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Trends in management and outcome of cystic pancreatic lesions - Analysis of 322 cases undergoing surgical resection

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Abstract

Background: Several guidelines for the management of cystic pancreatic lesions (CPL) exists. From 2013, Oslo University Hospital adapted the European consensus guidelines (ECG) in the decision making as to whether patients should be advised to have resection or observation for CPL. The aims of the study were to assess changes over time in the workup and diagnostic accuracy of resected CPL, and the short-term surgical outcome. **Methods:** Preoperative radiological work-up, clinicopathological characteristics, and perioperative outcomes were retrospectively reviewed in three consecutive time periods (early:2004-2008, intermediate:2009-2012, late:2013-2016). The rate of concordance between the ECG recommendations for resection (ECG+) or observation (ECG-) and the final histological diagnosis were assessed. **Results:** A total of 322 consecutive patients underwent resection for CPL (early:n=89, intermediate:n=108, late:n=125). The most common diagnoses were intraductal papillary mucinous neoplasia (IPMN, 36.0%), serous cystic neoplasm (SCN, 23.9%), mucinous cystic neoplasm (10.6%), pseudocyst (9.6%), solid pseudopapillary neoplasm (7.8%), and cystic pancreatic neuroendocrine tumour (5.3%). The proportion of ECG+ CPL undergoing surgery increased significantly (42.7% vs 60.7% vs 70.4%, p<0.001). The relative proportion of patients undergoing resection for SCN decreased (38.2% vs 21.3% vs 16.0%), whereas it increased for IPMN (31.5% vs 30.6% vs 44.0%). The use of magnetic resonance imaging and endoscopic ultrasound increased. There were no differences in postoperative severe complications (23.0% vs 23.6%) or 90-day mortality (2.3% vs 0.8%) between ECG+ and ECG- patients. **Conclusion:** Several changes in the management of CPL were revealed during time. Adherence to guidelines is important in order to avoid unnecessary surgery for CPL.

Introduction

Cystic pancreatic lesions (CPL) are increasingly detected. Several guidelines for the management of CPL have been introduced during the last decade[1-5]. Current guidelines are based on the assumption that these lesions can be classified correctly by preoperative imaging[6]. However, a certain degree of overlap between different lesions exists, and the rate of inaccurate preoperative diagnoses and unnecessary surgical resections varies between centres[6, 7]. Importantly, surgical resection for CPLs is associated with significant rates of morbidity and some mortality[8, 9].

It has been argued that operative resection has been overutilized for CPL[10]**.** Surgeons and gastroenterologists care for an increasing number of patients with CPL, often as incidental findings, and an appropriate utilization of surgical resection for CPL is of great importance. A multidisciplinary approach is considered mandatory to ensure optimal decision making in each patient with a pancreatic lesion[11]. From 2013, Oslo University Hospital adopted the European consensus guidelines (ECG) for the decision making between surgical resection or observation for CPL[1]. Importantly, in contrast to other guidelines the ECG deals with all common CPL and aims to improve the diagnosis and management of all entities of CPL. Trend analysis of the diagnostic accuracy and outcome of CPLs undergoing pancreatic resection in a single centre may prove useful in detecting opportunities of improvement[8, 9]. We hypothesized that a multidisciplinary approach and adherence to the ECG recommendations regarding optimal management of CPL improved patient selection for surgery. The aims of the study were to assess changes over time in the diagnostic accuracy and management of resected CPL by comparing the final histological diagnosis with the indication for resection according to the ECG. In addition, we aimed to assess the short-term surgical outcome of patients undergoing resection for CPL.

Methods

Patients

This was a retrospective review of all patients undergoing pancreatectomy for presumed neoplastic CPLs at Oslo University Hospital between January 2004 and December 2016. Pancreatic surgery in the South-Eastern region of Norway is centralised to Oslo University Hospital and currently serves a population of 2.9 million inhabitants. Patients undergoing resection for preoperatively diagnosed symptomatic pseudocysts were excluded from the study. Patients selected for observation were not recorded. Data were obtained retrospectively and included data on patient demographics, clinical presentation, preoperative diagnostic work-up, intra- and postoperative outcomes, and histopathological characteristics. The following types of comorbidities were distinguished and included in the analysis: cardiovascular disease, hypertension, chronic obstructive pulmonary diseases and diabetes mellitus. Type of procedure, duration of operation, perioperative blood loss and rate of severe complications were recorded. The hospital review board approved the study according to the general guidelines provided by the regional ethics committee. The manuscript was completed in accordance with the STROBE statement[12].

