. In Vankemmel et al. study [30], 1 of 7 patients treated with octreotide demonstrated a sustained, 87-month remission, 6 patients experienced recurrent symptoms within 0 to 25 months after drug withdrawal, and 5 of them were subjected to surgery. After failure of conservative therapy, minimally invasive surgical procedures were performed similarly to those used for the treatment of pancreatic pseudocysts, that is, endoscopic cystogastrostomy [55], fenestration [56], and endoscopic and percutaneous cyst aspiration with the success rate of less than 50% and follow-up periods of up to 38 months. In the study by Vankemmel et al. [30], two patients had undergone endoscopic cystoduodenostomy followed by PD after 18 and 20 months due to recurrent symptoms. Vankemmel et al. [30] suggest that endoscopic procedures are of no therapeutic value, if lesions cannot be removed, and are justified only when one or two very large cysts are present in the duodenal wall or the diagnosis of DD has to be verified histologically. The PD was the operation of choice for DD patients. However, with improved quality of preoperative diagnosis, new treatment options are evolving. Rebours et al. [7] reported that only 27% of 105 DD patients had undergone surgery, including PD in 2/3 of cases and bypass operation in the rest of cases. Vankemmel et al. [30] reported a series of 23 patients of whom 14 had undergone surgery, including PD in 12 cases (after failure of conservative and endoscopic treatment), and found no recurrences within up to 47 months postoperatively. In one case, symptoms had recurred after cystoenterostomy, and in the other case symptoms had recurred within 55 months after double bypass surgery. The majority of authors agree that the use of octreotide and its analogues, endoscopic interventions, and cyst aspiration do not guarantee long-term elimination of symptoms in patients with duodenal dystrophy, and PD remains the most effective method of DD management [25–35], although entailing high risk of postoperative endo- and exocrine pancreatic insufficiency. More conservative surgical interventions, such as pancreatic head resection and suprapapillary segmental resection of the duodenum, have been reported [27, 60] as case reports.

Our observations demonstrate that the cystic form of duodenal dystrophy can be reliably diagnosed preoperatively using up-to-date diagnostic methods and they confirm that the affected part of the duodenum must be surgically removed. Primary localization of the lesion is critical for the choice of treatment strategy and type of surgery. Dealing

with this disease, we first assumed that the primary locus of pathology lies in the area of the minor duodenal papilla and is associated with the main pancreas [61]. This explains the use of draining procedures and duodenum-preserving resections of the head of the pancreas during early period of our study. These interventions, however, were not effective, pain and other symptoms relapsed very often. Surgical treatment was provided to 84% of patients after failed conservative therapy. Seventy five percent of surgical interventions involved resection and in 40 cases was associated with severe orthotopic pancreatitis, PD or its Nakao modification was the operation of choice.

Pathomorphological findings in the resected tissues, particularly in specimens with moderate inflammation, strongly convinced us that the primary lesion is the pancreatic ectopy into the duodenal wall but not an inflammation in a part of the orthotopic gland. Time of symptomatic manifestation probably depends on the distance between inflamed ectopic tissue and major papilla: when the distance is great, symptoms of main pancreatic duct obstruction appear at later terms. This can underlie the development of orthotopic pancreatitis in two patients at the age of 73 years, one of whom was a woman with no history of alcohol consumption. DD patients demonstrated resolution or significant improvement of symptoms and significantly higher body weight gain only after the resectional surgery that involved removal of the ectopic pancreatic tissue, although 17% of patients developed steatorrhea and/or diabetes mellitus 1 year after PD. The pancreas-preserving duodenal resections for DD were implemented in 2009 [62] and that was a conceptually new method of treatment targeted only at the duodenum as the primary site of the problem. Absence of diabetes and good dynamics of weight gain in patients following pancreas-preserving duodenal resections can be explained by minimal parenchyma loss caused by the pancreas preservation and absence or reversibility of orthotopic pancreatitis. Technical complexity of such procedures is comparable to that of PD, but their obvious advantage is the minimal risk for endocrine and exocrine insufficiency. Absence of symptoms in 90% of patients within 12 to 56 months postoperatively, rapid weight gain, regression of inflammation, and narrowing of the main pancreatic and common bile ducts on CT and MRCP (Figures 13–15) attest to the effectiveness of surgical treatment of DD by the duodenectomy.

The efficacy of pancreas-preserving duodenal resections for duodenal dystrophy strongly indicates that the disease affects the duodenum but not the orthotopic gland. This, in turn, translates in the following conclusions: (1) DD is a "duodenal" but not a "paraduodenal" lesion; (2) DD patients can be offered a surgical operation, which is more effective whilst less destructive than PD; and (3) gastroenterologists, radiologists, and surgeons are to be encouraged to diagnose this disease at earlier stages.

P.S. In two more patients successful pancreas-preserving duodenal resection was performed few months ago but results will be assessed after one-year follow-up.

The composition of patients groups is constantly changing. A few months ago, two patients from the group of conservative treatment have undergone PD because of persistent intractable pain and ineffective analgesia and severe changes of the orthotopic pancreas, and one patient was moved to the group of draining procedures because of jaundice; hence, she is scheduled for PD as well.

Ethics

Our institutional review boards approved this study. Patient informed consent for the operation was required in all the cases. Possibility of pancreas-preserving duodenal resections for duodenal dystrophy was discussed with patients in all the cases when such a procedure was planned.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

Acknowledgments

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Clinical Study

Efficacy of Combined Endoscopic Lithotomy and Extracorporeal Shock Wave Lithotripsy, and Additional Electrohydraulic Lithotripsy Using the SpyGlass Direct Visualization System or X-Ray Guided EHL as Needed, for Pancreatic Lithiasis

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Introduction. To evaluate the efficacy of combined endoscopic lithotomy and extracorporeal shock wave lithotripsy (ESWL), and additional electrohydraulic lithotripsy (EHL) as needed, for the treatment of pancreatic duct stones, we retrospectively evaluated 98 patients with chronic pancreatitis and pancreatic lithiasis. *Methods*. For the management of main pancreatic duct (MPD) stones in 98 patients, we performed combined endoscopic treatment (ET)/ESWL therapy as the first treatment option. When combined ET/ESWL was unsuccessful, EHL with the SpyGlass Direct Visualization system or X-ray guided EHL was performed. Outpatient ESWL was reserved as one of the final treatment options. *Results*. Fragmentation was successful in 80 (81.6%) patients as follows: combined ET/ESWL: 67 cases; SpyGlass EHL: 4 cases; X-ray guided EHL: 3 cases; and outpatient ESWL: 6 cases. Successful outcome was obtained by combined ET/ESWL in 67 of the 98 patients (74.5%), by EHL in 7 of 14 patients (7.1%), and by outpatient ESWL in 6 of 6 patients (6.1%). Negotiating the guidewire through a severe MPD stricture was significantly associated with a higher rate of stone fragmentation ($P = 0.0003$). *Conclusions*. In cases where combined ET/ESWL was not successful for stone clearance, EHL using the SpyGlass system or X-ray guided EHL was effective in cases where the guidewire could be negotiated through the MPD stricture and it increased the fragmentation rate.

1. Introduction

Pancreatic lithiasis in chronic pancreatitis, especially in the main pancreatic duct (MPD), may cause pain due to pancreatic stasis or increased MPD pressure. Pancreatic stone elimination is a suitable treatment for pain removal and prevents acute exacerbation of pancreatitis [1]. Extracorporeal shock wave lithotripsy (ESWL) is typically the first treatment option in Japan, because it is minimally invasive and has fewer early complications than other treatments [2]. Complications of ESWL include acute obstructive pancreatitis due to stone lithotripsy, and patients should therefore be admitted for postmonitoring of ESWL and for preventing complications requiring endoscopic pancreatic sphincterotomy (EPST) [3]. Management in cases of large-diameter stones requires lithotripsy, for which combined endoscopic treatment (ET)/ESWL therapy is more effective than ESWL therapy alone [4]. However, in cases where such combination therapy is unsuccessful, surgical or similar intervention is typically required for symptomatic patients [5]. Electrohydraulic lithotripsy (EHL) is one such intervention that has been shown to be efficacious [6]. In addition, an outpatient ESWL approach can be helpful in shortening hospital stays for those patients whose pain can be temporarily relieved, who cannot afford a long hospital stay due to financial or work-related reasons, or whose stone has been incompletely

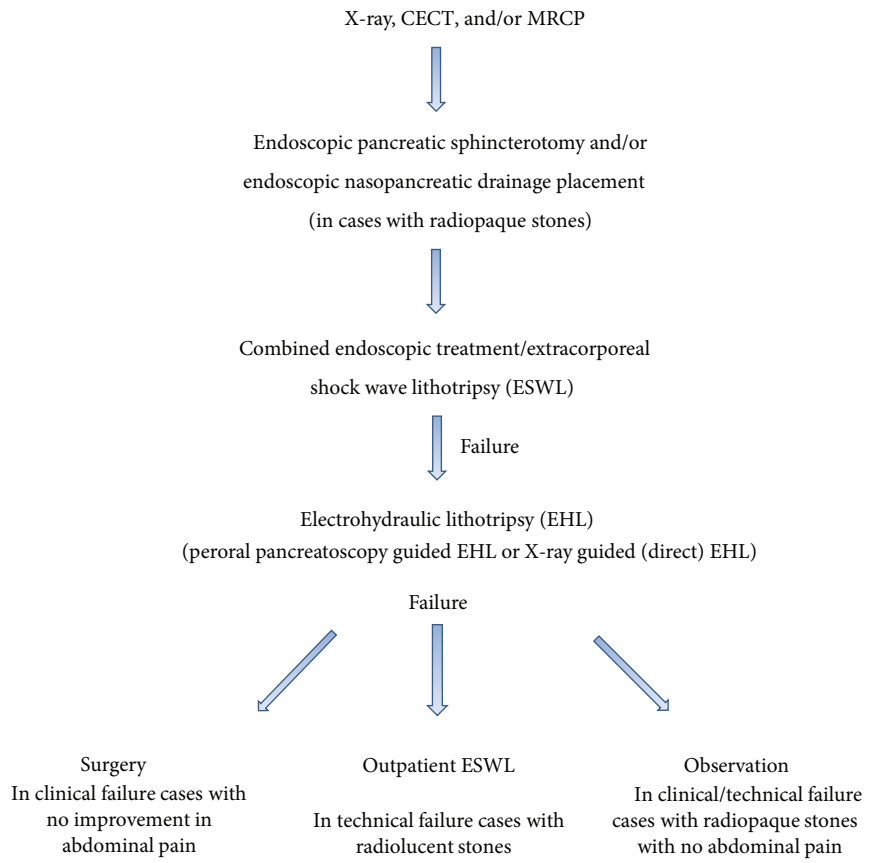

Figure 1: Management flow of pancreatic lithiasis.

fragmented by ESWL. Accordingly, our department performs EHL as a second treatment option, and, in the event that EHL is unsuccessful, outpatient ESWL is performed in cases of temporary pain relief or radiolucent stones. In this study, to evaluate the efficacy of combined endoscopic lithotomy and ESWL, and additional EHL as needed, for the treatment of pancreatic duct stones, we retrospectively evaluated cases of symptomatic pancreatic duct stones treated at our institution.

2. Indications, Patients, and Methods

The management flow of chronic pancreatic lithiasis performed at our center during the study period is shown in Figure 1. Indication for chronic pancreatic lithiasis treatment was defined as "absolute" or "relative," as shown in the following.

Treatment Indications Are as Follows

(1) Absolute indication ((a) + (b)):

(a) presence of abdominal symptoms,

(b) presence of pancreatic duct stone in the Santorini duct or Wirsung duct, and upstream MPD dilatation detected by diagnostic imaging (CECT, MRCP).

(2) Relative indication:

(a) no abdominal symptoms in patients with diabetic mellitus and exacerbation of glucose tolerance on diagnostic imaging with 1(b).

All patients underwent X-ray, contrast-enhanced computed tomography (CECT), and/or magnetic resonance cholangiopancreatography (MRCP) before treatment to distinguish radiolucent from radiopaque stones. Standard endoscopic retrograde cholangiopancreatography (ERCP) was performed before treating the pancreatic duct stones in all cases, and ESWL was considered in cases of endoscopically unremovable stones.

All procedures were performed with a TJF240 or TJF260V duodenoscope (Olympus Medical Systems, Tokyo, Japan). EPST was always performed as the first step, and when selective intubation was difficult, precutting was performed with EPST as a secondary procedure [7]. When pancreatic duct stricture was recognized on pancreatography, a guidewire was negotiated through the tail of the pancreatic duct as close as possible to the tail of the MPD, and dilatation was attempted. Although we typically used 0.035-inch Revowave standard type and Revowave hard-type guidewires (Piolax Medical Devices, Inc. Kanagawa, Japan), we used a 0.025-inch Visi-Glide guidewire (Olympus Medical

Figure 2: Dilators for MPD stricture.

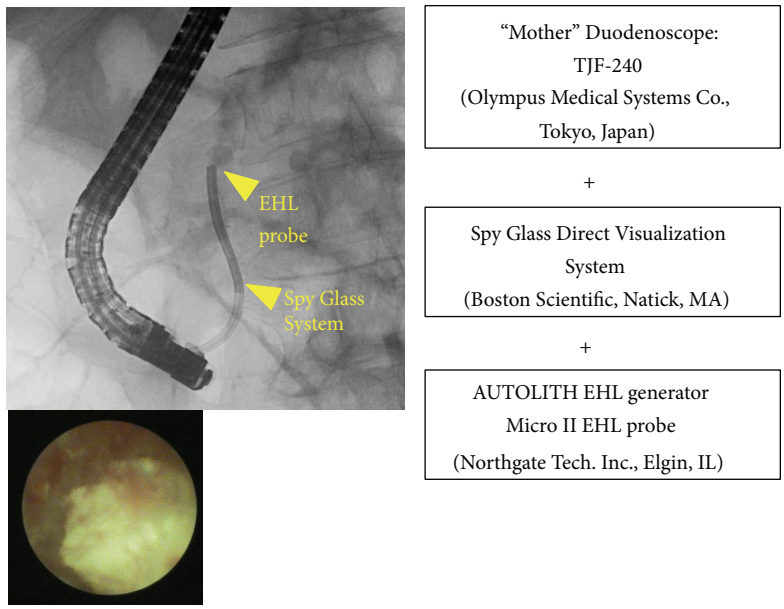

Figure 3: Peroral pancreatoscopy guided EHL using the SpyGlass Direct Visualization system.

Systems) when stricture was severe because traversing the stricture effectively with a standard guidewire is difficult. When the guidewire was negotiated through the tail of the MPD, a dilatation device such as a Soehendra biliary dilatation catheter (SBDC; Wilson Cook Medical, Winston-Salem, NC), Soehendra stent retriever catheter (SSR; Wilson Cook Medical), or Maxpass (Olympus Medical Systems) was used (Figure 2). In cases of radiopaque stones, an endoscopic nasopancreatic drain (ENPD) was placed, and contrast media was infused through the ENPD during ESWL to identify stones. To improve the efficacy of lithotripsy, a slow shock wave (45 pulses/min) was applied using an electromagnetic Siemens Lithoskop (Siemens AG, Munich, Germany).

