Surgery for pancreatic disease

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Purpose of review
Surgery for pancreatic diseases is one of the most studied fields in general surgery and continues to evolve. This review focuses on recent advances in pancreatic surgery and summarizes the published research.

Recent findings
Surgery for pancreatic diseases is an evolving field with a wide range of innovations. Especially, contributions by high-volume pancreas centers have greatly improved outcomes in pancreatic surgery. In chronic pancreatitis, recent studies demonstrate that early surgical treatment should be favored over repeated endoscopic interventions, and local organ-preserving resection techniques should be preferred over classic Whipple resection. Major advances have also been made on the diagnosis of pancreatic cystic lesions; however, the assessment of the current guidelines is still evolving. In pancreatic cancer, neoadjuvant treatment regimens appear to be promising, and extended pancreatic resections with vascular resection can now be offered with lower mortality and morbidity rates. Minimal-invasive laparoscopic and robotic surgical techniques are being used more frequently for the resection of pancreatic tumors and have seen major progress.

Summary
In recent years, the outcome of patients undergoing pancreatic surgery improved due to better knowledge about the biology of the disease, more accurate diagnostic modalities, the application of organ-preserving surgical techniques in benign disorders and new advances in management strategies.

Keywords
acute pancreatitis, chronic pancreatitis, pancreatic cancer, pancreatic cystic neoplasms, pancreatic surgery

INTRODUCTION

In the past months, several interesting studies on surgery for pancreatic disease have been published and have led to major improvements. Nevertheless, even in high-volume centers pancreatic surgery is associated with a considerable postoperative morbidity and mortality, which is why the prevention and management of postoperative complications is an important factor. In April 2016, a case vignette, followed by two short essays in the *New England Journal of Medicine*, started a discussion on the clinical effect of surgical volume for pancreatic head resections [1▪▪]. Even though there is strong evidence in the literature that surgery in high-volume centers by high-volume surgeons is associated with a significantly lower mortality, more than one-third of participants of the poll favored a Whipple operation at low-volume centers [1▪▪]. This article aims at addressing the knowledge gaps, such as the strong inverse association between hospital volume and mortality [2]. In addition, this review highlights recent publications from basic and clinical research with an impact on surgical strategies for pancreatic diseases, such as acute and chronic pancreatitis, endocrine neoplasms, cystic lesions, and pancreatic cancer. Moreover, this article calls for a critical assessment of new developments, such as the application of alternative treatment strategies. Due to improved interventional and endoscopic techniques some indications for surgical intervention have changed and led to similar outcomes with less operative trauma. However, these developments must be critically evaluated, as these interventions could also lead to a prolonged disease state with worse outcomes such as pseudocyst formation, duodenum, and bile duct obstruction. In addition, some minimal-invasive and robotic approaches become more and more popular. This review highlights some of the recent studies in pancreatic surgery,

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KEY POINTS

- In acute necrotizing pancreatitis, laparoscopic (transgastric) necrosectomy and laparoscopy-assisted open cystogastrostomy are new feasible techniques, which add to the minimal-invasive arsenal of procedures (drainage, retroperitoneal necrosectomy, and endoscopic transgastric necrosectomy).
- In the management of pain for obstructive chronic pancreatitis, surgery is superior to endoscopy in terms of pain relief and pancreatic function, especially, if surgical intervention is performed at an early stage of the disease.
- Current international consensus guidelines for the management of IPMNs remain imperfect, and further work is needed to define additional diagnostic measures that allow a more precise cut off for malignancy.
- Patients with either locally advanced or borderline resectable pancreatic cancer seem to have a better oncological outcome after neoadjuvant FOLFIRINOX; however, the accuracy of imaging in determining resectability after neoadjuvant therapy is imprecise.
- Centralization of high-volume centers is key to an improved short-term and long-term outcome of patients undergoing surgery for pancreatic diseases, and a practical implementation of highly specialized pancreas centers is the best strategy for the future.

thus leaving room for interpretation by the practicing surgeon, who is eventually in charge of patient selection and the application of new technical approaches for patients with diseases of the pancreas.