Two of the authors (KÅ and KJL) reviewed all cases by the criteria stated in the ECG, based on the preoperative symptoms and findings[1]. Consequently, patients were classified as ECG+ if the surgical indication was correct according to ECG or ECG- if not. The evaluations were done independently by the first and last author. In cases of discordance, a collaborative review was completed before final classification.

Patients were classified as ECG+ according to criteria based on symptoms, imaging features and biochemistry. The following CPL were defined as ECG+: all malignant lesions, all symptomatic lesions, all main duct IPMN, all SPN, and all MCN. Asymptomatic branch duct (BD)-IPMN were considered ECG+ in case of mural nodules, dilatation of the main

pancreatic duct >6 mm, cyst diameter >4 cm, elevated CA 19-9 and rapidly increasing size. SCNs were generally classified as ECG-, but tumours >6 cm in the head of the pancreas were accepted as ECG+. Histopathological diagnosis was made in accordance with the WHO classification[13].

Complications

Surgical procedures were performed as previously described[14-16]. Postoperative complications were graded according to the Clavien-Dindo classification[17]. Severe complications were defined as at least grade IIIa, including complications requiring surgical, endoscopical or radiological intervention as well as single or multiorgan dysfunction or death. The Clavien-Dindo grading was used to calculate the Comprehensive Complication Index (CCI) by means of the online tool (https://www.assessurgery.com/about_cci-calculator/). Pancreatic fistulas were defined and graded according to criteria set by the International Study Group on Pancreatic Fistula[18]. Duration of hospital stay was calculated from the day of surgery until discharge. Ninety-day mortality defined as death within 90 days after surgery was recorded.

Time intervals

The early period (2004-2008) consisted of a 5-year interval, while the intermediate (2009-2012) and late (2013-2016) intervals each comprised 4 years. From 2004 to 2011, pancreatic surgery was performed at two different hospitals: Ullevål Hospital and Rikshospitalet. In October 2011, the departments merged into the high-volume centre it is today, with all procedures being performed at Rikshospitalet. During the whole study period the two hospitals had a formal collaboration and laparoscopic distal pancreatic resections were performed at Rikshospitalet. Decision-making by a multidisciplinary team (MDT) for

pancreatic tumours was performed routinely throughout the whole study period, but for CPL a more systematic approach was initiated in 2008[19]. From 2013 and onward, the ECG was adopted[1].

Statistics

Continuous variables are presented as a median (range) or mean (SD), depending on data distribution. The chi-squared test was used to compare frequencies. The Mann-Whitney U test was used for comparison of skewed continuous variables. One-way analysis of variance and Kruskal-Wallis test were used for comparisons of normally and non-normally distributed variables, respectively, across the time periods. Mann-Whitney U test and post hoc tests were applied to explore the differences. A $p<0.05$ was considered statistically significant. Statistical analyses were performed using IBM SPSS Statistics version 25 (IBM Corp. Armonk, NY).

Results

A total number of 322 patients underwent pancreatectomy for presumed neoplastic CPL. Patient demographics, preoperative work-up and surgical indication according to ECG for the entire study cohort and the three study periods are shown in Table 1. Median patient age at the time of surgery was 63 years (range: 14-83 years), and 58.4% of the patients were female. Symptoms resulting in the identification of the lesion occurred in 160 patients (49.7%). At the time of surgery, the median cyst size was 3.5 cm (range: 0.2-15.5 cm). CT was performed in all except one patient (99.7%), and MRI in 152 patients (47.2%). Endoscopic ultrasound (EUS) was performed in 92 (28.6%), and in 86 of these patients fine-needle aspiration (FNA) was undertaken. When comparing patient data between the three time periods, the median age, gender, and ASA grade of the patients did not significantly differ. Patients from the last

time period had a higher BMI, and comorbidity was more common. The use of MRI increased significantly in the last period. The use of EUS/EUS-FNA and the time from diagnosis to surgery increased significantly from the first to the intermediate and last period.