If the endoscopic lithotomy/ESWL combination was unsuccessful, EHL was performed as a second attempt. Before 2010, we used a 3.5 mm diameter CHF TYPE BP 260 baby scope (Olympus Medical Systems) for EHL. However, because of its naïve characteristics and fragility, we switched to the 10 Fr SpyGlass Direct Visualization system (Boston Scientific, Natick, MA) for EHL. The NORTECH MICRO II 1.9 Fr 250 cm EHL Probe (Northgate Technologies Inc., Elgin, IL) and NORTECH AUTOLITH EHL Generator (Northgate Technologies Inc.) were optimized for use with the SpyGlass Direct Visualization system (Figure 3). Alternatively, X-ray guided EHL using a 7 Fr biliary dilator as an outer sheath was performed when a 10 Fr SpyGlass system delivery catheter was difficult to insert into the MPD stricture (Figure 4).

Stone location in the MPD was defined as head or body/tail. The number of stones in the MPD was defined as single or multiple. MPD stricture was defined as stricture or severe stricture (requiring the use of a SSR or SBDC).

Analysis was conducted to determine the outcomes of our management flow: combined ET/ESWL as the first option, peroral pancreatography (POPS) guided EHL or X-ray guided EHL as the second option, and continuing outpatient ESWL as the third option when the previous

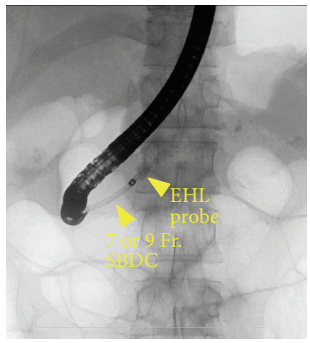

Figure 4: X-ray guided EHL.

treatments had failed. Clinical success (improvement in abdominal complaints) and technical success (clearance of target pancreatic stone) and the efficacy of POPS guided EHL and direct EHL were evaluated as follows.

Definitions for Clinical and Technical Success

Clinical Success. Clinical success is defined as improvement in abdominal symptoms (e.g., abdominal pain, back pain, and abdominal discomfort) after EPST/precutting and/or pancreatic lithiasis treatment.

Technical Success. Technical success is defined as clearance of the target pancreatic stone after the treatment (e.g., endoscopic treatment/ESWL/EHL).

In addition, using multiple logistic regression analysis, we examined the factors of stone clearance (alcohol etiology, stone location, stone number, stone size, and success/failure of guidewire negotiation).

Written informed consent was obtained from each patient prior to performing treatment. The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki and was approved by the institutional review committee of Toho University Omori Medical Center.

2.1. Statistical Analysis. Statistical analysis was performed using SPSS for Windows, version 11.0J (SPSS Inc., Chicago, IL). All continuous variables are presented as means ± standard error. A P value < 0.05 was considered significant. Comparisons of the outcome variable (stone fragmentation) were analyzed using the Chi-squared test or Fisher's exact test.

3. Results

A total of 98 patients with symptomatic chronic pancreatitis underwent endoscopic lithotomy for chronic calcific pancreatitis at our center between May 2005 and December 2012 (Table 1). Patient background and stone factors are given in Table 1.

In total, 89 patients (90.8%) had abdominal symptoms with abdominal pain or discomfort (Table 2(a)). Of the 82 patients with abdominal pain, target pancreatic stones were successfully removed from 64. Although the 17 remaining patients in which stone clearance initially failed were defined as technical failures, they were finally determined to be clinical successes because abdominal pain was improved.

Table 1: Outcomes of ERCP/ESWL based on patient background and stone characteristics.

Factor	Value
Age, years (median, range)	54.8 ± 13 (21–81)
Sex	
Male/female	78/20
Etiology	
Alcohol	77
Divisum	8
Idiopathic	6
Genetic	1
Hyperparathyroidism	1
Other	5
Stone size	—
>15 mm/≤15 mm	11/87
Stone location	
Single (n = 24)	
Head	18
Body/tail	6
Multiple (n = 74)	
Head	58
Body/tail	16
MPD stricture	
Yes/no	62/36

ESWL: extracorporeal shock wave lithotripsy; MPD: main pancreatic duct.

Of the patients in whom abdominal pain was not improved by treatment, 2 underwent successful stone lithotripsy by ESWL at another institution, 1 continued pancreatic stent placement, 3 underwent surgery because of continuing pain, and 1 was placed under observation according to the patient's request. Nine patients (9.2%) with no abdominal symptoms and 1 patient defined as a technical failure were followed as outpatients (Table 2(b)).

Stone fragment extraction by combined ET/ESWL therapy was successful in 67 of 98 patients (74.5%), while that by additional EHL was successful in 7 patients (7.1%; 3 cases with the SpyGlass system and 4 cases with direct EHL). Direct

Table 2: Treatment outcomes (clinical success and technical success).

(a) Abdominal symptoms before treatment (n = 89, 90.8%)

Clinical success	n	Clinical failure (no pain improvement)	n
Technical success	64	Technical success	0
Technical failure (outcomes)		Technical failure outcome (outcomes)	
Surgery	0	Surgery	3
Outpatient ESWL	1	ESWL at other institutions	2
Pancreatic stent placement	0	Pancreatic stent placement	1
Observation	17	Observation	1
	82 (83.7%)		7 (7.1%)

(b) No abdominal symptoms before treatment (n = 9, 9.2%)

	n
Technical success	8
Technical failure (outcomes)	
Observation	1
	9 (9.2%)

EHL was useful in cases when ENPD or EPS placement was unsuccessful. In the 6 (6.1%) cases where EHL was not successful, outpatient ESWL was successful in all 6 cases (Table 3).

Table 4 shows the 31 cases where combined ET/ESWL was not successful. Twelve patients had radiolucent stones, 5 of whom failed to respond to selective pancreatic duct cannulation. One patient subsequently underwent successful outpatient ESWL. Although 15 patients were asymptomatic at this point, they were followed as outpatients, and 2 ultimately required surgery because of no improvement in pain. Table 5 shows the treatment outcomes of the POPS guided EHL procedures including the SpyGlass Direct Visualization system. Reasons for failure were insufficient dilatation of MPD stricture in 2 patients, direct vision failure in 2 patients, and equipment failure in 1 patient. In addition, perforation by the guidewire occurred in 1 patient. Pancreatitis was improved by conservative treatment in 1 patient (Cotton classification [8]: mild). Table 6 shows the outcomes of X-ray guided EHL procedures. Yet, 4 of the 6 cases of X-ray guided EHL in this study were treated successfully, and even though the remaining 2 cases were defined as unsuccessful, 1 was successfully treated by ESWL at another institution. However, severe pancreatitis (Cotton classification: severe) due to guidewire perforation occurred in 1 successful case.

Univariate analysis revealed that guidewire negotiation was associated with a significantly higher rate of stone fragmentation than the other methods ($P = 0.0004$) (Table 7). This finding was confirmed by multiple logistic regression analysis of factors in the success group and failure group ($P = 0.0003$) (Table 8).

4. Discussion

The high safety and efficacy of ESWL make it the preferred treatment for patients with painful calcified chronic pancreatitis, and it has been the treatment of choice for clearing pancreatic stones since 1987 [2, 3]. Combined systematic endoscopy with ESWL has been reported to increase the cost of patient care without improving the outcome of pancreatic pain [3]. In our experience, treatment improved abdominal symptoms in 82 of 89 patients. The most ideal treatment is to remove the target stone and dilate the severe stricture of the MPD. However, several cases of severe MPD stricture resulted in a decreased rate of stone clearance. In these cases, EPST or precut reduced MPD hypertension, which in turn reduced abdominal pain.

Cholangioscopy, initially introduced in 1975 using the mother-baby system, has been used to evaluate indeterminate pancreatobiliary diseases. However, the conventional baby scope is a fragile instrument requiring frequent repairs [9, 10]. We chose, therefore, to use the SpyGlass optical probe, which is 0.9 mm in diameter and can be inserted through an endoscopic ERCP catheter [11]. ERCP can, therefore, be performed more easily and quickly than conventional mother-baby cholangiopancreatoscopy. As in cases of pancreatic lithiasis with MPD stricture, ultimate upangulation is required, but this leads to optical probe damage. The SpyGlass system uses a replaceable optical probe and a disposable access catheter, and it has 4-way deflected steering with separate dedicated irrigation channels which obviates the need to send out the cholangioscope for repairs. Furthermore, because the SpyScope is a disposable catheter, which means it is cost effective, it is considered the first choice for pancreatic lithiasis EHL cases [12].

With regard to POPS guided EHL outcomes, Craigie et al. reported the following factors for the mother-baby scope system: (a) stone burden (i.e., near total impaction of concretions in the pancreatic head); (b) acute angulation of the main pancreatic duct at the genu and inability to navigate this junction with a guidewire or scope; and (c) baby scope failure due to the instrument being fragile [6]. Based on these findings, even though the SpyGlass Direct Visualization system has a 4-way angled system, it has limited front-viewing control in severe cases of MPD stricture compared with that in the wider common bile duct [13].

On the other hand, performing X-ray guided EHL in the pancreatic duct carries the risk of duct perforation and bleeding. In our department, X-ray guided EHL is performed by the same highly skilled surgeon, which may be one of the factors contributing to the successful outcomes. However, like in our experience with the successful cases of severe pancreatitis, no previous studies have reported X-ray guided EHL similar to the procedure used at our department, suggesting the efficacy of pancreatic stone lithotripsy.

Although combined ET/ESWL therapy is typically an effective treatment for pancreatic stones >10 mm, patients are limited to a hospital stay of 30 days at our institution. Among our 98 patients, 74 had multiple stones and 62 had MPD stricture. Accordingly, only about 10–15 ESWL sessions could be performed during the hospitalization period. Therefore,

Table 3: Outcomes of pancreatic stone treatments.

	Successful ENPD placement or EPST		Total	(%)
	Yes (%)	No (%)		
Combined ET/ESWL therapy success	50	17	67	74.5%
EHL success (POPS EHL/X-ray EHL)	4 (3/1)	3 (0/3)	7 (3/4)	7.1%
Outpatient ESWL success	2	4	6	6.1%
	56 (57.1)	24 (24.5)	80	81.6%

ENPD: endoscopic nasopancreatic drain; EPST: endoscopic pancreatic sphincterotomy; ET: endoscopic treatment; ESWL: extracorporeal shock wave lithotripsy; EHL: electrohydraulic lithotripsy; PPS: prophylactic pancreatic stent.

Table 4: Failure cases of combined ET/ESWL treatment ($n = 31$).

	Successful ENPD placement or EPST		Total success (%)
	Yes	No	
PPS EHL ($n = 8$)			
Success	3	—	3
Failure			
ESWL (success)	1	3	4
Followup	—	1	
Direct EHL ($n = 6$)			
Success	1	3	4
Failure			
ESWL (success)	1	—	1
Followup	1	—	
Radiolucent stones ($n = 12$)			
Followup	2	9	
Surgery	—	1	
EPST or precut failure ($n = 5$)			
ESWL success	—	1	1
Followup	—	3	
Surgery	—	1	
Total success cases	6/9	7/22	13/31 (41.9)

ENPD: endoscopic nasopancreatic drain; EPST: endoscopic pancreatic sphincterotomy; ET/ESWL: combined endoscopic treatment/extracorporeal shock wave lithotripsy; EHL: electrohydraulic lithotripsy; PPS: prophylactic pancreatic stent.

Table 5: Outcomes of peroral pancreatography-guided EHL procedures.

Number	Location	Stone diameter (mm)	Number of stones	Reason for failure	ENPD placement/EPST	Complication	Outcome
1.	Head	13	Multiple	—	Success	—	
2.	Head	12	Multiple	—	Success	—	
3.	Head	14	Single	—	Success	—	
4.*	Head	20	Diffuse	Severe stricture	Failure	—	Other institution ESWL
5.	Head	10	Single	Severe stricture	Failure	—	Outpatient ES
6.	Head	10	Multiple	Direct vision failure	Failure	Perforation	Observation
7.	Head	12	Single	Direct vision failure	Failure	Pancreatitis	Observation
8.	Head	10	Single	Equipment failure	Failure	—	Combined ET/ESWL

*CHF BP 260 was used in case 4 for EHL.

Table 6: Outcomes of X-ray guided EHL procedures.

Number	Location	Stone diameter (mm)	Number of stones	Reason for failure	ENPD placement/EPST	Complication	Outcome
1.	Head	8	Multiple	—	Success	—	
2.	Body	10	Multiple	—	Success	—	
3.	Head	16	Single	—	Success	Pancreatitis, GW perforation, and pancreatic abscess	Discharge
4.	Head	9	Multiple	—	Success	—	
5.	Body	7	Multiple	Severe stricture	Failure	—	Other institution ESWL
6.	Body	10	Multiple	Severe stricture	Failure	Pancreatitis	Observation

Table 7: Univariate analysis of stone clearance.

	Success group ($n = 74$)	Failure group ($n = 24$)	OR (95% CI)	P
Alcohol etiology (yes/no)	60/14	19/5	1.13 (0.26–5.05)	0.87
Stone location (head/body or tail)	57/17	18/6	3.46 (0.80–14.87)	0.09
Stone number (single/multiple)	21/53	6/18	0.69 (0.16–2.88)	0.61
Guidewire negotiation (success/failure)	68/6	9/15	32.1 (7.67–134.97)	0.0004
Stone size (≤15 mm/>15 mm)	75/9	12/2	0.89 (0.77–1.03)	0.13

OR: odds ratio; CI: confidence interval.

Table 8: Multivariate analysis of stone clearance.

	Success group	Failure group	OR (95% CI)	P
Guidewire negotiation (success/failure)	68/6	9/15	14.1 (0.46–43.21)	0.0003

OR: odds ratio; CI: confidence interval.

when the stone remains after 10 ESWL sessions and treatment is expected to be prolonged, either POPS guided EHL or X-ray guided EHL should be performed. Our findings revealed that, in cases where combined ET/ESWL therapy was not successful, a next attempt at EHL increased the stone fragmentation rate.

Furthermore, in cases of failed EHL treatment, we could continue ESWL on an outpatient basis if there was at least some "space" in the MPD. In these cases, the ENPD or pancreatic stent could not be placed as no treatments are suitable for radiolucent stones in cases with severe MPD stricture. Unfortunately, cases of unresolved abdominal pain require surgical treatment [14, 15].

Previous studies reported that the presence of a downstream stricture and stone size and location influence stone fragmentation and clearance [16, 17]. In our study, based on the results of univariate and multivariate analysis, as shown in Tables 7 and 8, no significant differences were observed between stone clearance and the different etiologies (alcohol, stone location, stone size, and stone number). In fact, complete stone clearance was significantly improved by guidewire negotiation, possibly because the success of guidewire negotiation through the MPD stricture has a greater therapeutic effect during ERCP stone clearance therapy.

There are several limitations to this study. First, it is a retrospective study. Second, the use of POPS guided or X-ray guided EHL was determined from the response to the combined ET/ESWL treatment and was not performed in a randomized fashion.

5. Conclusions

In cases where stone clearance was unsuccessful by combined ET/ESWL treatment, EHL using the SpyGlass system or X-ray guided EHL was effective when the guidewire could be negotiated through the MPD stricture. Furthermore, although the SpyGlass system has 4-way tip deflection, it is necessary to pay attention in cases of extremely tortuous and narrow MPD. Further prospective randomized EHL studies are needed to verify our findings.

Conflict of Interests

The authors declare no conflict of interests.