ACUTE PANCREATITIS

Acute pancreatitis, an inflammatory disorder of the pancreas, is one of the leading causes of hospital admissions worldwide and mortality of the disease can be up to 30% in subgroups depending on the clinical course [3]. Patients in high-volume centers with multidisciplinary expertise in endoscopy, interventional radiology, and general surgery are known to have a 25% lower relative risk of death than patients being treated in low-volume centers [3,4]. Recently, management strategies for acute necrotizing pancreatitis (with documented presumed infection) have made an about-face with the majority of cases being primarily treated conservatively. Even though an operation might be indicated in individual cases, potent antibiotics are usually able to stabilize the situation and prevent organ failure until the necrosis has become walled off [5]. The step-up approach that consists of percutaneous or endoscopic (transgastric) drainage followed by minimally invasive retroperitoneal necrosectomy has become generally accepted after a randomized multicenter prospective study showed it to be superior to primary open necrosectomy [6]. Although this study was not sufficiently powered to evaluate a difference in mortality, it resulted in a decrease of complications (multiple organ failure, diabetes, or need for pancreatic enzymes) and was, thus, able to support other studies that showed a decrease in mortality after delayed surgery [5]. In addition, minimally invasive retroperitoneal necrosectomy is amended by laparoscopic or endoscopic necrosectomy techniques [7]. Primary surgical intervention in acute pancreatitis is an exception and is limited to complications, such as symptomatic pancreatic pseudocysts with superinfected necrosis or septic shock. In 2016, Gerin *et al.* [8▪▪] published a small, prospective, single-center observational study to evaluate the feasibility and efficacy of laparoscopy-assisted open cystogastrostomy for the treatment of this disease and showed that an adequate internal drainage with few postoperative complications, and shortened hospital stay can be achieved by this surgical procedure. On a cautionary note, however, the authors remark that this technique should be performed carefully due to the risk of vascular injury in this delicate setting [8▪▪].

CHRONIC PANCREATITIS

Chronic pancreatitis describes a progressive fibroinflammatory condition resulting in structural damage to pancreatic parenchymal tissue that can cause severe epigastric pain and pancreatic insufficiency and often leads to other major complications, such as the development of pseudocysts, duodenal, biliary or pancreatic duct obstruction, portal vein thrombosis, or pancreatic cancer [9]. The management of chronic pancreatitis has changed significantly in the past decades and demands a multidisciplinary team approach combining medical therapy, endoscopic intervention, or surgery [9]. To advance the management of chronic pancreatitis and identify the most efficient treatment strategy, more randomized clinical trials need to be performed [10]. Currently, two randomized controlled trials indicate that in long-term follow-up surgical intervention is more effective than recurrent endoscopic intervention (e.g., stenting) [11▪▪]. In addition, in patients undergoing surgery for severe pain within 3 years of onset, the pain decrease is much more effective than in patients with longer medical treatment. Therefore, persistent pain, biliary stricture, duodenal stenosis, or suspicion of

malignancy are clear indications for surgical intervention.

With regard to surgical approaches, pancreatic head resection is the method of choice for cases with an inflammatory pancreatic head mass. In addition to the Kausch–Whipple procedure with resection of the complete pancreatic head, gallbladder, duodenum, and gastric antrum, organ-preserving procedures, the pylorus-preserving pancreaticoduodenectomy (Traverso–Longmire procedure) and the duodenum-preserving pancreatic head resection have led to major improvements in outcomes and have become the surgical standard [12]. The most common variation of duodenum-preserving pancreatic head resections includes the Beger procedure, where the neck of the pancreas is divided over the portal vein, and the head and uncinate process are subtotally excised preserving the duodenum and the intrapancreatic bile duct, the Frey procedure, a variation of the Beger procedure that combines longitudinal pancreaticojejunostomy with a local pancreatic head excision without transection of the pancreas above the portal vein, and the Berne (Büchler)/Farkas technique, a partial resection of the pancreatic head without a lateral pancreaticojejunostomy that also avoids the transection of the pancreas above the portal vein and combines the advantages of the Beger and Frey operations [12,13]. Depending on disease and location, other organ-preserving procedures include the longitudinal 'V-shape excision' of the ventral pancreas in patients suffering from 'small duct' pancreatitis, the middle segmental pancreatic resection for focal chronic pancreatitis in the corpus of the pancreas, the pancreatic left resection, or total pancreatectomy with or without autotransplantation of pancreatic islets in severe cases of chronic pancreatitis with affection of the entire gland.