Type of procedures and perioperative outcomes are presented in Table 2. Distal pancreatectomy, performed in 198 patients (61.6%), was the most common procedure. Pancreatoduodenectomy was performed in 89 patients (27.6%), enucleation in 19 patients (5.9%), total pancreatectomy in 14 patients (4.3%), and middle-preserving pancreatectomy in two patients (0.6%). In total 211 resections (65.5%) were performed laparoscopically (192 distal resections, 18 enucleations, and one pancreatoduodenectomy). Comparison between the time periods revealed a significant reduction in the proportion of pancreatoduodenectomies between the early and intermediate (p=0.012), and early and late period (p=0.007). The laparoscopic approach was increasingly chosen over the three time periods (p=0.048), reflecting the relative decrease of pancreatoduodenectomies (routinely by the open approach) and relative increase of distal pancreatectomies (routinely by the laparoscopic approach). Severe complications occurred in 75 patients (23.3%), and five patients (1.4%) died within 90 day of surgery.

Final histological diagnoses are presented in Table 3. The most common diagnoses were intraductal papillary mucinous neoplasia (IPMN, 36.0%), serous cystic neoplasm (SCN, 23.9%), mucinous cystic neoplasm (MCN, 10.6%), pseudocyst (9.6%), solid pseudopapillary neoplasm (SPN, 7.8%), and cystic pancreatic neuroendocrine tumours (cPNET, 5.3%). During the intermediate period, the relative distribution of histopathological diagnosis of resected CPL changed. The most common resected lesion within the first period of the study was SCN, and this significantly decreased during the intermediate period (38.2%

vs 21.3% vs 16.0%). The percentage of patients who underwent resection for IPMN increased in the last period of the study (31.5% vs 30.6% vs 44.0%). The relative proportion of resected MCN, SPN, cPNET and pseudocysts did not change over time.

All CPLs were categorised into different groups and evaluated with respect to the correct indication for surgery according to the ECG; ECG+ versus ECG-. ECG+ cysts constituted a significantly higher proportion of resected CPLs in the intermediate and last period (n=42.7% vs 60.7% vs 70.4%, p<0.001) (Table 3). ECG- CPLs were identified in the following CPL entities: IPMN (16.4%), SCN (88.3%), non-neoplastic/non-inflammatory cysts (76.5%), and pseudocysts (100 %) (Table 4). Frequency of the type of surgical procedure is shown in Table 4. Distal pancreatectomy or enucleation were performed in 83.9-96.0% of the cases with MCN, SPN, non-neoplastic inflammatory cysts, pseudocyst, and cPNET, whereas for IPMN and SCN major pancreatectomy was undertaken in 59.5% of IPMN and 27.3% of SPN. There was no significant difference in the rate of severe complications (23.0% vs 23.6%, p=0.896), postoperative pancreatic fistula (18.3% vs 19.8%, p=0.732) or 90-day mortality (2.1% vs 0.8%, p=0.343) between patients undergoing resection for an ECG+ vs an ECG- CPL.

Discussion

The diagnosis and management of CPL remain a challenge. This study documents an increase in the annual number of patients undergoing resection for CPL during a 13-year study period. The percentage of patients undergoing resection of SCN decreased, whereas the percentage of patients undergoing resection of IPMN increased. The results from the current study demonstrate an improvement in the diagnostic accuracy and the correct indication for surgery within a single institution. However, still a relatively high number of patients with benign CPL underwent resection, even in the late study period, and SCN and pseudocysts

were the two most common diagnoses undergoing unnecessary surgery. Although there were no differences in the rate of severe complications or 90-day mortality between patients undergoing resection for ECG+ and ECG- CPL, patients undergoing surgery for ECG- CPL still had a significant complication rate.

The spectrum of histopathological diagnoses changed over the 13-year study period. While SCN was the most commonly resected CPL in the initial study period, IPMN ranked first in the last period. A similar pattern has been observed in other studies[7]. In studies from experienced centres SCN constitute between 13% and 23.4% of resected CPL[6-9]. During the last two decades the recommendations for surgery for SCN have changed. In 1998, Beger et al. recommended surgical resection of SCN because symptoms could develop and malignant transformation to serous cystadenocarcinoma was deemed possible[20]. In 2005, Tseng et al. recommended resection of SCN measuring >4 cm, regardless of the presence or absence of symptoms[21]. However, a large multinational study based on 2622 cases of SCN concluded that surgical treatment of SCN should be proposed only if the diagnosis remained uncertain after complete workup, in cases of significant and related symptoms or, exceptionally, when in case of suspicion of malignancy[22]. Importantly, the recent ECG from 2018 concludes that SCN is a benign entity, and that there are essentially no deaths attributable to malignant behaviour of an SCN[23]. Thus, there should be a strict indication for surgical resection of SCN[22]. However, the distinction between SCN and other diagnoses may be difficult. Del Chiaro et al. showed that of 33 resected SCN, 25 lesions had an incorrect preoperative diagnosis of IPMN, MCN, pancreatic cancer, cPNET or gastrointestinal stromal tumor[7]. An increased ability to identify SCN radiographically or by the use of EUS, as well as a general acknowledgement that these lesions are benign and do