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Review Article

Surgical Technique in Distal Pancreatectomy: A Systematic Review of Randomized Trials

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Despite recent improvements in surgical technique, the morbidity of distal pancreatectomy remains high, with pancreatic fistula being the most significant postoperative complication. A systematic review of randomized controlled trials (RCTs) dealing with surgical techniques in distal pancreatectomy was carried out to summarize up-to-date knowledge on this topic. The Cochrane Central Registry of Controlled Trials, Embase, Web of Science, and Pubmed were searched for relevant articles published from 1990 to December 2013. Ten RCTs were identified and included in the systematic review, with a total of 1286 patients being randomized (samples ranging from 41 to 450). The reviewers were in agreement for application of the eligibility criteria for study selection. It was not possible to carry out meta-analysis of these studies because of the heterogeneity of surgical techniques and approaches, such as varying methods of pancreas transection, reinforcement of the stump with seromuscular patch or pancreaticoenteric anastomosis, sealing with fibrin sealants and pancreatic stent placement. Management of the pancreatic remnant after distal pancreatectomy is still a matter of debate. The results of this systematic review are possibly biased by methodological problems in some of the included studies. New well designed and carefully conducted RCTs must be performed to establish the optimal strategy for pancreatic remnant management after distal pancreatectomy.

1. Introduction

Distal pancreatectomy is the surgical procedure of choice for the treatment of lesions in the body and tail of the pancreas. The mortality associated with this procedure has decreased rapidly in the past decades due to refinements in operative technique, introduction of new surgical devices, and improvements in postoperative care, including new interventional radiology techniques; however, morbidity remains high [1–6]. The main reason for postoperative morbidity is the postoperative pancreatic fistula (POPF), which is also regarded as the most ominous complication [7]. POPF is not a life-threatening condition in most cases, but nevertheless it prolongs the hospital stay, increases the cost of the treatment and delays adjuvant treatment in malignant disease [8].

Distal pancreatectomy is performed less frequently than pancreaticoduodenectomy [5, 9]. This is because of the lower incidence of pancreatic disease in the body and tail of the pancreas and the later appearance of clinical symptoms in this part of the organ. Pancreatic adenocarcinoma is found in the left part much less frequently than in the head. However, continuous improvement in the quality of imaging studies and frequent use of ultrasonography for all kinds of indications have resulted in higher incidence of the findings of lesions in this part of the pancreas, for example, asymptomatic cystic or endocrine tumors [9].

Compared to pancreaticoduodenectomy, fistulas that occur after distal resections are usually clinically less severe [5, 9]. Sauvanet et al. suggested that POPF originating from pancreaticoenteric anastomosis seems to have a worse prognosis than POPF originating from a pancreatic remnant

[10]. This may be due to the activation of pancreatic juice by enterokinase, which is a necessary mechanism that stimulates the proteoclastic activity of various pancreatic enzymes [11]. This process may contribute to the differences between POPFs after operations that require enteric reconstructions (pancreaticoduodenectomy and central pancreatic resection) and those that do not (distal pancreatectomy and enucleation). Pratt et al. suggested that clinically relevant fistulas after pancreaticoduodenectomy require more aggressive management in intensive care settings compared to those that occur after distal resections. Surgical exploration, when indicated, is more often urgent. On the other hand, fistulas that occur after distal resections often require prolonged drainage of intra-abdominal collections and multiple hospital readmissions, usually for image-guided percutaneous drainage [5].

As POPF has significant clinical and economic consequences, attention has focused on lowering the POPF rate. Besides the use of somatostatin or its analogues in high-risk patients [12], these efforts comprise mainly surgical technique and the strategy for pancreatic remnant management. New methods have emerged including experimental studies [13] in order to develop new techniques in distal pancreatectomy.

There have been few retrospective studies to compare the various techniques for management of the pancreatic remnant. The results are heterogeneous and often contradictory: several authors have shown lower fistula rates in manual oversewn closure compared to stapler transection [6, 14–16], while others favored stapler [17–19]. Even though some of the new surgical techniques show promising results in a retrospective cohort setting [20], the expected advantage diminishes in randomized controlled trial (RCT) [21]. Another example would be the use of pancreatic duct stent with favorable results in a retrospective study [22, 23], but not confirmed in a randomized trial [24]. This shows the importance of well-designed RCTs in decision making and estimation of treatment effect in surgical interventions [25, 26].

Several reviews have studied the various surgical techniques in distal pancreatectomy. They focused mainly on the two most commonly practiced interventions: stapler versus manual oversewn closure of the pancreatic remnant [27–29]. However, there are more surgical techniques available and more issues to face. Other less common techniques include pancreatic transection using various energy devices, reinforcement of the stump with a seromuscular patch or pancreaticoenteric anastomosis, sealing with fibrin sealants, the use of various meshes, and pancreatic stent placement [28, 30].

Two meta-analyses which comprised mostly retrospective trials [28, 29] did not achieve firm conclusions. Zhou et al. showed a trend in favor of the stapler-closure technique, although it did not reach statistical significance [29]. The meta-analysis performed by Knaebel et al. favored the stapler closure as well; however, the result was not statistically significant [28]. Both authors concluded that a large RCT must be conducted in order to confirm the results of the meta-analyses. This was accomplished by Diener et al. in the DISPACT trial [27]. This again shows the importance of well-designed RCTs and their predominance over retrospective studies. For this reason we carried out a systematic review of RCTs dealing with surgical techniques in distal pancreatectomy to summarize up-to-date knowledge on this topic.

2. Methods

2.1. Search Strategy and Study Selection. We searched the Cochrane Central Registry of Controlled Trials, Embase, Web of Science, and Pubmed (=Medline) for relevant articles published from January 1990 to December 2013. The search was performed independently by two authors (FC and BJ) using the terms: "distal pancreatectomy," "pancreatic resection," "pancreatic fistula," "pancreas," and "postoperative complication." The full search strategy is shown in the appendix (Literature search).

The reference lists of relevant studies were screened to retrieve any further potential studies. No unpublished data or data from abstracts were encountered or used. No language restriction was applied to the search.

Abstracts of all potentially relevant articles were read and assessed. All studies comparing various strategies in distal pancreatectomy were retrieved, and only randomized clinical trials were included in the systematic review.

2.2. Inclusion and Exclusion Criteria. We considered only RCTs comparing various strategies and surgical techniques of distal pancreatectomy for the review. Nonrandomized trials and clinical observational studies were excluded. Studies without data available for retrieval or studies describing only one technique were excluded. Studies comparing various techniques in pancreaticoduodenectomy or other procedures were also excluded, as were experimental studies on animals.

2.3. Data Analysis and Statistical Methods. All data of selected studies were analyzed independently by two reviewers (FC and BJ). We extracted data on methodology, level of evidence, population, interventions, outcome measures including POPF rate, postoperative morbidity and mortality, and definition of pancreatic fistula [31, 32]. Disagreements were resolved in group discussions. Methodology followed the standard guidelines outlined in the Cochrane Handbook for Systematic Reviews of Interventions [33] and the PRISMA statement (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) [34]. The risk of bias of the studies was assessed independently by two authors based on individual components.

3. Results

The initial search strategy retrieved 532 publications. 464 were excluded in the primary selection (not relevant or dealing with pancreaticoduodenectomy or another procedure) and 58 were excluded in the secondary selection after reading the full-text of the potentially relevant studies (nonrandomized trials, experimental trials). Ten RCTs were identified and included in the systematic review, with a total 1286 patients being randomized (samples ranging from 41 to

450) [21, 24, 27, 35–41]. The reviewers came to agreement for application of the eligibility criteria for study selection. A flowchart of the literature search strategy is shown in Figure 1.

The main characteristics of the selected trials are shown in Table 1 [21, 24, 27, 35–41]. Three studies were multicentric [27, 38, 41], one study was from 2 centers [21], and the others represent single-center experience [24, 35–37, 39, 40]. The definition of POPF was not uniform throughout the studies, and hence the POPF rate cannot be compared among the studies. Not surprisingly, the POPF rate ranged from 3.7% up to 68.5%. It was clearly shown that POPF definition is the most important factor of the POPF rate [31].

Only two RCTs compared stapler versus hand-sewn closure [27, 37]. Meta-analysis of those two techniques was included in the report of the DISPACT trial [27]; it did not show a difference between the two techniques (odds ratio OR 0.87; 95% CI 0.3–2.55; $P = 0.80$). Whereas the results of 16 observational studies were in favor of stapler closure (OR 0.68; 95% CI 0.51–0.89; $P = 0.006$); it emphasizes the limitations of nonrandomized trials in surgery again [27]. We found it unnecessary to perform the same meta-analysis again. Comparability between the other studies was compromised because of the heterogeneous surgical techniques and approaches, such as the various methods of pancreas transection, reinforcement of the stump with a seromuscular patch or pancreaticoenteric anastomosis, sealing with fibrin sealants, and pancreatic stent placement. It was thus not possible to conduct a meta-analysis of such trials. The following studies were identified and analyzed.

Suzuki et al. reported the results of the first RCT comparing the application of fibrin glue with a control group [35]. This small RCT contained 56 patients; fibrin glue was applied in 26 patients to the suture line on the proximal stump, with ligation of the main pancreatic duct. In the control group, the transection and suture were carried out in the same manner, only without fibrin glue application. POPF occurred less frequently in the fibrin glue group compared to the control group. The validity of the results must be questioned for several reasons: firstly, the small sample size; secondly, there was poor selection of the study population, 75% of patients had been operated on for gastric cancer; and thirdly, the data on postoperative morbidity was not shown.

The second study was also conducted by Suzuki et al. [36]. The authors reported the value of ultrasonic dissection in a RCT containing 58 patients. In the experimental group, the pancreas was transected by ultrasonic dissector, and even small pancreatic ducts were exposed and ligated. POPF occurred less frequently in the experimental group compared to the control group. The drawback of the new technique is the need to ligate all the pancreatic ducts; approximately 20–30 tubes including the pancreatic ducts and small blood vessels were ligated per patient, resulting in longer time required for division of the pancreas in the ultrasonic dissection group (23.0 minutes versus 9.1 minutes, resp.; $P = 0.039$). Moreover this trial was subject to the same drawbacks lowering its credibility as the trial mentioned above, that is, the small sample size, 86% of the patients operated on for gastric cancer, and data on morbidity and mortality not shown. Furthermore, the authors did not explain why they did not use fibrin glue, after having shown in their previous study that it produced superior results.

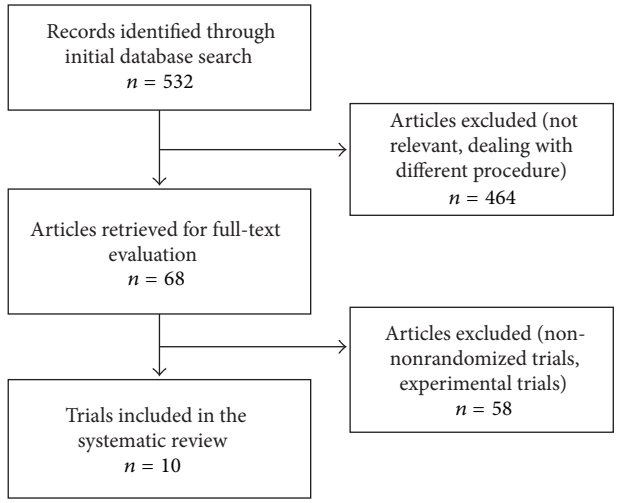

Figure 1: Flowchart of the literature search strategy.

Bassi et al. conducted a pilot RCT with 69 patients being randomized into 5 groups which included suture closure, suture closure ± fibrin glue, suture closure ± polypropylene mesh, pancreaticojejunostomy, and stapler closure [37]. Although the POPF rates ranged from 7.1% to 33.3%, the results were not statistically significant. This is clearly due to the small sample size of this pilot study. However, the authors showed interesting comparison of various techniques of management of the pancreatic stump.

Suc et al. conducted a multicenter RCT including 182 patients from 15 centers, of whom 41 underwent distal pancreatectomy [38]. A wide range of techniques was allowed, such as suture-closure, Roux-en-Y jejunal loop anastomosis, and omentoplasty. Patients were randomized to receive temporary fibrin glue occlusion of the main pancreatic duct or not. The pancreatic fistula rate did not vary between the groups. This study was underpowered because the sample size was calculated for both pancreaticoduodenectomy and distal pancreatectomy. Moreover, the heterogeneity of the surgical techniques and the multicenter nature of the study decreased the credibility of the results.

Oláh et al. conducted a RCT comparing stapler closure versus stapler closure with jejunal seromuscular patch [39]. Overall pancreas-related morbidity (POPF, intra-abdominal collection, or both) was significantly lower in the jejunal patch group; however, the incidence of clinically significant POPF grades B/C was comparable between the groups. The authors concluded that addition of a jejunal seromuscular patch to stapler closure reduced the rate of pancreatic fistula and abdominal collections, but it did not affect clinically relevant outcomes. This study was underpowered as the number of analyzed patients did not reach the calculated sample size.

Table 1: The main characteristics and results of the selected trials.

Reference	Year		Age	Sex (M/F)	Definition of pancreatic fistula	Interventions	Group size	Mortality	Morbidity	Fistula rate	P
Suzuki et al. [35]	1995	SC	58,7 ± 15,5* 61,5 ± 9,4*	19/7 21/9	Any amount, concentration 3x normal serum value lasting for at least 7 days	Fibrin glue control group	26 30	1,8%	N/A N/A	15,4% 40,0%	0,04
Suzuki et al. [36]	1999	SC	57,7 ± 10,9* 58,5 ± 11,9*	18/9 18/13	Any amount, concentration 3x normal serum value lasting for at least 7 days	Ultrasonic dissection Control group	27 31	N/A N/A	N/A N/A	3,7% 25,8%	0,02
Bassi et al. [37]	1999	SC	N/A N/A N/A N/A N/A	N/A N/A N/A N/A N/A	More than 10 mL/d with amylase 1000 IU/L beyond POD 7	Suture closure Suture closure + fibrin glue Suture closure + polypropylene mesh Pancreaticojejunostomy Stapler closure	15 11 15 14 14	0% 0% 0% 0% 0%	N/A N/A N/A N/A N/A	33,3% 27,3% 13,3% 7,1% 14,3%	NS
Suc et al. [38]	2003	MC	N/A N/A	N/A N/A	Any amount, concentration 4x normal serum value lasting for at least 3 days	Occlusion of the main duct with fibrin glue Control group	22 19	0% 5,3%	27,20% 26,30%	18,2% 15,8%	NS
Oláh et al. [39]	2009	SC	65 (52–70)** 51 (42–59)**	21/14 20/15	ISGPF	Stapler + seromuscular patch Stapler	35 35	0% 2,8%	11,4%+ 31,4%+	8,6% 20,0%	N/A
Diener et al. [27]	2011	MC	59,8 ± 14,1* 59,8 ± 13,6*	85/92 76/99	ISGPF	Stapler Suture	177 175	<1% 1%	49,2% 40,0%	35,6% 36,6%	0,84
Frozanpor et al. [24]	2012	SC	N/A N/A	12/15 14/12	ISGPF	Distal pancreatectomy Distal pancreatectomy + stent	27 26	0% 0%	100,0% 100,0%	37,0% 50,0%	0,122
Hamilton et al. [40]	2012	SC	58,6 ± 13,4* 57,5 ± 15,6*	25/21 20/34	More than 50 mL/d, concentration 3x normal serum value after day 3	Stapler Stapler + mesh reinforcement	46 54	0% 0%	60,9% 38,9%	56,5% 38,9%	0,001
Montorsi et al. [41]	2012	MC	60,5 ± 14,9* 61,6 ± 14,2*	64/81 39/91	ISGPF	TachoSil control group	145 130	0% 0%	28,3%++ 29,2%++	62,1% 68,5%	0,267
Carter et al. [21]	2013	DC	62,5 (29–84)*** 65,0 (20–82)***	22/28 19/32	ISGPF	Falciform patch and fibrin glue control group	50 51	0% 0%	N/A N/A	20,0% 20,0%	1

SC: single center, MC: multicenter, DC: dual-center, N/A: not available, NS: not significant, *mean ± standard deviation, **median (interquartile range), ***median (range), +pancreas-related morbidity, ++postoperative complications excluding POPF.