Several researchers who have investigated the optimal surgical technique for chronic pancreatitis have also published long-term follow-up data for their existing studies. Two monocentric randomized controlled trials initially showed tailored organ-sparing procedures, such as the Beger or Frey procedures, to be superior to the classic Whipple and the pylorus-preserving Whipple procedure in regard to pain relief, weight gain, endocrine pancreatic function, and duration of hospital stay [14,15]. Fifteen years later, these advantages were no longer significant as none of these studies was powered for long-term follow-up and significance losses in patients due to death or being lost to follow-up [16]. Similarly, two independent randomized trials, comparing the pylorus-preserving pancreaticoduodenectomy with the Frey procedure, found the latter to provide a better quality of life with no significant difference in pain relief [17,18]. A long-term follow-up of these two studies showed comparable excellent pain control and pancreatic function, though survival rates were better for the duodenum preserving operation [19,20]. In a randomized prospective trial comparing the Beger and Frey procedures, both were found to be equally well tolerated and effective in pain relief, postoperative quality of life, control of complications affecting adjacent organs, and exocrine or endocrine pancreatic function [21]. These findings were confirmed in a 10-year follow-up study showing no difference in mortality, quality of life, pain, or pancreatic insufficiency within the two groups [22]. In another controlled, prospective, and randomized study, Koninger *et al*. [23] were able to show that the Berne (Büchler)/Farkas technique is associated with significantly shorter operation times and hospital stays compared with the Beger procedure, but the quality of life was found to be similar. Hence, no difference in patient-relevant outcome parameters between the Beger and Berne (Büchler)/Farkas procedures was seen in a 10-year follow-up study published in 2016 [24▪▪]. Several systematic reviews and meta-analyses of randomized controlled trials on the surgical treatment of chronic pancreatitis showed duodenum-preserving pancreatic head resections to be better compared with partial pancreatoduodenectomy in terms of length of hospital stay, quality of life, professional rehabilitation, and preservation of exocrine function whereas no significant difference could be detected for postoperative pain relief, endocrine pancreatic function, or perioperative morbidity [25,26].

Another development for a subset of chronic pancreatitis patients with a widely diseased gland that has been recently evaluated is total pancreatectomy with autologous islet autotransplantation. Two recent single-center observational studies showed that this procedure successfully reduces pain under stable glycemic control and improves quality of life [27,28]. Despite these favorable outcomes, more studies and standard operating procedures are needed, and one should bear in mind that this operation should only be considered once other surgical treatment options have been exhausted or are unlikely to improve symptoms of these patients [29].

In general, several randomized controlled trials provide strong evidence that surgical therapy for painful obstructive chronic pancreatitis leads to significantly better long-term results than endoscopic interventions and that early surgical intervention is associated with improved postoperative pain relief, reduced risk of pancreatic insufficiency,

and decreased re-intervention rates in comparison with conservative 'step-up approaches' [30]. Nevertheless, we need to raise awareness for early surgical intervention, as shown in a recent retrospective analysis stating that surgical management of chronic pancreatitis occurs only in a minority of patients in the United States [31]. Despite methodological limitations of some of the analyzed studies, a recent Cochrane Database systematic review points out that patients with obstructive chronic pancreatitis and dilated pancreatic duct should undergo surgery at an early stage of chronic pancreatitis [11▪▪]. Not only is early surgical intervention for chronic pancreatitis associated with improved postoperative pain relief and pancreatic function, but postponing surgery also has a negative influence on the treatment outcome.

PANCREATIC CYSTIC NEOPLASMS

Pancreatic cystic neoplasms represent a heterogeneous group of tumors with broad histologic differentials, various genetic alterations, diverse clinical presentations, and varying risks of malignancy [32]. As these lesions are being increasingly detected due to improved cross-sectional imaging or endosonographic methods, the understanding of the molecular features of mucinous cystic neoplasms (MCN), serous cystadenoma, and intraductal papillary mucinous neoplasms (IPMNs) continues to grow [32]. In recent years, the management of cystic pancreatic lesions has changed dramatically as a result of increasing knowledge about these tumors [33,34]. It has been shown that patients with pancreatic cystic tumors have a significantly higher overall risk of pancreatic cancer development than the general population, and roughly one-third of IPMNs have an associated invasive adenocarcinoma at the time of resection [33–35]. Although selection criteria are still being refined with regard to radiographic features or cyst fluid analysis, surgical intervention is the mainstay of treatment of symptomatic pancreatic cystic neoplasms [32]. A large US-American multicenter, retrospective cohort study from 2016 identified five independent predictors associated with surgical referral in patients with pancreatic cystic lesions: symptoms of weight loss on presentation, endosonographic findings of an associated solid mass, main-duct communication, multilocular macrocystic morphology, and fine-needle aspiration findings of mucin on cytology [36]. The importance of adequate patient selection has been demonstrated by a retrospective analysis from our institution analyzing surgery for cystic pancreatic lesions in 86 patients, out of which nine patients could have avoided surgery with the correct preoperative diagnosis [34]. As underscored by this study, cystic pancreatic tumors pose a major diagnostic challenge and require a dedicated multidisciplinary approach that accounts for both the risk of surgery and the long-term risk of malignancy for these lesions [34]. Hence, a study from the Massachusetts General Hospital was able to identify patients who are unlikely to benefit from further IPMN observation or pancreatic resection by classifying comorbidities according to the age-adjusted Charlson comorbidity index [37]. This observation should help physicians, patients, and their families to identify the best individual treatment decision, especially if patients are at a high risk of death from factors other than IPMNs [37].