not warrant resection except in the presence of symptoms, will most likely contribute to less unnecessary surgery for SCN[8].

The increased incidence of IPMN is likely due to the widespread use of cross-sectional imaging, a growing elderly population, an increased ability to identify these pre-malignant lesions, as well as a desire to resect these lesions prior to the development of invasive disease[8, 24]. International guidelines define the indications for surgical treatment of IPMN or observation[5, 23, 25]. However, a major challenge is that recommendations for the surveillance of asymptomatic branch duct IPMNs <3 cm differ between these guidelines in terms of imaging modality and intervals between and length of follow-up. According to ECG from 2013 a MCN should be resected if the patient is fit for surgery[1]. However, following the updated guidelines from 2018, only MCNs ≥4 cm and MCNs that are symptomatic or have risk factors (i.e. mural nodule) should undergo resection, irrespective of size. Thus, similar surveillance is now recommended for BD-IPMN and MCN <3 cm[23]. In the current study, MCN constituted 10.6 % of the resected CPLs, but given the recent guidelines more patients with small MCN will probably undergo surveillance in the future.

The median age of the patients throughout the three study periods was 63 years. Of note, patients from the last time period had a significantly higher BMI, and comorbidity was more common. Both factors are major concerns in patients undergoing pancreatic surgery. IPMN is a disease of the elderly and often frail patients. Current guidelines do not address the treatment of elderly and/or multi-morbid patient, except that the patients should be “fit for pancreatic surgery” to undergo either surgery or surveillance[26]. Previous reports have shown that patients with an IPMN that formally requires surgery, but who cannot be operated because of general contraindications, have a relatively high IPMN-specific survival[27, 28].

This mandates a thorough and balanced discussion of risks and benefits with these patients, especially in patients with comorbidity or high risk of surgical complications.

The results of the current study should be interpreted in light of several limitations, most of which are inherent to the retrospective design. Surgery was considered justified in retrospect for malignancy, BD-IPMN >4 cm or with mural nodules, SPN, cPNET, MCN or symptom improvement. By retrospectively evaluating the indication for surgery based on final histology, bias is inevitably introduced, because definitive diagnosis and grade of dysplasia can only be determined reliably with histopathology[29]. Moreover, preoperative diagnosis versus final histology was not systematically recorded and could not be evaluated in this study. As in several other reports, the current study validated current guidelines on the basis of resected CPLs, while an audit of CPL not undergoing resection was not performed[6, 7, 29]. However, in a recent study, none of 110 patients undergoing observation for CPL in our institution developed malignancy at a median follow-up of 46.5 months (range 4 - 86 months)[30]. The lack of patient-reported outcomes may limit the clinical relevance of defining a correct or incorrect indication for surgery in CPL based exclusively on final pathology. Interestingly, Puri et al. showed that patients with a resected CPL were highly satisfied with their decision to have surgery, regardless of the final diagnosis or clinical outcome[31]. Fear of cancer is the main driver in the decision-making process, and the anxiety of harbouring a CPL seems to be a greater cause of distress than postsurgical lifestyle changes[31]. This last point shows that strict adherence to guidelines is not practically possible. Ultimately, the CPL should be considered in the context of the individual patient, weighing up their anxiety, comorbidities and cyst characteristics against the risks and benefits of a pancreatic resection[32]. Finally, the ECG was adopted in 2013, and it is of interest that the resection rate of ECG+ lesions only increased from 60.7 % in the intermediate to 70.4 %

in the late period (p=0.102). The working group behind the ECG from 2013 initiated their work in 2011 based on an up-to-date review of the literature. Although there was a more effective utilization of the published ECG from 2013 and onward, it is likely that some of the recommendations were implemented at an earlier timepoint based on published literature.