A large multicenter trial was designed to compare suture closure versus stapler closure [27]. The trial was well designed and carefully conducted among 21 centers in Europe; 450 patients were randomized and 296 analyzed. The primary end-point was POPF and death until the 7th POD. The authors themselves admit that the assessment period for the POPF up to 7th POD might be too short. Both methods were shown to be comparable in terms of POPF rate, mortality, overall morbidity, and hospital stay. Unfortunately the authors did not analyze the cost of the treatment; opponents of the stapling method argue against the higher price of the device. The operating time with stapler was not significantly shorter; thus, use of the stapler does not speed up the procedure.

A small RCT by Frozanpor et al. showed no benefit for prophylactic pancreatic duct stenting [24]. Even though the study may be underpowered, there was not even a trend towards a lower rate of complications in the stented group. Moreover, according to the authors prophylactic stenting may even be harmful. One of the many contributing factors could be luminal bacteria seeding through the stent [42].

Hamilton et al. showed that mesh reinforcement decreases the rate of clinically significant POPF (grades B/C) and the overall POPF rate [40]. Unfortunately the authors did not use the generally accepted POPF definition of ISGPF, thus precluding comparison of the results with those from other studies. The pancreatic fistula definition was quite narrow, but nevertheless the POPF rate was still relatively high (47%). This was the only study in which the results indicated a credible advantage for one technique over another.

A multicenter RCT by Montorsi et al. showed that the application of a biological sealing agent (TachoSil) over the pancreatic stump as an addition to standard suturing or stapling did not result in a significant reduction in the overall POPF rate [41]. The amylase level in the drain fluid was lower in the TachoSil group on day 1, which suggests that TachoSil may be effective in sealing the pancreatic remnant in the immediate postoperative period. There was a certain degree of heterogeneity regarding the type of surgery (laparotomy versus laparoscopy, suture versus stapler, and spleen preservation or not). The heterogeneity was even greater because of the large number of centers involved (19). However, the authors claim that the results reflect real-life practice more conclusively.

Carter et al. sought to decrease the POPF rate by adding a falciform ligament patch and fibrin glue to the pancreatic remnant in a dual-institution randomized study [21]. However, they were not successful; the POPF rates were not significantly different between the groups at a scheduled midterm data analysis (at 52.5% enrolment). Thus the study was closed to enrolment. This study has several drawbacks; firstly, complications beyond 30 days postoperatively were not fully included; then the surgical technique used in the trial was not consistent, stapler or manual suture; and finally, the method of constructing the falciform ligament patch prevents a pure comparison with the literature.

4. Discussion

This systematic review includes 10 RCTs, which described the techniques used for pancreatic remnant management after distal pancreatectomy [21, 24, 27, 35–41].

The surgical techniques ranged from the standard techniques used most commonly (stapler closure and manual hand-sewn closure [27, 37]) to techniques used less frequently (ultrasonic dissection, closure with jejunal seromuscular patch, polypropylene mesh [36, 37, 39]). Fibrin glue was used in various ways: simple application of fibrin glue on the suture line [35, 37], fibrin glue occlusion of the main pancreatic duct [38], and falciform ligament patch with fibrin glue [21]. Other techniques included application of a biological sealing agent (TachoSil) [41], prophylactic pancreatic duct stenting [24], or pancreaticojejunostomy [37]. Because of the heterogeneous surgical techniques and approaches, the comparability between the studies was compromised.

Moreover, different definitions of morbidity and POPF were used. Only five of the included studies [21, 24, 27, 39, 41] used the definition according to ISGPF [32] which nowadays is the most commonly used and has been validated [8, 43].

Pancreatic fistula according to the ISGPF was defined as output via operatively or postoperatively placed drains of any measurable volume of drain fluid on or after postoperative day 3, with amylase content greater than three times the upper normal serum value. Three grades of pancreatic fistula were determined according to the clinical severity [32]. Grade A fistula, also called "transient fistula" has no clinical impact. It requires little or no change in the clinical management of the patient. Grade B fistulas are symptomatic and clinically apparent, and they require changes in clinical management or adjustment of the clinical pathway. The patients are usually supported by enteral or parenteral nutrition, and the peripancreatic drains are usually kept in place or new drains may be inserted. Grade C fistulas are severe and clinically significant, requiring major adjustments in clinical management. Clinical intervention is aggressive; patients are often in the intensive care unit (ICU) and have enteral or parenteral nutrition, antibiotics, and somatostatin analogues. Surgical revision may be indicated in some cases [32].

The other studies used different criteria such as amylase concentrations in the fistula fluid, fluid amounts, methods of detection, and time points for description. Not surprisingly, the POPF rates vary from 3.7% to 68.5%; thus, it is not possible to make comparisons between individual studies and surgical techniques. When the various definitions of POPF are applied to identical groups of patients, the rate of pancreatic fistula can range from 10% to 29% according to which definition is applied [31]. Naturally, broad POPF definition will result in higher POPF rates [31, 32].

RCT is the method showing the best evidence excluding possible bias which may be encountered in nonrandomized retrospective or cohort studies [26]. RCT is regarded as the gold standard for evaluating results of various surgical methods or other interventions. A well designed RCT guards against systematic and random errors. RCTs minimize the

Table 2: Assessment of methodological quality and risk of bias of the selected trials.

Reference	Year	Group size calculation	Randomization and concealment of allocation	Blinding	Complete followup	Risk of bias
Suzuki et al. [35]	1995	Missing	Drawing lots	Missing	Missing	High
Suzuki et al. [36]	1999	Missing	Drawing lots	Missing	Missing	High
Bassi et al. [37]	1999	Missing	Missing	Missing	Missing	High
Suc et al. [38]	2003	POPF rate 40%, reduction to 20%, one-tailed test alfa 5%, power of 80%	Telephone call to the coordinating center, computerized random-number tables	Patients and nursing staff	30 days after discharge	Unclear
Oláh et al. [39]	2009	POPF rate 25%, reduction to 15%, alfa 5%, power of 80%	Sealed envelopes	Missing	Hospital stay	Low
Diener et al. [27]	2011	POPF rate 35%, reduction of 15%, two-sided alfa 5%, power of 80%	Central randomisation system	The patient and the outcome assessor	POD 30	Low
Frozanpor et al. [24]	2012	POPF rate 40%, reduction to 0%, two-sided alfa 5%, power of 80%	Opaque sealed envelopes	Missing	POD 30	Low
Hamilton et al. [40]	2012	POPF rate 20%, reduction to 5%, two-sided alfa 5%, power of 80%	Random number generator	The patient and the outcome assessor	POD 30	Low
Montorsi et al. [41]	2012	POPF rate 30%, reduction to 15%, two-sided alfa 5%, power of 80%	Two separate randomization lists at each center (laparoscopic and open)	Missing	2 months after discharge	Low
Carter et al. [21]	2013	POPF rate 30%, reduction to 15%, one-tailed test alfa 5%, power of 80%	Opaque sealed envelopes	Missing	May 2012 (7 months after trial closure)	Low

POD: postoperative day; POPF: postoperative pancreatic fistula.

risk of confounding factors; they provide the highest level of evidence in terms of validity as they are more likely to closely reflect a true effect than other types of studies [26].

Even though some of the new surgical techniques show promising results in the retrospective cohort setting [20], the expected advantage diminishes in RCT [21]. Even results of meta-analyses including mostly retrospective or cohort studies [28, 29] are compromised compared to a well-designed and well-conducted RCT [27]. We decided to conduct a review solely of RCTs to gather together the up-to-date evidence in surgical techniques in distal pancreatectomy.

The results from RCT are more valid and trustworthy than nonrandomized retrospective or cohort studies, but only when it is well conducted. The results of small, underpowered, and poorly designed surgical RCTs with high risk of bias may be overvalued because their design provides them with unwarranted credibility [25].

RCTs in surgical trials should adhere to methodological principles to minimize errors. The methods include sequence generation (randomization), concealment of allocation, blinding, intention-to-treat principle, complete followup, and sample size calculation [33]. The included RCTs have their drawbacks (Table 2). Allocation concealment relates to what happens before randomization of the patients and seeks to eliminate selection bias. Blinding relates to what happens after randomization and seeks to reduce performance and detection bias [25]. Several individuals have potential to introduce bias if they have knowledge of which intervention the participants have received. Obviously surgeons cannot be usually blinded, but participants, nursing staff, data collectors, and outcome assessors can be blinded [25]. Most of the included trials misinformation are about concealment allocation and blinding.

The first three trials are missing important information about group size calculation, randomization, blinding, and followup [35–37] and thus were assessed as having a high risk of bias. The risk of bias of the study performed by Suc et al. is unclear; mainly because it was a part of a larger study including both pancreaticoduodenectomy and distal pancreatectomy [38].

Because of the limits of the included studies, we must analyze the results with caution. The studies by Carter et al., Frozanpor et al., Diener et al., Suc et al., and Montorsi et al. did not show significant differences between the study arms [21, 24, 27, 38, 41]. Oláh et al. found a lower rate of overall pancreas-related complications in the seromuscular patch group over the stapling alone group (11.4% versus 31.4%, $P = 0.041$), but there was no significant difference between the groups regarding the complications requiring intervention (5.7% versus 14.3%; $P = 0.428$) [39]. Such conflicting results might be due to the underpowered sample size.

Table 3: Ongoing trials on surgical techniques in distal pancreatectomy.

Department, Country	Study number	Commencement	Planned sample size	Intervention
University of Heildelberg, Heildeberg, Germany [44]	DRKS00000546	December 2010	150	Coverage with falciform ligament versus standard technique
Mayo Clinic, Rochester, MN, USA	NCT01051856	December 2009	400	Stapler closure with bioabsorbable staple line reinforcement (SEAMGUARD) versus radiofrequency ablation device (Tissuelink)
Seoul National University Hospital, Seoul, Republic of Korea	NCT01550406	November 2011	150	TachoComb (collagen sheet coated with fibrinogen) versus polyglycolic acid (biodegradable, thermoplastic polymer)
Wakayama University, Wakayama, Japan	NCT01384617	June 2011	136	Roux-en-Y anastomosis versus stapler closure
Massachusetts General Hospital, Massachusetts, USA	NCT00671463	April 2008	Withdrawn	Placing a stent into the pancreatic duct prior to surgery

The only study with low risk of bias which showed significant advantage of one method over another was conducted by Hamilton et al. [40]. The authors showed that mesh reinforcement to stapler suture reduces the rate of clinically significant POPF grades B/C (1.9% versus 23.9%; $P = 0.001$). However, the POPF rate was still on the high side despite the POPF definition used.

It is difficult to reach conclusive results and draw firm conclusions due to the drawbacks and possible bias of the included studies, various surgical techniques, and various POPF definitions. The best method of pancreatic remnant management in distal pancreatectomy is still debated. We can speculate that the perfection of a technique at each individual institution or by an individual surgeon is just as important as the actual technique applied.

New studies are currently underway which compare various surgical techniques of pancreatic remnant management after distal pancreatectomy (Table 3). An RCT comparing the radiofrequency ablation device (Tissuelink) technique with the stapling device (SEAMGUARD) is being conducted in the USA. Another Japanese multicenter RCT compares duct to mucosa pancreaticojejunal anastomosis and simple stapler closure. A Korean multicenter RCT compares TachoComb and polyethylene glycolic acid (PGA) in distal pancreatectomy. TachoComb is a ready-to-use hemostatic agent consisting of a collagen sheet coated on one side with human fibrinogen, bovine thrombin, and bovine aprotinin. Polyglycolide or Polyglycolic acid (PGA) is a biodegradable, thermoplastic polymer and the simplest linear, aliphatic polyester. Both arms will be compared to a control arm, in which no mesh will be applied to the cut surface of the pancreas. The German trial DISCOVER is testing the method of coverage of the pancreatic remnant with a falciform ligament [44]. Another study from the Massachusetts General Hospital, Boston, USA, was planned to lower the POPF rate with pancreatic duct stenting prior to the surgical procedure, the same technique which was used by Frozanpor et al. [24]. However, this study was withdrawn prior to enrolment due to the high risk of pancreatitis according to the authors.

5. Conclusion

Management of the pancreatic remnant after distal pancreatectomy is still a matter of debate. It remains a clinically significant problem. The results of this systematic review are possibly biased by methodological problems within some of the included studies. New well designed and carefully conducted RCTs must be performed to establish the optimal strategy for pancreatic remnant management after distal pancreatectomy. Such studies are currently underway and we can eagerly await their results.

Appendix

Literature Search

PubMed: ((((((distal pancreatectomy) AND postoperative complication*)) OR (("Pancreatectomy" [Mesh]) AND (("Postoperative Complications" [Mesh]) AND "Pancreatic Fistula" [Mesh])))))) OR (postoperative complication AND pancreatic fistula AND pancreatic resection AND distal pancreatectomy AND pancreas*).

Web of Science: Topic: (distal pancreatectomy) AND Topic: (postoperative complications).

Embase: (distal pancreatectomy and postoperative complications) in all fields.

EBM Reviews: The Cochrane Central Register of Controlled Trials: (pancreatectomy AND postoperative complications) in all fields.

Conflict of Interests

There is no conflict of interests declared.

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Review Article

The State of the Art of Robotic Pancreatectomy

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During the last decades an increasing number of minimally invasive pancreatic resections have been reported in the literature. With the development of robotic surgery a new enthusiasm has not only increased the number of centers approaching minimally invasive pancreatic surgery in general but also enabled the use of this technique for major pancreatic procedures, in particular in minimally invasive pancreatoduodenectomy. The aim of this review was to define the state of the art of pancreatic robotic surgery. No prospective randomized trials have been performed comparing robotic, laparoscopic, and open pancreatic procedures. From the literature one may conclude that robotic pancreatectomies seem to be as feasible and safe as open procedures. The general idea that the overall perioperative costs of robotic surgery would be higher than traditional procedures is not supported. With the current lack of evidence of any oncologic advantages, the cosmetic benefits offered by robotic surgery are not enough to justify extensive use in cancer patients. In contrast, the safety of these procedure can justify the use of the robotic technique in patient with benign/low grade malignant tumors of the pancreas.