Regarding the validity of the existing international consensus guidelines for the management of IPMNs, several studies call for an adjustment of the 2012 Sendai criteria as both main-duct and branch-duct IPMNs represent premalignant lesions [38,39▪▪]. Two independent studies from 2015 showed that main-duct IPMNs with a main pancreatic duct diameter of less than 10 mm bear a significant risk of malignancy [39▪▪,40]. Therefore, in patients with a main-duct diameter of more than 5 mm, surgical treatment should be considered, whereas residual side-branch IPMNs in the pancreatic remnant do not significantly impact the outcome and can be safely followed [39▪▪,41]. Pancreatic enucleation is a surgical technique that is used increasingly for small cystic and solid tumors. A study from 2015 assessed risk-dependent perioperative outcome parameters for pancreatic enucleation and showed it to be a safe procedure in appropriately selected patients; however, postoperative pancreatic fistulas, as main determinant of the outcome, have been found to be more frequent after the enucleation of cystic lesions [42].

Another important question that has been analyzed by several studies in the past months deals with patterns of recurrence and survival after surgical resection of IPMNs that may be significant in the case of IPMN-associated early invasive carcinoma [41,43▪▪]. In a single-center retrospective analysis from the United States, the recurrence of noninvasive branch-duct IPMNs was infrequent; however, an invasive component and a positive resection margin for IPMNs were strong predictors of recurrence [41]. In 2016, a multi-institutional analysis from the Unites States showed the lymphatic spread and T3 stage to be predictive of the recurrence after resection of small IPMN-associated carcinomas with invasive components measuring 20 mm or less, whereas a tubular carcinoma type was the most predictive of poor overall survival (OS) [43▪▪].

PANCREATIC CANCER

Pancreatic cancer ranks fourth in cancer-related deaths across all ages, and the overall 5-year survival rate for patients with pancreatic cancer is currently as low as 8% accounting for more than 200 000 deaths every year worldwide [35,44]. These dismal figures are partly because more than 50% of cases are diagnosed at an advanced stage, and many patients go undiagnosed until they present with locally advanced or metastasized tumors, for which 5-year survival is only 2% [35,45]. Pancreatic ductal adenocarcinoma is by far the most common pancreatic neoplasm arising from noninvasive precursor lesions, such as pancreatic intraepithelial neoplasias (PanINs), IPMNs, and MCNs with the majority most likely developing from PanINs [35,45].

When classified according to the extent of local invasion, pancreatic cancer without distant metastasis can be divided into resectable, borderline resectable, and locally advanced tumors; and surgical resection is regarded as the only treatment for cure resulting in significantly longer survival compared with other treatment options [35].

As recommended by the International Study Group of Pancreatic Surgery (ISGPS), criteria for borderline resectability should be applied using a specialized pancreatic computed tomography protocol, and all cases should be discussed by a multidisciplinary tumor board in high-volume centers [46]. The ISGPS endorses operative exploration and resection in the case of involvement of the mesentericoportal venous axis, whereas formal arterial resections are not recommended with an exception for individual therapeutic approaches under experimental protocols [46].

The management of borderline resectable pancreatic cancer was one of the leading issues in pancreatic surgery in the past years. In 2015, the largest series of neoadjuvantly treated folinic acid, fluorouracil, irinotecan, oxaliplatin (FOLFIRINOX) patients, who underwent surgical resection, was published: Surgical and clinicopathologic outcomes of pancreatic resections after neoadjuvant FOLFIRINOX therapy were determined by analyzing 40 patients with borderline resectable pancreatic cancer after FOLFIRINOX therapy and 87 patients without neoadjuvant therapy [47▪▪]. The FOLFIRINOX group had a significant increase in OS as underlined by a significantly lower operative morbidity, lymph node positivity, and perineural invasion [47▪▪]. In addition, the accuracy of imaging in determining resectability was evaluated by this retrospective study: Even though post-FOLFIRINOX imaging suggested continued unresectability, 92% of patients had an R0 resection, thus, demonstrating that the historical imaging criteria for resectability are no longer accurate when evaluating posttreatment imaging after chemotherapy [47▪▪].