In conclusion, this study revealed that several aspects of the management of CPL changed over time. Adherence to guidelines is important in order to avoid unnecessary surgery for CPL. Continuous audit and implementation of updated guidelines in each centre may lead to further improvement in the selection of patients for surgery for CPL. In the future, better knowledge of the molecular and genetic aspects of CPL, and the identification of molecular biomarkers have the potential to improve the diagnostic work-up and decision making of CPL[33].

References

1 Del Chiaro M, Verbeke C, Salvia R et al. European experts consensus statement on cystic tumours of the pancreas. Dig Liver Dis. 2013;45:703-11.

2 Tanaka M, Chari S, Adsay V et al. International consensus guidelines for management of intraductal papillary mucinous neoplasms and mucinous cystic neoplasms of the pancreas. Pancreatology. 2006;6:17-32.

3 Tanaka M, Fernandez-del Castillo C, Adsay V et al. International consensus guidelines 2012 for the management of IPMN and MCN of the pancreas. Pancreatology. 2012;12:183-97.

4 Vege SS, Ziring B, Jain R, Moayyedi P, Clinical Guidelines C, American Gastroenterology A. American gastroenterological association institute guideline on the diagnosis and management of asymptomatic neoplastic pancreatic cysts. Gastroenterology. 2015;148:819-22; quize12-3.

5 Tanaka M, Fernandez-Del Castillo C, Kamisawa T et al. Revisions of international consensus Fukuoka guidelines for the management of IPMN of the pancreas. Pancreatology. 2017;17:738-53.

6 Salvia R, Malleo G, Marchegiani G et al. Pancreatic resections for cystic neoplasms: from the surgeon's presumption to the pathologist's reality. Surgery. 2012;152:S135-42.

7 Del Chiaro M, Segersvard R, Pozzi Mucelli R et al. Comparison of preoperative conference-based diagnosis with histology of cystic tumors of the pancreas. Ann Surg Oncol. 2014;21:1539-44.

8 Gaujoux S, Brennan MF, Gonen M et al. Cystic lesions of the pancreas: changes in the presentation and management of 1,424 patients at a single institution over a 15-year time period. J Am Coll Surg. 2011;212:590-600; discussion -3.

9 Valsangkar NP, Morales-Oyarvide V, Thayer SP et al. 851 resected cystic tumors of the pancreas: a 33-year experience at the Massachusetts General Hospital. Surgery. 2012;152:S4-12.

10 Allen PJ. Operative resection is currently overutilized for cystic lesions of the pancreas. J Gastrointest Surg. 2014;18:182-3.

11 Prades J, Remue E, van Hoof E, Borras JM. Is it worth reorganising cancer services on the basis of multidisciplinary teams (MDTs)? A systematic review of the objectives and organisation of MDTs and their impact on patient outcomes. Health Policy. 2015;119:464-74.

12 von Elm E, Altman DG, Egger M et al. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. Lancet. 2007;370:1453-7.

13 Bosman FT CF, Hruban RH, Theise ND. WHO classification of tumours of the digestive system. 4th ed. Lyon: International Agency for Research on Cancer; 2010.

14 Kleive D, Sahakyan MA, Berstad AE et al. Trends in indications, complications and outcomes for venous resection during pancreatoduodenectomy. Br J Surg. 2017;104:1558-67.

15 Haugvik SP, Marangos IP, Rosok BI et al. Long-term outcome of laparoscopic surgery for pancreatic neuroendocrine tumors. World J Surg. 2013;37:582-90.

16 Rosok BI, Marangos IP, Kazaryan AM et al. Single-centre experience of laparoscopic pancreatic surgery. Br J Surg. 2010;97:902-9.

17 Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. Ann Surg. 2004;240:205-13.

18 Bassi C, Marchegiani G, Dervenis C et al. The 2016 update of the International Study Group (ISGPS) definition and grading of postoperative pancreatic fistula: 11 Years After. Surgery. 2017;161:584-91.

19 Nordby T, Ikdahl T, Lothe IM et al. Opportunities of improvement in the management of pancreatic and periampullary tumors. ScandJ Gastroenterol. 2013;48:617-25.