1. Introduction

At the Karolinska Institutet, Hans-Christian Jacobeaus made the first laparoscopic procedure in humans in 1910. The Swedish surgeon used a cystoscope for a diagnostic laparoscopy in 17 patients with ascites [1]. The use of diagnostic laparoscopy for the staging of pancreatic cancer was introduced some months later by Bernheim at Johns Hopkins University [2]. However, only in the late 80s diagnostic laparoscopy for staging of pancreatic cancer was used on a more regular basis [3, 4]. In 1992, Shimi et al. published a series of patients undergoing laparoscopic cholecystojejunostomy for treatment of jaundice [5]. At the beginning of the 90s, the development of higher quality laparoscopic instruments, imaging monitors, and improved surgical techniques enabled not only palliative procedures for unresectable pancreatic cancer to be performed but also the first series of pancreatic resections. In 1994, Gagner and Pomp described the first laparoscopic pancreatoduodenectomy [6]. Even if large series of laparoscopic pancreatoduodenectomies, including complex operation associated with vascular resection, have been published today with comparable results to open procedures [7, 8], the safety of laparoscopic pancreatic procedure is mostly limited to distal pancreatic resections and enucleations [9]. The major problems for the spreading of laparoscopic pancreatoduodenectomy are the dissection of retroperitoneal margin, the complicated reconstruction phase (further complicated by laparoscopic instruments), the length of operating time, and the lack of scientifically proved advantages compared to the conventional open technique. With the development of robotic surgery, however, a new enthusiasm in minimally invasive pancreatic surgery and in particular in minimally invasive pancreatoduodenectomy has grown. The aim of this review is to offer an up to date summary of the state of the art of robotic pancreatic surgery.

2. Methods

Search of MEDLINE and PubMed databases was performed using the keywords "robotic pancreatectomy" and "robotic pancreatic surgery" from 1990 to 2013. Additional articles were identified using a manual search. Series with less than 5 procedures performed were excluded by the analysis and

Table 1: Perioperative results of robotic pancreatoduodenectomy.

Author	Year	Number of patients	Morbidity (%)	Mortality (%)	Mean OT (min)	Mean POS (days)
Zureikat et al. [12]	2013	132	63	3.8	527	10
Giulianotti et al. [13]	2010	60	NR	3.3	421	22
Zeh et al. [14]	2012	50	56	NR	568	10
Buchs et al. [15]	2011	44	36	4.5	444	13
Boggi et al. [16]	2013	34	56	2.9	517	23
Chalikonda et al. [17]	2012	30	30	3.3	476	9.8
Lai et al. [18]	2012	20	50	0	491	14
Chan et al. [19]	2011	8	NR	0	NR	NR
Zhou et al. [20]	2011	8	75	0	718	28
Kendrick and Cusati [21]	2010	8	NR	NR	NR	NR
de Vasconcellos Macedo et al. [22]	2011	5	60	0	640	26
Narula et al. [23]	2010	5	0	0	420	9.6

Table 2: Pathology of resected specimens after robotic pancreatoduodenectomy.

Author	Year	Number of patients	Malignant diseases (%)	Mean lymph nodes harvested	R1 (%)
Zureikat et al. [12]	2013	132	80	NR	NR
Giulianotti et al. [13]	2010	60	75	18	11
Zeh et al. [14]	2012	50	74	18	11
Boggi et al. [16]	2013	34	63	32	0
Chalikonda et al. [17]	2012	30	47	13	0
Lai et al. [18]	2012	20	75	10	27
Zhou et al. [20]	2011	8	100	NR	0
de Vasconcellos Macedo et al. [22]	2011	5	40	NR	NR
Narula et al. [23]	2010	5	20	16	0

reported eventually to describe particular aspects or techniques. An analysis of the result of major robotic pancreatic procedure was performed.

3. Results

3.1. Pancreatoduodenectomy (PD). With the advent of the robotic era, some of the limitations of laparoscopy are overcome. The robot offers advantages in terms of 3D vision, dexterity, and ergonomy [10]. Giulianotti and coworkers described the first robotic PD in 2003 [11]. In this experience the authors showed the feasibility of this procedure with robotic approach with an acceptable morbidity rate (37.5%), but with a very high mortality rate (12.5%). Today several larger series have been reported in the scientific literature [12–23]. Even though one series contains more than 100 patients [12], the number of procedures per center is still quite small, half of them with less than 10 patients (Table 1). The perioperative results of robotic PD are similar to the open procedures described in the literature. The morbidity and mortality rates range from 60% to 0 and from 4% to 0, respectively. The operative time seems to be longer compared to the open procedure and the mean postoperative stay comparable (Table 1). However to date, no prospective randomized trial has been performed comparing the open with the laparoscopic or robotic procedure. Currently, only 4 nonrandomized studies compared the outcome of open and robotic PD [15, 17, 18, 20]. The operation time was significantly shorter in the open procedure in three and robotic in one of these studies. Furthermore, the mean length of stay (LOS) was shorter in the robotic compared to the open group in three of the studies. No statistical significant differences were found in morbidity and mortality comparing the two groups of procedures. Only one paper in the literature compares the mean costs of robotic versus open PD procedures showing excess of € 6200 with the robotic approach [16]. Robotic PD has been performed for both benign and malignant diseases. As shown in Table 2, the rate of R1 resections for malignant diseases ranges from 0 to 27%; these data most probably reflect different definitions of pathological margin assessment. However, the median number of lymph nodes retrieved in some series is not adequate according to current guidelines to treat pancreatic malignancies [23] (Table 2).

3.2. Distal Pancreatectomy (DP). Minimally invasive DPs are today extensively performed around the world for the treatment of pancreatic tumors and some authors even consider this technique "standard of care" [9]. Today, in most cases the traditional laparoscopic technique is preferred to the robotic approach. The reason is that distal pancreatectomies are less complicated procedures compared to PD without a technically demanding reconstructive phase. In the last decade, however, the number of reports of robotic DP has

Table 3: Perioperative results of robotic distal pancreatectomy.

Author	Year	Number of patients	Morbidity (%)	Mortality (%)	Mean OT (min)	Mean POS (days)
Zureikat et al. [12]	2013	83	72	0	256	6
Giulianotti et al. [13]	2010	46	NR	NR	NR	NR
Suman et al. [24]	2013	40	40	0	203	5
Daouadi et al. [25]	2013	30	66	0	293	6
Hwang et al. [26]	2013	22	9.1	0	398	7
Kang et al. [27]	2011	20	10	0	348	7
Waters et al. [28]	2010	17	18	0	298	4

Table 4: Pathology of resected specimens after robotic distal pancreatectomy.

Author	Year	Number of patients	Malignant diseases (%)	Mean lymph nodes harvested	R1 (%)
Zureikat et al. [12]	2013	83	72	NR	NR
Giulianotti et al. [13]	2010	46	NR	NR	NR
Suman et al. [24]	2013	40	32	NR	NR
Daouadi et al. [25]	2013	30	43	19	0
Hwang et al. [26]	2013	22	0	NR	0
Kang et al. [27]	2011	20	0	NR	NR
Waters et al. [28]	2010	17	0	5	0

increased. The results of these studies confirm the safety and feasibility of robotic DP [12, 13, 24–28]. No mortality has been reported in the published series. The morbidity ranges from 9 to 72% and length of stay from 4 to 7 days (Table 3). There are no prospective randomized studies comparing the open, laparoscopic, and robotic DP. A retrospective study comparing the robotic to the traditional laparoscopic technique showed that the robotic technique was associated with a significant increase of spleen preservation rate, operative time, and costs [25]. Another study, retrospectively comparing the results of open, laparoscopic, and robotic DP, confirmed that robotic DP was associated with an increased operative time and spleen preservation rate but significant reduction in LOS compared to both laparoscopic and open DP. Interestingly, the costs of the robotic DP, even if no statistical significant differences were found, seemed to be associated with certain cost reduction [28]. Only three studies have reported on robotic DP for malignancy but data regarding R1-rate or number of lymph nodes retrieved are scarcely reported [12, 13, 24–28] (Table 4).

3.3. Robotic Pancreatectomies Associated with Vascular Resection. Three reports of small series of patients undergoing pancreatectomy associated with vascular resection for cancer have been found in the literature. In the first paper [29], 5 patients were included. The mean operative time was 392 minutes and the mean intraoperative blood loss 200 mL. One patient developed postoperative complications (20%). In two cases in which a portal vein reconstruction was required, the mean time of superior-mesenteric/portal vein clamping was 22 minutes. The 6-month survival rate was 80%. In the second paper [16] three cases are described, but no details on the perioperative results and outcome are reported. In the 3rd paper [12] four Appleby operations were reported without perioperative mortality, but with 100% morbidity. The mean operative time was 204 minutes.

3.4. Others Robotic Pancreatic Procedures. Many case reports, or small series, of robotic pancreatectomy, are reported in the last year's literature. Enucleation of pancreatic tumors seems to be a safe and effective procedure. Zureikat et al. [12] reported 10 cases performed with no perioperative mortality and 50% morbidity. Few cases of central pancreatectomy, probably also for the rare indication for this procedure [30], are reported in the literature. In a recent series of 13 patients robotically treated [12], there was no perioperative mortality, but 100% morbidity. In another retrospective study [31] including five patients treated robotically and 10 patients treated with open central pancreatectomy, no differences were found regarding overall complication rate and perioperative mortality, but the intraoperative blood loss was significantly lower in the robotic group. In contrast the operative time was longer in the robotic group compared to the open procedure. No significant difference was found in the length of hospital stay. A few small series of total pancreatectomies are also reported [12, 32]. In the Zureikat experience [12], 5 patients were analyzed with no postoperative mortality and with 100% of complication rate. In the Giulianotti series [32], there was no perioperative mortality and 2 patients of 5 (40%) developed postoperative complications. In this study the mean operative time was 456 minutes and the mean length of hospital stay was 7 days. Robotic total pancreatectomies associated with autoislet transplantations have also been described for the treatment of chronic pancreatitis [33, 34].

3.5. Overall Evaluation of Results of Robotic Pancreatic Surgery. From the analysis of the current literature, robotic pancreatectomies seem to be feasible and as safe as open

procedures. In a recent meta-analysis, Zhang et al. [35] showed a statistical significant advantage of robotic surgery compared to open procedures in terms of overall complication rate, reoperation rate, positive resection margin rate, mean hospital stay, and mean intraoperative blood loss. No differences were found in incidence of postoperative pancreatic fistula, postoperative mortality, and operation time. More complicated is the comparison between robotic and laparoscopic procedures for the lack of comparative data.

4. Discussion

During the last decade there has been an increasing interest in minimally invasive pancreatic surgery. The use of traditional laparoscopy, mostly limited to DPs and enucleations [9], has increasingly been described in large series of PD in the last years [7]. The introduction of the robot increased the interest in many centers for minimally invasive pancreatic surgery, even in performing more complicated operations. The improved 3-dimensional imaging, the enhanced dexterity, the better visualization and increased magnification, and the improved ergonomics associated with robotic surgery [10] are some of the most important reasons for the development of robotic pancreatic surgery. The robot offers also the possibility of performing a minimally invasive operation in a way much more similar to traditional open surgery compared to the laparoscopic approach. This difference facilitates the work of the surgeon and can reduce the intraoperative stress [36]. Even if no prospective randomized trials are available comparing results of robotic, open, and laparoscopic pancreatic surgery, data from literature show that robotic pancreatectomies can be performed as safe as the open procedures in experienced centers. However, in all these analyses there is an important bias: the retrospective nature of the studies. The advantages of robotic surgery, compared to the open one, seem to be the traditional ones of minimally invasive surgery, that is, decreased intraoperative blood loss and shorter hospital stay. How much these advantages impact the perioperative costs is very difficult to analyze because there are contradictory results in different retrospective comparative studies. Anyway, the general idea that robotic surgery is more expensive than traditional one is not supported by the literature. Even more complicated is the comparison of robotic and laparoscopic pancreatic surgery. Considering the experience reported in performing PD with the two methods, we can say that robotic technique is more suitable to approach major pancreatectomies. In contrast in DPs, it is difficult to identify advantages. The only reasonable explanation for the use of robot in these procedures can be the easier performing of spleen preserving distal resection and the shorter learning curve to approach these operations. The learning curve aspect is also a topic that should be more investigated [37], even considering the institutional impact on reducing costs. The real problem coming out from this literature analysis is that no long term results of these procedures are available. No data comparing survival in cancer patients are available. For this reason, without a strong evidence of oncologic advantages of robotic surgery and with similar short term results, the cosmetic advantages offered by this technique seem to be not enough to justify an extensive use of it without reasonable cost/effectiveness for cancer patients. In contrast, the safety of these procedures can justify the use of the robotic technique in young patients with benign/low grade malignant tumors of the pancreas that can mostly benefit from a cosmetic operation.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publishing of this paper.

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Clinical Study

Morphohistological Features of Pancreatic Stump Are the Main Determinant of Pancreatic Fistula after Pancreatoduodenectomy

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Introduction. Pancreatic surgery is challenging and associated with high morbidity, mainly represented by postoperative pancreatic fistula (POPF) and its further consequences. Identification of risk factors for POPF is essential for proper postoperative management. *Aim of the Study.* Evaluation of the role of morphological and histological features of pancreatic stump, other than main pancreatic duct diameter and glandular texture, in POPF occurrence after pancreaticoduodenectomy. *Patients and Methods.* Between March 2011 and April 2013, we performed 145 consecutive pancreaticoduodenectomies. We intraoperatively recorded morphological features of pancreatic stump and collected data about postoperative morbidity. Our dedicated pathologist designed a score to quantify fibrosis and inflammation of pancreatic tissue. *Results.* Overall morbidity was 59,3%. Mortality was 4,1%. POPF rate was 28,3%, while clinically significant POPF were 15,8%. Male sex ($P = 0.009$), BMI ≥ 25 ($P = 0.002$), prolonged surgery ($P = 0.001$), soft pancreatic texture ($P < 0.001$), small pancreatic duct ($P < 0.001$), pancreatic duct decentralization on stump anteroposterior axis, especially if close to the posterior margin ($P = 0.031$), large stump area ($P = 0.001$), and extended stump mobilization ($P = 0.001$) were related to higher POPF rate. Our fibrosis-and-inflammation score is strongly associated with POPF ($P = 0.001$). *Discussion and Conclusions.* Pancreatic stump features evaluation, including histology, can help the surgeon in fitting postoperative management to patient individual risk after pancreaticoduodenectomy.

1. Introduction

Pancreatoduodenectomy (PD) has become over the years the treatment of choice for benign and malignant diseases of the periampullary region [1, 2]. The outcomes of this procedure gradually improved, due to more accurate indications and advances in surgical techniques and in perioperative care (before, during, and after surgery) and also by pancreatic surgery centralization in high-volume centers [3]. All these improvements have led to a considerable and progressive decrease in mortality, keeping rates below 5% in referral centers; nevertheless, similar effects are still not observed on morbidity, remaining close to 50%, even in high-volume surgical settings as described by large series in the literature [4].

Postoperative pancreatic fistula (POPF) is frequently observed, with reported incidence between 8% and 30%, and substantially contributes to overall morbidity [5]. This complication can have catastrophic consequences, particularly sepsis and hemorrhage, and remains the leading risk factor for postoperative death, longer hospital stay, and increased hospital costs after PD [6–8]. For these reasons, a reliable POPF prediction could lead to postoperative management fitting to patient personal risk.

In recent years there has been considerable interest in POPF risk factors, searching for strategies for its prevention; the choice of technical tricks and the improvement of patient perioperative management were the most debated. Several

risk factors for POPF were proposed in the literature: amongst them, most authors focused on soft pancreas, pancreatic duct caliber, the underlying pancreatic pathology, regional blood supply, and surgeon's experience [9–13].

In detail, macroscopically normal or soft pancreas, especially in presence of a small pancreatic duct, sets up a more technically challenging anastomosis that is ultimately more prone to develop a postoperative leakage. Different studies examined morphological features of the pancreatic stump, searching for their relationship with POPF onset: they especially analyzed the glandular texture, as intraoperatively assessed by the surgeon, the presence of pancreatic tissue alteration at histology, and main pancreatic duct diameter. However, there are limited reports in the literature describing with statistical significance the association between Wirsung duct diameter, pancreatic texture, pancreatic tissue histology, and POPF occurrence; moreover, there are no studies concerning Wirsung position in pancreatic stump area and its mobilization extent before performing anastomosis.