Another study from 2016 analyzed 69 patients with primarily resectable pancreatic cancer that received neoadjuvant therapy [48]. Nine patients of the total cohort were not resected because of the development of metastatic disease or an inadequate performance status. In the remaining cohort, R0 resection was achieved in 97% leading to a median survival of 44.9 months for patients who completed neoadjuvant chemotherapy and resection compared with 8.1 months for the patients who were not resected [48]. In both studies, the group of patients receiving preoperative FOLFIRINOX had a zero pancreatic fistula rate, an otherwise major complication of pancreatic cancer resections [47▪▪,48]. Even though these and other studies support neoadjuvant therapy for locally advanced and borderline pancreatic cancer, they are highly susceptible to bias due to a short follow-up and a less number of patients. Therefore, the results of large multicenter randomized studies are eagerly awaited before giving a general recommendation in favor of neoadjuvant therapy.

In recent years, laparoscopic and robot-assisted approaches for benign and malignant pancreatic lesions have gained acceptance and are, thus, being used increasingly for both distal pancreatectomy and pancreaticoduodenectomy, but randomized data are needed to assess outcomes [49].

Many recent studies were able to show the prognostic importance of centralization in pancreatic surgery due to an inverse relationship between hospital volume and operative mortality, including a retrospective analysis of the english national health service database that determined a proficiency curve relationship by inspecting surgeon volume–mortality graphs [50]. A recent Dutch study showed that patients with nonmetastatic pancreatic cancer have a greater likelihood of undergoing surgical treatment when the diagnosis was established in a high-volume hospital pancreatic center with at least 20 resections per year [51]. Dealing with pancreatic diseases in centralized high-volume centers that make use of multidisciplinary tumor boards leads to improved decision-making on the most appropriate treatment, which is why patients undergoing pancreatic resection are able to reduce their risk of operative death by selecting a high-volume hospital [50,52].

Even though the evidence on the association of hospital procedural volume with improved patient outcome is conclusive, it is not being sufficiently implemented in reality as seen in several recent studies [53,54]. Hence, a German study from 2016 that was analyzing unbiased mortality rates for

pancreatic surgery procedures at a nationwide level showed surprisingly high mortality rates in low-volume facilities, higher than anticipated from previous studies [54]. Similarly, an American study showed the vast majority of patients undergoing a minimally invasive distal pancreatectomy in low-volume hospitals with less than five cases per year, although it is known that they would greatly benefit from referral to high-volume hospitals [53]. In our opinion, efforts should be made to disseminate information and centralization of high-volume centers should be one of the main goals for the future to create a better research environment with optimal patient selection and outcomes.

CONCLUSION

In summary, many interesting studies on surgery for pancreatic disease have been published in recent years leading to a better knowledge about the biology of the disease, more accurate diagnostic modalities, improved organ-preserving surgical techniques, and new advances in management strategies. In acute pancreatitis, the present strategy for infected necrotizing pancreatitis is to choose an appropriate antibiotic and to eventually use a step-up approach rather than performing an immediate surgical debridement unless severe complications call for a limited surgical intervention [5]. Surgery for painful or complication-associated chronic pancreatitis should be performed in an interdisciplinary high-volume center with expertise in pancreatic surgery and gastroenterology and should be tailored to the needs of patients being as problem-oriented and organ-sparing as possible. In this context, early timing of surgical therapy has a major influence on the outcome of patients with painful chronic pancreatitis and should thus be considered early since delayed salvage surgery after multiple endoscopic interventions might lose effectiveness. With regard to pancreatic cystic neoplasms, there has been a strong focus in the literature toward identifying IPMNs that are at the highest risk for malignant transformation and that should be resected at a curable stage [43▪▪]. The important predictors that influence the patterns of recurrence after surgery for pancreatic cystic lesions include the presence of an invasive component, the status of the pancreatic resection margin, and the IPMN subtype [41]. These factors are important for postoperative surveillance to properly diagnose recurrences benefiting from reoperation, whereas unnecessary imaging and follow-up investigations can be avoided in others [41]. The outcome of patients with pancreatic cancer undergoing surgery improved in the past years due to contributions by high-volume pancreas centers and novel neoadjuvant treatment regimens. Extended pancreatic resections with vascular resection can now be offered with lower mortality and morbidity rates and minimal-invasive laparoscopic and robotic surgical techniques are being used more frequently. Centralization of high-volume centers should be one of the main goals for the future due to the strong association of hospital procedural volume with improved patient outcome.

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Conflicts of interest

There are no conflicts of interest.

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- ▪ of special interest
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