20 Siech M, Tripp K, Schmidt-Rohlfing B et al. Cystic tumours of the pancreas: diagnostic accuracy, pathologic observations and surgical consequences. Langenbecks Arch Surg. 1998;383:56-61.

21 Tseng JF, Warshaw AL, Sahani DV, Lauwers GY, Rattner DW, Fernandez-del Castillo C. Serous cystadenoma of the pancreas: tumor growth rates and recommendations for treatment. Ann Surg. 2005;242:413-9; discussion 9-21.

22 Jais B, Rebours V, Malleo G et al. Serous cystic neoplasm of the pancreas: a multinational study of 2622 patients under the auspices of the International Association of Pancreatology and European Pancreatic Club (European Study Group on Cystic Tumors of the Pancreas). Gut. 2016;65:305-12.

23 European Study Group on Cystic Tumours of the Pancreas. European evidence-based guidelines on pancreatic cystic neoplasms. Gut. 2018;67:789-804.

24 Aronsson L, Andersson R, Ansari D. Intraductal papillary mucinous neoplasm of the pancreas - epidemiology, risk factors, diagnosis, and management. Scand J Gastroenterol. 2017;52:803-15.

25 Elta GH, Enestvedt BK, Sauer BG, Lennon AM. ACG Clinical Guideline: Diagnosis and Management of Pancreatic Cysts. Am J Gastroenterol. 2018;113:464-79.

26 Sahora K, Ferrone CR, Brugge WR et al. Effects of Comorbidities on Outcomes of Patients With Intraductal Papillary Mucinous Neoplasms. Clin Gastroenterol Hepatol. 2015;13:1816-23.

27 Del Chiaro M, Ateeb Z, Hansson MR et al. Survival Analysis and Risk for Progression of Intraductal Papillary Mucinous Neoplasia of the Pancreas (IPMN) Under Surveillance: A Single-Institution Experience. Ann Surg Oncol. 2017;24:1120-6.

28 Crippa S, Bassi C, Salvia R et al. Low progression of intraductal papillary mucinous neoplasms with worrisome features and high-risk stigmata undergoing non-operative management: a mid-term follow-up analysis. Gut. 2017;66:495-506.

29 Lekkerkerker SJ, Besselink MG, Busch OR et al. Comparing 3 guidelines on the management of surgically removed pancreatic cysts with regard to pathological outcome. Gastrointest Endosc. 2017;85:1025-31.

30 Anonsen K, Fagerland MW, Edwin B et al. Cyst Fluid CEA Concentration Discriminates Between Benign and Premalignant/Malignant Pancreatic Cystic Lesions. A Prospective Cohort Study. EC Gastroenterology and Digestive system. 2017;2:426-36.

31 Puri PM, Watkins AA, Kent TS et al. Decision-Making for the Management of Cystic Lesions of the Pancreas: How Satisfied Are Patients with Surgery? J Gastrointest Surg. 2018;22:88-97.

32 Kent TS, Vollmer CM, Jr., Callery MP. Intraductal papillary mucinous neoplasm and the pancreatic incidentaloma. World J Gastrointest Surg. 2010;2:319-23.

33 Plougmann JI, Klausen P, Karstensen JG et al. Molecular biomarkers have the potential to improve the diagnostic work-up of pancreatic cystic lesions. Scand J Gastroenterol. 2017;52:932-40.