This study was designed to evaluate the relationship between the development of postoperative pancreatic fistula in patients undergoing PD and intraoperative findings as glandular consistency, main pancreatic duct diameter, and its location in the area of pancreatic stump, in association with histological fibrosis and inflammation of pancreatic tissue.

2. Materials and Methods

We derived all mentioned information from our prospective electronic database, regarding all patients undergoing pancreatic surgery at the Section of Pancreatic Surgery, Department of Surgery, Humanitas Research Hospital of Milan, Italy; data collection received the approval of our hospital ethics committee.

Between March 2011 and April 2013 we performed 145 consecutive PD operations for benign and malignant periampullary disease: pancreatic cancer (53%), periampullary cancer (27%), endocrine tumors (7%), pancreatic cystic lesions (7%), chronic pancreatitis (5%), and other indications for surgery (2%). All operations were performed by head surgeon with 25 years of experience in pancreatic surgery helped by a dedicated surgical team. During the reconstruction phase we generally performed a manual end-to-side pancreatojejunostomy in double layer; in few cases we realized a duct-to-mucosa anastomosis. No pancreaticogastrostomies were performed and no ductal stents were used. At the end of each procedure, two laminar drains were routinely left in place, respectively, ventral and dorsal to the pancreaticojejunostomy, and exteriorized through the left flank.

We prospectively recorded surgeon's judgment about pancreatic texture as soft, medium, or hard by palpation of the pancreatic remnant before reconstruction.

In the intraoperative period, too, we acquired with a sterile ruler the measurement of main pancreatic duct diameter (Figure 1) and of the distance between Wirsung and pancreatic resection margins orthogonally considered (Figure 2) and the extension of gland mobilization from the vessels plane. The whole stump area has been calculated by approximating an ellipse.

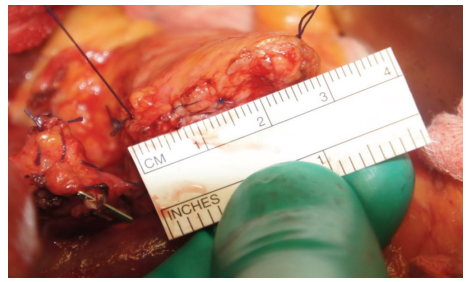

Figure 1: Pancreas measures.

An index of Wirsung decentralization has been designed considering the main pancreatic duct position relative to stump orthogonal axes, obtaining a value ranging from −1 to +1 in relation to the area's center: on the craniocaudal axis, the index ranged from −1 to +1 moving from cranial to caudal edge and approaching a zero value near the geometric center of the stump; in a similar way, on the anteroposterior axis, the index ranged from −1 to +1 moving from anterior to posterior margin and reaching a zero value in proximity of the stump center.

We then recorded POPF rate and its clinical impact, according to ISGPF classification [14]. In the postoperative period patients were managed according to our usual clinical protocol: intravenous infusion until the 4th postoperative day, oral feeding from the 4th postoperative day (in absence of clinical contraindications), abdominal CT scan in presence of any clinical or biochemical suspicion of abdominal collection, and specific antibiotic therapy in case of positivity of intraoperative bile culture or of postoperative drain fluid culture. All patients received somatostatin analogues by subcutaneous injection until oral feeding recovery.

2.1. Histological Analysis and Score Definition. Histological analysis was performed retrospectively by a single dedicate pathologist, who assessed blindly, with optical microscopy, the degree of fibrosis and inflammation of pancreatic tissue on stained slides derived from the resection margin. At pathological analysis the presence of fibrosis was graded on a scale of five levels, starting from normal pancreatic parenchyma, consisting in lobes separated by connective tissue organized in fine septa ("no fibrosis" grade) and reaching the complete replacement of the parenchyma by fibrosis, with rare residual areas of acinar glandular tissue ("subtotal fibrosis" grade). Intermediate steps were identified considering the presence of perilobular fibrosis, (connective tissue involving the lobes, but no penetrating them), focal or extensive, and periacinar fibrosis (fibrosis within the lobes, respecting the acini), focal or extensive, too (Figure 3).

The chronic tissue infiltration by inflammatory lymphocytes was also classified by our pathologist in three grades: absent, focal, or generalized.

A numeric progressive value was given to each grade of fibrosis and each grade of inflammation. As shown in Table 1,

Table 1: Fibrosis and inflammation grading at histology and final score computation.

Pancreatic stump fibrosis-and-inflammation score			
Grade of fibrosis	Score	Grade of inflammation	Score
No fibrosis	0	No inflammation	0
Local Fibrosis (lobular or acinar)	1	Focal inflammation	1
Lobular generalized fibrosis	2	Generalized inflammation	2
Acinar generalized fibrosis	3		
Subtotal fibrosis	4		
Final score computation			
0–2	Regular pancreas or mild alterations: perilobular or periacinar fibrosis, no inflammation or focal inflammation		
3-4	Moderate tissue alterations: perilobular generalized fibrosis, focal or diffuse inflammatory infiltrate		
5-6	Generalized fibrosis with total or subtotal disruption of acinar structure, intense inflammation		

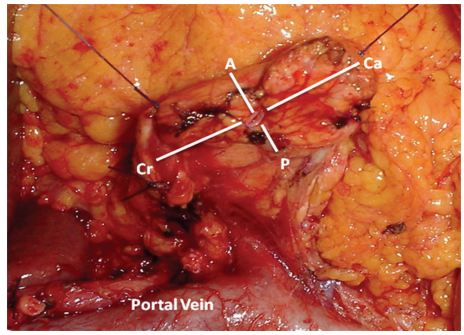

Figure 2: Identification of main pancreatic duct and orthogonal stump axis: craniocaudal (Ca-Cr) and anteroposterior (A-P).

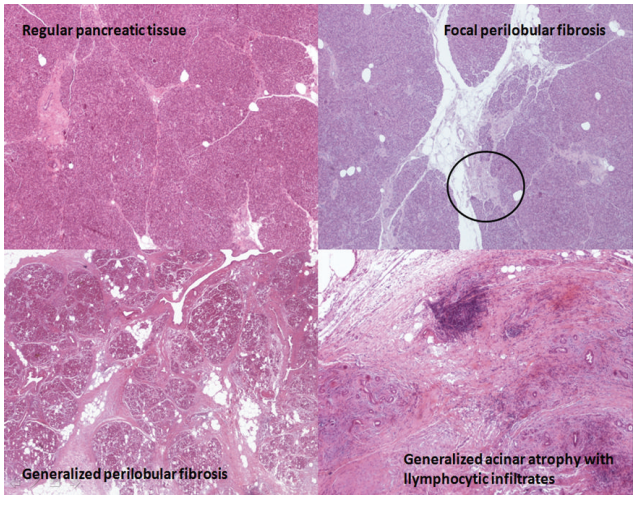

Figure 3: Pancreatic fibrosis and inflammation at histology.

values resulting from the sum of the valid points for each criterion were further classified into three groups:

(i) Group I: normal pancreas or with mild alterations;

(ii) Group II: pancreas with moderate fibrosis and inflammation;

(iii) Group III: pancreas with severe fibrosis and inflammation.

2.2. Statistical Analysis. All calculations were realized with PASW Statistics 18th version (SPSS Inc., Chicago, IL). Data were appropriately analyzed by using Student's t-test, Wilcoxon test, and chi-square test. A linear regression was employed for multivariate analysis considering significant variables at univariate analysis.

A *P value* less than 0.05 was considered statistically significant.

3. Results

We considered in the analysis all the performed consecutive 145 PD operations. All descriptive statistics regarding preoperative, intraoperative, and postoperative variables are shown in Table 2.

The median length of hospital stay (LOS) was 12 days. Overall morbidity was 59,3%. Single postoperative complication rates are listed in Table 2. There were 6 deaths (4,1%): two patients died at postoperative days 3 and 7, due to intestinal ischemia and stroke, respectively, while the others died due to septic complications and sequels secondary to pancreatic fistula occurrence. The incidence of POPF was 28,3%; clinically significant POPF rate (ISGPF grade B-C) was 15.8%.

Analyzing patient personal risk factors for POPF development (Table 3), the univariate analysis showed that male sex ($P = 0,009$), higher BMI ($P = 0,002$), and prolonged surgery duration ($P = 0,001$) were associated with a higher risk of pancreatic fistula.

We then turn to morphological risk factors analysis (Table 4). A soft pancreatic texture resulted strongly associated whit POPF development (73% versus 14%; $P < 0,001$) and whit high grade POPF, as 42% of patient with soft

Table 2: Descriptive statistics regarding the study population.

Patients population ($n = 145$)	
Age (yy)	65,97 ± 10,74
Sex (M : F)	85 : 60
BMI (kg/m^2)	23,94 ± 4,08
ASA score	
1	18 (12,4%)
2	83 (57,2%)
3	41 (28,3%)
4	3 (2,1%)
Diabetes	32 (22,1%)
Preoperative biliary stenting	76 (52,4%)
Albumin (g/dL)	4,12 ± 0,37
Cholinesterase (kUI/L)	8,41 ± 2,31
Total blood protein (g/L)	68,65 ± 6,15
Hemoglobin (g/dL)	12,99 ± 1,60
Hematocrit (%)	38,29 ± 4,56
Neoadjuvant CT-RT	12 (8,30%)
Intraoperative blood loss (mL)	373,10 ± 265,75
Surgery time (min)	468,91 ± 68,61
Blood transfusion	26 (18%)
Pylorus preserving PD	128 (88,2%)
LOS (days, median, and range)	12 (3–108)
Overall morbidity	89 (59,3%)
Mortality	6 (4,1%)
Clavien	
0	59 (40,70%)
I	6 (4,1%)
II	48 (33,1%)
IIIa	16 (11,0%)
IIIb	7 (4,8%)
IV	3 (2,10%)
V	6 (4,10%)
POPF	41 (28,3%)
Grade A	18 (12,4%)
Grade B	16 (11,0%)
Grade C	7 (4,8%)
Biliary fistula	10 (6,90%)
Lymphatic fistula	9 (6,20%)
Postoperative bleeding	19 (13,10%)
Delayed gastric empting	4 (2,8%)
Reintervention	9 (6,20%)
Readmission	9 (6,20%)

Table 3: Univariate analysis of preoperative and intraoperative clinical risk factors for POPF.

	POPF ($n = 41$)	No POPF ($n = 104$)	P value
Age	63,99 ± 11,39	66,75 ± 10,42	0,164
Sex (M : F)	31 : 10	54 : 50	0,009
BMI	25,57 ± 3,50	23,29 ± 4,12	0,002
ASA score			
1	8 (19,5%)	10 (9,6%)	0,228
2	24 (58,5%)	59 (56,7%)	
3	9 (22%)	32 (30,8%)	
4	0	3 (2,9%)	
Diabetes	5 (12,2%)	27 (26%)	0,072
Jaundice at surgery	13 (34,6%)	36 (33%)	0,886
Preoperative biliary stenting	22 (55%)	54 (52,4%)	0,782
Albumin	4,16 ± 0,34	4,10 ± 0,38	0,421
Cholinesterase	8,29 ± 1,91	8,46 ± 2,46	0,699
Total blood protein	69,77 ± 5,11	68,22 ± 6,48	0,177
Hemoglobin	13,39 ± 1,66	12,84 ± 1,56	0,073
Bile infection	26 (58,3%)	60 (65%)	0,459
Blood loss (mL)	419 ± 264	354 ± 265	0,188
Surgery time (min)	498,88 ± 57,41	456,98 ± 69,28	0,001
Blood transfusion	6 (14,6%)	20 (19,2%)	0,516
Gastric resection	5 (12,2%)	12 (11,5%)	0,912

pancreas developed a high grade fistula, compared to 4% of patient with hard or medium texture ($P < 0,001$).

Main pancreatic duct diameter was smaller among patients who developed fistula compared to the others ($P < 0,001$). We identified a main pancreatic duct caliber cut-off for POPF development equal to 3 mm: Wirsung dilatation over 3 mm had a protective role, as 81% of dilated duct did not experience an anastomotic leak ($P < 0,002$). This cut-off was also reliable for high grade POPF: 65% of patients with clinically relevant fistulas carried a Wirsung duct smaller than 3 mm ($P = 0,022$).

Main pancreatic duct decentralization on the stump anteroposterior axis, especially if close to the posterior margin, was related to higher risk to develop pancreatic fistula ($P = 0,031$), while we did not find a similar correlation on the stump craniocaudal axis. This association did not appear when we considered only high grade POPF.

Continuing morphologic analysis, we observed an increased incidence of POPF when resection area was wider ($P < 0,001$); pancreatic stump in high grade POPF group was larger than the others (223,82 versus 149,59; $P = 0,003$). Finally, POPF rate and high grade POPF rate were higher in more mobilized stumps (resp., $P < 0,001$ and $P = 0,003$).

At multivariate analysis, as shown in Table 5, male gender ($P = 0,043$), soft pancreatic texture ($P = 0,000$), and longer stump mobilization ($P = 0,001$) resulted associated with POPF development. When we considered only high grade POPF (ISGPF B-C), soft pancreatic texture was the only independent factor related to pancreatic leakage ($P = 0,000$; 95%CI: 0,221–0,499).

The fibrosis-and-inflammation score computation was realized on a subgroup of 113 patients, containing the first 113 consecutive PD operations. This subgroup revealed uniformity with respect to the entire pool of patients considering all the principle preoperative variables (age, sex, BMI, preoperative albumin, previous diabetes diagnosis, surgery duration,

Table 4: Univariate analysis of morphological features of pancreatic stump as risk factors for POPF.

	Patients with POPF ($n = 41$)	Patients without POPF ($n = 104$)	P value	Patients with grade B-C POPF ($n = 23$)	Other patients ($n = 122$)	P value
Pancreatic texture by surgeon						
Soft ($n = 45$)	30	15	<0,001	19	26	<0,001
Medium or hard ($n = 100$)	11	89		4	96	
Wirsung diameter (mm)	3,19 ± 1,21	4,29 ± 1,73	<0,001	3,08 ± 1,42	4,14 ± 1,69	0,006
≤3 mm ($n = 63$)	26	37	0,002	15	48	0,022
>3 mm ($n = 82$)	15	67		8	74	
Wirsung decentralization						
Anteroposterior axis	0,31 ± 0,34	0,23 ± 0,30	0,031	0,28 ± 0,40	0,25 ± 0,31	0,131
Craniocaudal axis	−0,17 ± 0,16	−0,12 ± 0,23	0,426	−0,20 ± 0,16	−0,13 ± 0,21	0,412
Stump area (mm^2)	219,21 ± 113,79	138,23 ± 99,08	<0,001	223,82 ± 110,42	149,59 ± 105,97	0,003
Stump mobilization (mm)	24,26 ± 5,42	20,59 ± 4,02	<0,001	24,34 ± 5,89	21,12 ± 4,33	0,003

Table 5: Multivariate logistic regression analysis regarding POPF occurrence.

	β	P value	CI (inf.–sup.)
Sex	−,142	0,043	−0,259–−0,004
BMI	,129	0,085	−0,002–0,031
Surgery duration	,013	0,166	−0,001–0,001
Stump soft texture	,443	0,000	0,285–0,590
Stump mobilization	,235	0,001	0,093–0,359
Stump area	,020	0,800	−0,001–0,001
Wirsung diameter	−,074	0,340	−0,060–0,001
Wirsung AP decentralization	,010	0,881	−0,176–0,205
Constant		0,044	

and blood loss); patient in this subgroup experienced a similar POPF rate, too ($P = 0,870$).

As shown in Table 6, the surgeon judgment about pancreatic texture corresponded to the histological grade of fibrosis ($P > 0,001$): among patients with low score (score 0–2), in only 3 cases the surgeon evaluated the pancreas tissue harder than it really was at histology.

We finally observed a strong association between the patient fibrosis-and-inflammation score and POPF occurrence ($P < 0,001$): pancreas with severe fibrosis and inflammation (score ≥ 3) experienced almost zero fistulas, while 90% of patients with lower scores (the clinic "soft pancreas") developed a pancreatic leakage (Table 7).

4. Discussion

Pancreatic fistula is the "Achilles' heel" of pancreatoduodenectomy, as it represents the major cause of morbidity. There is an extensive literature illustrating many predictive factors for POPF development, classified as patient-related, operative, and gland-related factors [15–17].

A reliable POPF risk prediction could be useful to choose the best management for patients undergoing pancreatic resections, including anastomotic techniques or perioperative precautions [18]. In agreement with the literature, in our experience male sex, high body mass index, and prolonged operation time appear to be predisposing to pancreatic fistula, even if only male sex was significant at multivariate analysis.

In our study, focused on pancreatic fistula occurrence in a series of 145 pancreatic head resections, we found a strong association between anastomotic leakage and anatomy of the pancreatic remnant.

As widely reported by previous studies, texture of pancreatic stump and pancreatic duct diameter are often considered risk factors for POPF [19–21]. In 2000 Yeo et al. [20] found that POPF rate was 0% among patients with hardened remaining pancreas and increased to 25% in patients with soft parenchyma. Other investigations confirmed low POPF rates in the presence of firm pancreatic consistency. These findings are similar in our sample, where 66% of patients with soft gland at macroscopic evaluation experienced pancreatic leakage. This result can be easily explained by the technical difficulties of a pancreatoenteric anastomosis in the presence of a soft, friable tissue, which cannot resist the sutures.

Friess et al. [22] demonstrated that increased fibrosis of pancreatic tissue is associated with decreased exocrine activity, resulting in a reduction of the pancreatic juice output. Conversely, all the factors increasing gland fibrosis, like chronic pancreatitis or cancer, had a protective role, allowing for a more secure anastomosis. For the same reason in our sample, too, no patient with hardened pancreatic texture had anastomotic fistula. Our multivariate analysis confirmed that pancreatic texture is an independent predictive factor for pancreatic fistula: it validates the palpatory prediction by the surgeon as reliable.

In the last years the use of the terms "soft/hard" pancreas became popular among the experts; however, it is based only on the intraoperative palpation of the gland. Some efforts have been dedicated to make the macroscopic judgement more objective, as the intraoperative use of a *durometer* for the evaluation of pancreatic hardness [23]. Other studies

Table 6: Fibrosis-and-inflammation score and surgeon judgment about pancreatic texture.

Fibrosis-and-inflammation score and surgeon judgment about pancreatic texture				
Final score	Hard texture	Medium texture	Soft texture	*P* value
0–2	3	16	35	<0,001
3-4	12	10	0	
5-6	25	12	0	

Table 7: Association between fibrosis-and-inflammation final score and POPF occurrence.

Fibrosis-and-inflammation score and POPF development			
Final score	POPF ($n = 30$)	No POPF ($n = 83$)	*P* value
0–2	27	26	<0,001
3-4	3	19	
5-6	0	38	

showed that the subjective surgical assessment was related to the histological grade of fibrosis [24, 25].

We decided to use the pancreatic sample obtained for intraoperative frozen section as an easily available substrate to quantify objectively the fibrosis and inflammation of the parenchyma; we then compared this result with the surgeon's palpatory evaluation; we finally investigated the eventual relationship with POPF development.

As regards histological grade, 65% of patients with low score, carrying a normal or almost normal pancreas, were classified by the experienced surgeon as patients with "soft" pancreas ($P < 0.001$); we also demonstrated that higher scores were associated with very low rate of pancreatic fistula (3 pt versus 56 pt, $P < 0.001$), showing that the more intense the fibrosis and the inflammation were, the more protective the effect on POPF development was.

The diameter of main pancreatic duct is another determinant of anastomotic leakage. Literature widely demonstrated that a duct size smaller than 3 mm increases POPF risk [10, 26]. In our experience, 63.4% of patients with POPF carried a small duct, while 64.4% of patients without POPF had a duct diameter larger than this cut-off. Patients with mean size of 4.29 mm did not experience POPF, while POPF patients had average values of 3.19 mm ($P < 0.001$). Moreover, the 65% of patients with clinically relevant fistula had a small duct (<3 mm), showing that patients with small diameter were also at higher risk of worst fistulas. These findings can be explained considering the fact that a nondilated pancreatic duct can make the duct-to-mucosa anastomosis difficult or even impossible to perform, even in expert hands.

In the present study we analyzed other less discussed morphological features of the pancreatic stump: the area of the section margin, the mobilization of pancreas remnant, and the pancreatic duct position into the cut surface. The evaluation of these variables as predictive factors of POPF has not yet been debated in the literature. Wellner et al. [25] considered the mobilization of the pancreatic remnant among the risk factors but did not show a statistical association.

On the contrary, our data show that an increased mobilization is associated with POPF development. An explanation could be the following: a wide mobilization was performed in high risk situations (soft pancreas with small duct), to facilitate a deep placement of the jejunum loop behind the pancreatic stump, and ultimately to improve anastomotic outcome. However, at multivariate analysis, a wide mobilization proved to be an independent predictor of anastomotic failure: this result could be explained by a relative ischemia at the cut surface caused by vascular discontinuation and also by the intrinsic characteristics of the pancreatic neck, which is a watershed of the glandular blood supply. Strasberg et al. [27] suggested that pancreatic neck has an increased risk of ischemia when divided. On the basis of these data, a wide mobilization of the pancreatic stump (greater than 2.5 cm) is not recommended.

Concerning the stump area, we identify an increased POPF rate in larger pancreatic areas (219 versus 138 mm^2, $P < 0.001$). This finding was similar among patients who experienced a clinically relevant fistula. This could be a possible explanation: larger cut surfaces have a higher fat infiltration, which is related to parenchyma softness [28]. Moreover, a wide stump area requires a wider opening in the jejunal loop: the greater the opening, the higher the likelihood of a leakage on the enteric side of the anastomosis, making the fistula a pancreatic-enteric fistula, at higher risk of vessel erosion.

As regards the pancreatic duct position along the anteroposterior or craniocaudal axis, the duct decentralization to the posterior margin showed a significant influence on fistula occurrence. According to this evidence we could assume that a central location has a protective role in the pancreaticojejunal anastomosis tightness, probably because a centrally located Wirsung duct makes it easier to place the opening of the jejunal loop accurately in front of the pancreatic stump, performing a more tension-free anastomosis. Moreover, when the duct is close to the posterior margin, less pancreatic parenchyma can be encompassed by stitches placed inside the Wirsung duct, making them at higher risk of failure.

Besides texture and morphological features of pancreatic stump, other parameters are useful to predict failure of pancreatic anastomosis: male sex, high BMI, and prolonged surgery duration were correlated in our series to fistula occurrence. Furthermore, multiparametric scores, including

morphological, clinical, and biochemical parameters, could be useful in prediction of pancreatic anastomosis failure; their value should be analyzed and validated in further studies.

5. Conclusions

The identification of factors influencing the failure of pancreatic anastomosis is useful for patients management (drainage, type of reconstruction, radiological evaluation, and postoperative care) allowing for their stratification in high or low risk.

Pancreatic texture, assessed by the surgeon, is a significant determining factor for pancreatic fistula and high grade pancreatic fistula and corresponds to pancreatic fibrosis grade.

Moreover, careful consideration should be given to the larger pancreatic stumps, small Wirsung duct, wide pancreatic remnant mobilization, and the duct decentralization on the stump anteroposterior axis. These morphological features influence anastomosis failure.

Our study confirmed that a standardized intraoperative assessment of pancreatic anatomical features of the pancreatic stump by experienced pancreatic surgeon can predict different levels of risk for the development of postoperative pancreatic fistula.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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Review Article

Splanchnicectomy for Pancreatic Cancer Pain

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Persistent pain is a serious problem that often contributes to a poor quality of life in pancreatic cancer patients. Medical management by opioid analgesics is often accompanied by side effects and incomplete pain relief. A celiac plexus block is a simple treatment which relieves pain, but the procedure demands a certain degree of proficiency and the duration of the effects obtained can be rather limited. Transhiatal bilateral splanchnicectomy achieves a certain denervation of splanchnic nerves, but it requires a laparotomy. Unilateral thoracoscopic splanchnicectomy is a minimally invasive procedure to cause definite denervation. Bilateral thoracoscopic splanchnicectomy is recommended for unsatisfactory cases or recurrent pain occurring after the initial unilateral splanchnicectomy. It is important to select the most suitable treatment depending on patients' actual medical state and the predicted outcomes.

1. Introduction

Persistent pain is a serious problem that often contributes to anorexia and a poor quality of life for pancreatic cancer patients [1]. Moreover, it has been suggested that continuous pain might shorten the survival of such patients [2, 3]. Therefore, controlling the pain would seem to be one of the major objectives that clinicians should pursue in the treatment of pancreatic cancer patients. Recently, many kinds of opioids or nonsteroidal anti-inflammatory drugs have been developed for this purpose. However, medical management by opioid analgesics is often accompanied by various side effects and incomplete pain relief [4]. In particular, the administration of narcotics results in the sedative effects on normal activities of daily living.

The greater, lesser, and least splanchnic nerves carry sympathetic pain innervation to the upper abdominal viscera, including the pancreas, from the 5th to 8th, 9th to 10th, and 11th thoracic ganglia, respectively [5]. Visceral pain arises from the stimulation of a celiac ganglion, which then sends a signal to the splanchnic nerves [6]. To treat the intractable pain caused by pancreatic cancer, different chemical therapies or mechanical neurolysis of the splanchnic nerves has been developed.

Celiac plexus nerve block (CPB) was first described by Kappis in 1914 [7]. A double-blind randomized controlled trial showed that intraoperative CPB by injecting alcohol on each side of the aorta at the level of the celiac axis, versus the same amount of saline placebo, significantly reduced the pain score of surviving patients, for up to six months of follow-up observations [3]. CPB is now mainly applied in a percutaneous way, and several studies have been reported on the effectiveness of CPB as well as on some of its adverse events [3, 8–11]. CPB is now being widely employed as a simple procedure which brings satisfactory pain relief, although the duration of this response may be limited [7].

As a mechanical neurolysis of splanchnic nerves, the left unilateral splanchnicectomy by laparotomy in patients with chronic pancreatitis was introduced by Mallet-Guy in 1942 [12]. Splanchnicectomy by thoracotomy was described by Sadar and Cooperman [13] and Stone and Chauvin [14]. Then, in 1993, unilateral thoracoscopic splanchnicectomy (TS) for

Table 1: Reported transhiatal bilateral splanchnicectomy.

Author	Journal	Year	Number of total patients	Number of cancer patients	Total procedures of splanchnicectomy	Approach	Side	Position
Sastre et al. [18]	Surgery	1992	Pancreatic cancer ($n = 51$)	51	51	Bilateral ($n = 51$)	Bilateral ($n = 51$)	Supine position
Shimada et al. [19]	Surg Today	1999	Pancreatic cancer ($n = 9$), chronic pancreatitis ($n = 1$), postcholedochojejunostomy ($n = 1$)	9	11	Bilateral ($n = 11$)	Bilateral ($n = 11$)	Supine position

Table 2: Results of reported transhiatal bilateral splanchnicectomy.

Author	Operation time (min)	Complications	Assessment of pain	Pain scores before/after surgery	Patients free of opioids (%)
Sastre et al. [18]	NR	Pneumothorax ($n = 1$), chylothorax ($n = 1$), splenic injury ($n = 1$)	Three-step scale	32 in good (after 3 months)	NR
Shimada et al. [19]	NR	Transient hypotension ($n = 8$), pleural damage ($n = 5$)	0–4 pain score	3.5/1.4 (after 2 months)	NR

pancreatic cancer pain control was described by Worsey et al. [15]. Nowadays, TS for pain relief of chronic pancreatitis is widely performed, and some reports have studied its main beneficial effects for pain reduction [5, 16, 17].

In this review article, we focused on mechanical splanchnicectomy as a treatment of intractable pain control for pancreatic cancer patients.

2. Transhiatal Bilateral Splanchnicectomy

The procedure for transhiatal bilateral splanchnicectomy (TBS) was first described by Sastre et al. and by us [18, 19]. After laparotomy, a vertical incision through the retroperitoneum and the crus of the diaphragm was made on the aorta. The right greater splanchnic nerve is located just to the right of the azygos vein, and the left greater splanchnic nerveis located in front of the lower left hemiazygos vein. After cutting both sides of the nerves, the transected crus of the esophagus and the retroperitoneum, they are then closed [19].

Sastre et al. reported on 51 patients treated with transhiatal bilateral splanchnicectomy for intractable pain caused by unresectable pancreatic cancer [18]. TBS alone was performed for 22 patients, and TBS with biliary or gastrointestinal bypass was performed in 29 cases. Forty patients experienced good pain reduction immediately after the TBS and 32 showed good results for 3 months.

We have previously reported on the beneficial effects of TBS [19]. TBS was performed on 9 pancreatic cancer patients, 1 chronic pancreatitis with hepatoma, and 1 postcholedochojejunostomy. In the 11 patients, the mean pain reduction percentage was 85% (60–100%). Although TBS necessitates a laparotomy, it is a simple and safe technique, which is useful for an accurate assessment for the resectability of the malignancy, and also allows for the addition of other needed abdominal operations such as a biliary and/or intestinal bypass.

We reviewed the previously published articles on TBS and the data is shown in Tables 1 and 2. TBS may be optimal for pancreatic cancer patients who are determined to be unresectable after laparotomy or for those who need bypass surgery as an additional operation.

3. Unilateral Thoracoscopic Splanchnicectomy

Worsey et al. [15] and Takahashi et al. [22] reported on the treatment of intractable pain reduction by unilateral TS for unresectable pancreatic cancer. The original reports concerning TS are reviewed and presented in Tables 3 and 4.

Lonroth et al. reported that unilateral TS treatment showed significant effectiveness for reducing the pain of 4 patients with pancreatic cancer, 1 with duodenal cancer, 3 chronic pancreatitis, and 1 portal vein thrombosis [23]. They used the visual analogue pain score to evaluate the degree of the patients' pain in the study. The mean visual analogue pain scores of all the patients at each point, before the treatment, immediately after, and after 3 months, were 8.1, 1.3, and 2.9, respectively. Those data indicated that unilateral TS could induce an adequate and long-acting pain reduction and spare patients from having to tolerate the unbearable pain caused by pancreatic cancer.

Pietrabissa et al. reported on 24 patients treated with unilateral TS [27]. Four TS procedures ended in technical failures due to pleural adhesions. One patient required a contralateral TS for right-sided back pain after the treatment by the left-sided TS. Despite the apparent successful effects in pain reduction, the recurrence of the pain of low intensity within 24 hours after TS was observed in 8 of 20 patients. The authors also assessed the quality of life after TS treatment by using the Nottingham Health Profile questionnaire, and

Table 3: Reported thoracoscopic splanchnicectomy.