Table 1
Patient demographics and preoperative imaging

	Total n=322	2004-2008 n=89	2009-2012 n=108	2013-2016 n=125	P
Patient demographics					
Age (years)*	60.3 (14.9)	60.3 (15.3)	59.1 (15.3)	61.3 (14.4)	0.562§
Sex ratio (F:M)	188:134	55:34	63:45	70:55	0.739$
BMI (kg/m^2)	25.6 (4.5)	24.9 (4.4)	25.0 (4.4)	26.5 (4.5)	0.012§
ASA fitness grade					
I	27 (8.4)	5 (5.6)	10 (9.3)	12 (9.6)	
II	206 (64.0)	55 (61.8)	73 (67.6)	78 (62.4)	0.269&
III	87 (27.0)	28 (31.5)	24 (22.2)	35 (28.0)	
IV	2 (0.6)	1 (1.1)	1 (0.9)	0 (0)	
Presence of comorbidity, n (%)	201 (62.4)	51 (57.3)	61 (56.5)	89 (71.2)	0.035$
Diabetes mellitus	44 (13.7)	7 (7.9)	12 (11.1)	25 (20.0)	0.025$
Cardiovascular disease	51 (15.8)	18 (20.2)	10 (9.3)	23 (18.4)	0.067$
Hypertension	72 (22.4)	22 (24.7)	19 (17.6)	31 (24.8)	0.347$
Chronic obstructive pulmonary disease	33 (10.2)	8 (9.0)	11 (10.2)	14 (11.2)	0.872$
Time from diagnosis to surgery (days)*	113 (144)	71 (80)	137 (154)	122 (165)	<0.001$
Incidental, n (%)	162 (50.3)	53 (59.6)	49 (45.4)	60 (48.0)	0.113$
Non-incidental, n (%)	160 (49.7)	36 (40.4)	59 (54.6)	65 (52.0)	
Tumour diameter*	4.3 (2.6)	3.9 (1.9)	4.6 (3.0)	4.3 (2.7)	0.215§
Preoperative imaging, n (%)					
Computed tomography	321 (99.7)	89 (100)	108 (100)	124 (99.2)	0.454$
		n/a	p = 0.352		
Magnetic resonance imaging	152 (47.2)	39 (43.8)	33 (30.6)	80 (64.0)	<0.001$
		p = 0.054	**p < 0.001**		
EUS	92 (28.6)	12 (13.5)	33 (30.6)	47 (37.6)	<0.001$
		p < 0.005	p = 0.259		
EUS-FNA	86 (26.7)	8 (9.0)	32 (29.6)	46 (36.8)	<0.001$
		p < 0.001	p = 0.247		
ERCP	27 (8.4)	11 (12.4)	6 (5.6)	10 (8.0)	0.225$
		p = 0.091	p = 0.462		
Positron emission tomography	10 (3.1)	3 (3.4)	0 (0)	7 (5.6)	0.048$
		p = 0.055	**p = 0.013**		
Octreotide scan	10 (3.1)	1 (1.1)	4 (3.7)	5 (4.0)	0.444$
		p = 0.252	p = 0.907		

Number of patients (per cent); *Mean (Std. deviation); §One-way analysis of variance (ANOVA); $Chi-Square test; &Kruskal-Wallis test.
EUS: Endoscopic ultrasound, FNA. Fine needle aspiration, ERCP: Endoscopic retrograde cholangiopancreatography, n/a.: not applicable.

Table 2

Comparison of procedures and perioperative outcomes across the time periods

	Total n=322	2004-2008 n=89	2009-2012 n=108	2013-2016 n=125	P[$]
Distal pancreatectomy, n (%)	198 (61.6)	46 (51.7)	70 (64.8)	82 (65.6)	0.082
Pancreatoduodenectomy, n (%)	89 (27.6)	35 (39.3)	26 (24.1)	28 (22.4)	0.014
Enucleation, n (%)	19 (5.9)	5 (5.6)	6 (5.6)	8 (6.4)	0.955
Total pancreatectomy, n (%)	14 (4.3)	3 (3.4)	4 (3.7)	7 (5.6)	0.676
Middle-preserving pancreatectomy[#], n (%)	2 (0.6)	0 (0)	2 (1.8)	0 (0)	n/a
Laparoscopic approach n (%)	211 (65.5)	49 (55.1)	74 (68.5)	88 (70.4)	0.048
Duration of operation (min)*	193 (29-655)	247 (68-480)	183.5 (29-655)	167.5 (30-560)	0.002[&]
Estimated blood loss*	100 (0-8000)	300 (0-3200)	100 (0-6000)	100 (0-8000)	0.009[&]
Red blood cell transfusions, n (%)	42 (13.1)	19 (21.3)	11 (10.3)	12 (9.6)	0.024
No. of erythrocyte units transfused*	0 (0-28)	0 (0-4)	0 (0-23)	0 (0-28)	0.025[&]
Severe complications, n (%)	75 (23.3)	23 (25.8)	28 (25.9)	24 (19.2)	0.384
CCI score*	0 (0-100)	0 (0-100)	0 (0-100)	0 (0-87.5)	0.172[&]
Pancreatic fistula grade B/C, n (%)	61 (18.9)	20 (22.5)	19 (17.6)	22 (17.6)	0.607
90-day mortality, n (%)	5 (1.2 %)	2 (2.2)	3 (2.8)	0 (0)	0.191
Duration of hospital stay (days)*	7 (2-90)	7 (2-79)	7 (2-58)	6 (2-90)	<0.001[&]

Values in parentheses are percentages unless indicated otherwise: *values are median (range). [$]Chi-squared test. [&]Kruskal-Wallis test. [#]One patient had a concomitant pancreatoduodenectomy and distal pancreatectomy, and one patient a concomitant pancreatoduodenectomy and enucleation. n/a.: not applicable.