Author	Journal	Year	Number of total patients	Number of cancer patients	Total procedures of splanchnicectomy	Approach	Side	Position
Worsey et al. [15]	Br J Surg	1993	Pancreatic cancer ($n = 1$)	1	1	Unilateral ($n = 1$)	Left ($n = 1$)	Lateral position
Cuschieri et al. [20]	J R Coll Surg Edinb	1994	Pancreatic cancer ($n = 3$), chronic pancreatitis ($n = 5$)	3	8	Bilateral ($n = 8$)	Bilateral ($n = 8$)	Prone position
Lin et al. [21]	Eur J Surg Suppl	1994	Pancreatic cancer ($n = 7$), hepatocellular carcinoma ($n = 2$), cholangiocarcinoma ($n = 2$), gastric cancer ($n = 1$), colon cancer with liver metastasis ($n = 1$), esophageal cancer ($n = 1$)	14	14	Unilateral ($n = 1$), bilateral ($n = 13$)	Right ($n = 1$), bilateral ($n = 13$)	Lateral position
Takahashi et al. [22]	Surg Endosc	1996	Pancreatic cancer ($n = 3$)	3	3	Unilateral ($n = 3$)	Left ($n = 3$)	Lateral position
Lonroth et al. [23]	Eur J Surg	1997	Pancreatic cancer ($n = 4$), duodenal cancer ($n = 1$), chronic pancreatitis ($n = 3$), portal vein thrombosis ($n = 1$)	5	5	Unilateral ($n = 5$)	Left ($n = 5$)	Lateral position
Le Pimpec Barthes et al. [24]	Ann Thorac Surg	1998	Pancreatic cancer ($n = 20$)	20	24	Unilateral ($n = 16$), bilateral ($n = 4$)	Left ($n = 15$), Right ($n = 1$), Bilateral ($n = 4$)	Lateral position
Ihse et al. [25]	Ann Surg	1999	Pancreatic cancer ($n = 23$), chronic pancreatitis ($n = 21$)	23	44	Bilateral ($n = 44$)	Bilateral ($n = 44$)	Prone position
Giraudo et al. [26]	Ann Oncol	1999	Pancreatic cancer ($n = 14$)	14	16	Unilateral ($n = 4$), bilateral ($n = 6$)	Left ($n = 2$), right ($n = 2$), bilateral ($n = 6$)	Lateral position
Pietrabissa et al. [27]	Arch Surg	2000	Pancreatic cancer ($n = 24$)	24	25 (technical failure in 4)	Unilateral ($n = 21$)	Left ($n = 15$), right ($n = 6$)	Lateral position
Saenz et al. [28]	Surg Endosc	2000	Pancreatic cancer ($n = 24$)	24	35	Unilateral ($n = 13$), bilateral ($n = 11$)	Left ($n = 13$), bilateral ($n = 11$)	Lateral position
Leksowski [29]	Surg Endosc	2001	Pancreatic cancer ($n = 26$)	26	26	Unilateral ($n = 26$)	Left ($n = 26$)	Lateral position
Krishna et al. [6]	Journal of Pain and Symptom Management	2001	Pancreatic cancer ($n = 1$)	1	1	Unilateral ($n = 1$)	NR	NR
Lang-Lazdunski et al. [30]	Ann Thorac Surg	2002	Adrenal metastasis ($n = 1$)	1	1	Unilateral ($n = 1$)	Left ($n = 1$)	Lateral position
Stefaniak et al. [31]	EJSO	2005	Pancreatic cancer ($n = 59$)	59	24	Unilateral ($n = 24$)	Left ($n = 24$)	Lateral position
Kang et al. [32]	Am J Surg	2007	Pancreatic cancer ($n = 15$), hepatic cancer ($n = 2$), gallbladder cancer ($n = 2$), bile duct cancer ($n = 1$), gastric cancer ($n = 1$)	21	21	Bilateral ($n = 21$)	Bilateral ($n = 21$)	Lateral position
Katri et al. [33]	J Laparoendosc Adv Surg Tech A	2008	Pancreatic cancer ($n = 12$)	12	15 (technical failure in 1)	Unilateral ($n = 10$), bilateral ($n = 2$, continuous)	Left ($n = 10$), Right ($n = 4$)	Lateral position

Table 3: Continued.

Author	Journal	Year	Number of total patients	Number of cancer patients	Total procedures of splanchnicectomy	Approach	Side	Position
Johnson et al. [4]	Pancreatology	2009	Pancreatic cancer ($n = 57$), gallbladder cancer ($n = 3$), bile duct cancer ($n = 1$), duodenal cancer ($n = 1$), unknown cancer ($n = 3$)	65	15	Bilateral ($n = 15$)	Bilateral ($n = 15$)	Prone position
Prasad et al. [34]	J Minim Access Surg	2009	Pancreatic cancer ($n = 1$)	1	1	Bilateral ($n = 1$)	Bilateral ($n = 1$)	Prone position
Śmigielski et al. [35]	Videosurgery and Other Miniinvasive Techniques	2011	Pancreatic cancer ($n = 89$)	89	121	Unilateral ($n = 121$)	NR	Lateral position
Tavassoli et al. [36]	Journal of Cardio-Thoracic Medicine	2013	Pancreatic cancer ($n = 20$)	20	20	Unilateral ($n = 20$)	Left ($n = 20$)	Lateral position

Table 4: Results of reported thoracoscopic splanchnicectomy.

Author	Operation time (min)	Complications	Assessment of pain	Pain scores before/after surgery	Patients free of opioids (%)
Worsey et al. [15]	80	NR	NR	Pain free (after 1 month)	NR
Cuschieri et al. [20]	NR	None	NR	NR	NR
Lin et al. [21]	NR	Transient hypotension ($n = 3$)	NR	NR	85.7
Takahashi et al. [22]	87	Transient hypotension ($n = 1$)	NR	NR	100
Lonroth et al. [23]	<60	Pneumonia ($n = 1$), transient intercostal neuralgia ($n = 2$)	Visual analog scale	8.6/1.8 (immediately after)/3.7 (after 3 months)	33 (after 3 months)
Le Pimpec Barthes et al. [24]	NR	Intermittent diarrhea ($n = 2$)	NR	NR	80
Ihse et al. [25]	NR	Bleeding ($n = 4$)	Visual analog scale	8/3 (after 1 week)	>50
Giraudo et al. [26]	Unilateral, 63; bilateral, 86	Pneumothorax ($n = 1$), cholangitis ($n = 1$)	NR	NR	83.3 (after mean 4 months)
Pietrabissa et al. [27]	25 ± 9	Pneumothorax ($n = 1$), transient intercostal neuralgia (common)	Visual analog scale	7.4 ± 1.7/0.6 ± 1.0 (after 1 day)	95 (after 3 months)
Saenz et al. [28]	Unilateral, 58 ± 22; bilateral, 93.5 ± 15.6	Intercostal neuralgia ($n = 4$), persistent plural effusion ($n = 1$), pneumothorax ($n = 1$)	Visual analog scale	8.5/3 (after 30 day)	84 (after 4 days)
Leksowski [29]	NR	Transient intercostal neuralgia ($n = 4$)	Numeric rating scale	Worst pain; 8.54/ 1.77 (after 7 days)/ 1.59 (1 month)/ 1.85 (2 months)/ 2.00 (3 months)/ 1.93 (4 months)/ 2.25 (5 months)/ 2.80 (6 months)	100 (until death)
Krishna et al. [6]	NR	NR	Numeric rating scale	Worst pain; 9/3 (after 3 days)	0 (after 2 weeks)
Lang-Lazdunski et al. [30]	<60	None	Visual analog scale	NR/5 (after 6 weeks)	0 (after 6 weeks)
Stefaniak et al. [31]	NR	Transient intercostal neuralgia ($n = 1$)	Visual analog scale	Effect size; 11.27 (after 2 and 8 weeks)	46.1% down of opioid consumption (after 8 weeks)
Kang et al. [32]	95	None	Numeric rating scale	8.52 ± 1.08/1.71 ± 1.10 (after 7 days)	52.4 (after 7 days)
Katri et al. [33]	31 ± 12	Intercostal neuralgia ($n = 2$), transient pleural effusion ($n = 1$)	Visual analog scale	8.08 ± 1/0.58 ± 0.79 (1 day)/1.08 ± 0.8 (after 1 month)	91.7
Johnson et al. [4]	NR	Wound infection ($n = 1$), intraoperative bleeding from diaphragm ($n = 1$)	Brief pain, inventory pain score	Worst pain; 6.11 ± 3.05/5.07 ± 2.76 (after 2 weeks)/5.00 ± 3.03 (2 months)	25 (after 2 months)
Prasad et al. [34]	NR	NR	Visual analog scale	8/2 (immediate postoperative period)	NR
Śmigielski et al. [35]	32 ± 18	Pneumothorax ($n = 2$)	Visual analog scale	5.66/2.33 (after 7 days)/1.78(30 days)	NR
Tavassoli et al. [36]	NR	Pneumothorax ($n = 1$)	Visual analog scale	8.2 ± 1.2/1.4 ± 1 (after 1 day)/1.7 ± 1.5 (1 week)/2.9 ± 1.2 (1 month)/4 ± 0.9 (3 months)	75

significant improvement in each area was observed for at least 1 month after the TS treatment.

Leksowski graded the degree of pain reduction after unilateral left TS in 26 pancreatic cancer patients based on detailed scoring factors including worst pain, least pain, general activity, mood, walking ability, relations with other people, sleep, and the enjoyment of life [29]. This study clearly revealed the long-acting effectiveness of unilateral TS on improving pain relief and the quality of life.

Recently, there have been several reports on TS [6, 30, 34–36] that propose its safety and effectiveness in improving the quality of life of pancreatic cancer patients. However, the necessity of contralateral TS and the time span of the pain reduction due to the treatment still remain controversial and undetermined.

4. Bilateral Thoracoscopic Splanchnicectomy

The usefulness of Bilateral TS for pain reduction in cases with pancreatic cancer was examined by Lin et al. [21] and Cuschieri et al. [20] in 1994. The former performed bilateral TS on 14 patients to reduce severe pain due to an upper abdominal cancer [21]. Sufficient pain reduction was observed in most of the patients except for two. But back pain was not completely relieved in one esophageal cancer patient or in one pancreatic cancer with vertebral bone invasion.

Cuschieri et al. introduced a bilateral TS performed through a posterior thoracoscopic approach [20]. They investigated 8 patients with intractable pain due to pancreatic cancer ($n = 3$) and chronic pancreatitis ($n = 5$). They demonstrated that the posterior route provided an excellent visual exposure of the mediastinum, chest wall, and sympathetic and splanchnic nerves without using single lung anesthesia.

Ihse et al. reported bilateral TS in a prone position [25]. They investigated the effects of bilateral TS on pain reduction and pancreatic function (standard secretin test, basal serum glucose, plasma insulin, and C-peptide) in 23 patients with pancreatic cancer and 21 with chronic pancreatitis, concluding that bilateral TS was beneficial for achieving good pain control and it does not entail any manifest deterioration of the pancreatic functions. Bilateral TS in a prone position is one of the favorable candidates as a reliable method to reduce the intractable pain due to upper abdominal cancer.

Kang et al. reported on 21 upper abdominal cancer patients treated with bilateral TS [32]. They also investigated the anatomy of splanchnic nerves and the sympathetic chain in 26 embalmed Korean cadaveric specimens. A frequent communication occurred between the greater and the lesser splanchnic nerves, which were both commonly found above the surface of the diaphragm. They emphasized that surgeons should learn more about the abundant distribution of the splanchnic nerve fibers to prevent the incomplete interruption of splanchnic nerves.

5. Comparison of Unilateral and Bilateral Thoracoscopic Splanchnicectomy

Saenz et al. reported on 13 patients treated with unilateral TS and 11 with bilateral TS [28]. Although the authors did not offer detailed data, they intimated that bilateral TS yields higher success rates than unilateral TS in pain control management.

Giraudo et al. reported on combining TS and laparoscopic gastrojejunostomy as a palliative treatment for unresectable advanced pancreatic cancer patients with uncontrollable pain and gastric outlet obstruction (unilateral TS: 4, bilateral TS: 4, and bilateral and laparoscopic gastrojejunostomy: 2) [26]. The mean operative time was 63 min for unilateral TS, 86 min for bilateral TS, and 190 min for the combination of bilateral TS and laparoscopic gastrojejunostomy. The authors emphasized the feasibility and safety of the endoscopic palliative treatment for various adverse symptoms due to advanced pancreatic cancer. The order of merit of unilateral and bilateral TS was not mentioned.

Le Pimpec Barthes et al. described the effectiveness of contralateral TS as an additional treatment in cases of insufficient pain reduction after unilateral TS [24]. They performed the pain-reducing treatment of unilateral TS, unilateral TS with associated vagotomy, and consecutive bilateral TS for 20 unresectable pancreatic cancer patients. The secondary TS of the contralateral side was applied for patients who did not have sufficient pain reduction after unilateral TS and the ensuing results were good. Therefore, they concluded that bilateral TS need not to be initially performed.

Katri et al. investigated the pain reductive effects of left- and right-sided TS performed for 12 pancreatic cancer patients [33]. They applied right-sided TS for the right-sided dominant pain and left-sided TS for the central, bilateral, and left-sided dominant pain. They reported that 2 patients required contralateral TS because of pain recurrence. One of the patients had successful pain relief lasting until death (9 months), and in the other patient the recurrence of the pain appeared after a period of 12 months.

Bilateral TS is not necessarily recommended as an initial palliative treatment for intractable cancer pain. The left-sided TS is mainly applied as a unilateral procedure, though it may be better to select either the left or the right unilateral TS depending on the actual location of the pain. A contralateral TS is recommended if the initial unilateral TS is not effective or the recurrence of the pain appears.

6. Comparison of Celiac Plexus Block and Thoracoscopic Splanchnicectomy

Some studies compared the effectiveness of CPB and TS. Stefaniak et al. investigated the intensity of the pain, quality of life, and opioid intake for 35 patients treated with CPB and 24 with unilateral TS [31]. They concluded that both procedures provided similar efficacy, but that CPB was preferable for its lower invasiveness and for having more positive effects on the quality of life.

On the other hand, Johnson et al. compared the efficacy of bilateral CPB, bilateral TS, and appropriate medical management alone among 65 patients with pancreatic or upper abdominal cancer [4]. In this randomized controlled study, they concluded that CPB or TS would not achieve sufficient pain reduction, when compared with appropriate medical management alone.

7. Conclusions

In general, the prognosis for advanced pancreatic cancer patients is extremely poor. Therefore, normally it is quite difficult to predict whether or which splanchnicectomy will lead to significant pain reduction and contribute to the quality of life of the patients. CPB is a simple procedure which brings pain relief, but it requires proficient skills and the duration of its effects may be limited. TBS can achieve a certain denervation of splanchnic nerve, although it necessitates a laparotomy. TBS can be also used as an additional operation when abdominal surgery is required for patients. Unilateral TS is a lesser invasive method than TBS to achieve a certain denervation level. Bilateral TS may be recommended for unsatisfactory cases or recurrent pain after the initial unilateral TS. There are lots of modalities to treat the intractable pain of pancreatic cancer patients. It is very important to select the most appropriate treatment depending on the individual patients' actual medical condition and predicted outcomes.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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