Table 3

Final histopathological diagnosis and surgical indication according to ECG

Histopathologic diagnoses[$], n (%)	**Total n=322**	**2004-2008 n=89**	**2009-2012 n=108**	**2013-2016 n=125**	**P**
Intraductal papillary mucinous neoplasm	116 (36.0)	28 (31.5)	33 (30.6)	55 (44.0)	0.059
		p = 0.891	*p = 0.035*		
Mucinous cystic neoplasm	34 (10.6)	7 (7.9)	10 (9.3)	17 (13.6)	0.243
		p = 0.520	*p = 0.302*		
Solid pseudopapillary neoplasm	25 (7.8)	4 (4.5)	12 (11.1)	9 (7.2)	0.215
		p = 0.091	*p = 0.299*		
Serous cystic neoplasm	77 (23.9)	34 (38.2)	23 (21.3)	20 (16.0)	<0.001
		p < 0.009	*p = 0.299*		
Cystic pancreatic neuroendocrine neoplasm	17 (5.3)	3 (3.4)	6 (5.6)	8 (6.4)	0.613
		p = 0.465	*p = 0.787*		
Pseudocyst	31 (9.6)	10 (11.2)	13 (12.0)	8 (6.4)	0.289
		p = 0.862	*p = 0.134*		
Acinar cell carcinoma	1 (0.3)	0 (0)	1 (0.9)	0 (0)	n.s.
Pancreatic ductal adenocarcinoma	3 (0.9)	0 (0)	1 (0.9)	2 (1.9)	n.s.
Cholangiocarcinoma	1 (0.3)	0 (0)	0 (0)	1 (0.8)	n.s.
Non-inflammatory/-neoplastic cystic lesions	9 (2.8)	2 (2.2)	6 (5.6)	1 (0.8)	n.s.
Lymphoepithelial cyst	5 (1.6)	1 (1.1)	2 (1.9)	2 (1.8)	n.s.
Enterogenic cyst	1 (0.3)	0 (0)	0 (0)	1 (0.8)	n.s.
Ciliated foregut cyst	1 (0.3)	0 (0)	1 (0.9)	0 (0)	n.s.
Multicentric acinar cell adenoma	1 (0.3)	0 (0)	0 (0)	1 (0.8)	n.s.
Surgical indication according to ECG[$], n (%)					
ECG positive	191 (59.3)	38 (42.7)	65 (60.7)	88 (70.4)	<0.001
		p = 0.014	p = 0.102		

[$]Chi-squared test, n.s..: not significant.

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Table 4
Histological diagnosis according to ECG+ versus ECG– surgical indication and major versus medium surgical procedure

Histological diagnosis, n (%)	ECG +	ECG -	Major surgery	Medium surgery
Intraductal papillary mucinous neoplasm	97 (83.6)	19 (16.4)	69 (59.5)	47 (40.5)
Mucinous cystic neoplasm	33	0	2 (6.1)	31 (93.9)
Solid pseudopapillary neoplasm	25	0	1(6.1)	24 (96.0)
Serous cystic neoplasm	9 (11.7)	68 (88.3)	21 (27.3)	56 (72.7)
Pancreatic ductal adenocarcinoma	3	0	2 (66.7)	1 (33.3)
Non-neoplastic/non-inflammatory	4 (23.5)	13 (76.5)	2 (11.8)	15 (88.2)
Pseudocyst	0	31	5 (16.1)	26 (83.9)
Acinar cell carcinoma	1	0	0	1
Cystic pancreatic neuroendocrine tumour	17	0	1 (5.9)	16 (94.1)
Multicentric acinar cell adenoma	1	0	1	0
Cholangiocarcinoma	1	0	1	0
Total			105 (32.6)	217 (67.4)

Major surgery: pancreatoduodenectomy, total pancreatectomy, middle-preserving pancreatectomy
Medium surgery: distal pancreatectomy, enucleation