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Short- and long-term outcomes of surgical management of chronic pancreatitis

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Contributions by Marko Murruste:
In all articles, Marko Murruste was involved in the design of the study, in patients' recruitment and follow-up, in performing the majority of operations, in collection and analysis of data, and in writing of the text of the manuscripts.

ABBREVIATIONS

CCI	comprehensive complication index
CI	confidence interval
CP	chronic pancreatitis
CT	computed tomography
DM	diabetes mellitus
ERCP	endoscopic retrograde cholangiopancreatography
EUS	endoscopic ultrasonography
GDA	gastroduodenal artery
GIT	gastrointestinal tract
HR	hazard ratio
ICU	intensive care unit
IQR	interquartile range
L-PJ	long pancreatojejunostomy
MRI	magnetic resonance imaging
MRCP	magnetic resonance cholangiopancreatography
NRS	numerical rating scale
PA	pseudoaneurysm
PEI	pancreatic exocrine insufficiency
PD	pancreatic duct
PDI	pain disability index
PF	pancreatic fistula
PJ	pancreatojejunostomy
PPC	pancreatic pseudocyst
PY	patient year
QOL	quality of life
SD	standard deviation
SF-36	36-item short form
SMR	standardized mortality ratio
S-PJ	short pancreatojejunostomy
T3cDM	type 3c diabetes mellitus
US	ultrasonography

1. INTRODUCTION

The pancreas has been considered a mysterious human organ throughout centuries. Its discovery as a distinct organ, as well as its anatomical description, clarification of function, and explanation of the relationship with various diseases have been accompanied by uncertainties and contradictions. Furthermore, compared to the other abdominal organs, the discoveries related to the pancreas took place with a dramatic delay, i.e. hundreds of years later. This could be explained by the 'hidden' location of the pancreas and by its relatively soft texture. The abdominal surgeons of the 19th and early 20th centuries called the pancreas 'the hermit organ' (Busnardo et al., 1983). To Theodor Billroth has been ascribed sentence: 'God put the pancreas in the back because he did not want surgeons messing with it' (W. C. Roberts, 2006).

Although the anatomical changes characteristic of chronic pancreatitis (CP), i.e. 'drunkard's pancreas', were described in the late 19th century (by Friedrich in 1878), it was only 1946 when Comfort explained in detail the clinical entity of CP and the connection between alcohol abuse and CP (Comfort et al., 1946).

Since then much has been achieved concerning the management of CP: the main clinical problems have been defined (chronic abdominal pain, continuous impairment of the pancreatic function, and local complications of CP), appropriate diagnostic tools have been identified (pancreatic imaging, functional tests, etc.), methods of conservative treatment have been adopted (pain management, pancreatic exocrine replacement therapy, treatment of diabetes, etc.), a wide armamentarium of minimally invasive procedures has been employed to overcome various local complications of CP (endoscopic and percutaneous procedures, pancreatic lithotripsy, angiographic procedures, etc.), and different types of surgical procedures have been implemented in the treatment of the most severe cases of CP (pancreatic resections and drainage procedures, or their combinations, and palliative operations).

Nevertheless, besides above achievements, there are also many unsolved issues in many part of the field of 'Chronic pancreatitis'. The complexity and diversity of the clinical and morphological presentation of CP and the lack of high quality randomized controlled trials and evidence based guidelines, have resulted in clinical decision making that is largely based on local expertise, beliefs and disbeliefs (Issa et al., 2017).

The present PhD thesis is focused on:

- long-term survival after surgical treatment of CP,
- risk factors and causes of death in a surgically treated cohort,
- complications of CP, and
- technical aspects of pancreatic drainage operations.

The prevalence of complications of CP in a surgically treated cohort is described, and the impact of the different types of the surgical treatment on the occurrence of new complications during follow-up is evaluated. As a part of this PhD thesis, a pathophysiological classification of complications of CP is pro-

posed and validated on the present study cohort. Data on the study cohort's long-term survival, risk factors and causes of death are provided and the role of different risk factors is discussed. This study also encompasses evaluation of the effect of the length of pancreatojejunostomy ('short' vs 'long' anastomosis) on the results of surgical treatment. Data on surgical characteristics and rate of complications, as well as data on pain relief and quality of life are presented.

2. REVIEW OF LITERATURE

As the current PhD thesis is concentrated on three main topics *('Long-term survival, risk factors and causes of death in surgically treated CP', 'Complications of CP in surgically treated cohort', 'Pancreatojejunostomy in the treatment of CP')* the following literature review is focused on the same topics accordingly.

A brief review of definitions, epidemiology and pathophysiology is also provided to introduce the topic.

2.1. Definition, pathophysiology and classification of chronic pancreatitis

2.1.1. Definition of chronic pancreatitis

According to the current most widely acknowledged mechanistically derived definition, CP is a pathologic fibroinflammatory syndrome of the pancreas in individuals with genetic, environmental, and/or other risk factors, who develop persistent pathologic response to parenchymal injury or stress (Whitcomb et al., 2016).

This definition is an attempt to address early CP, the stage with preserved pancreatic function and potentially reversible features, in which targeted therapy is likely to be most effective. The most recent input into identifying early CP was 'International Consensus Statement on Early CP' of 2018 (Whitcomb et al., 2018). The working group suggested the criteria that define early, possible and definitive CP. However, no consensus was achieved either on a definition of early CP, or on the diagnostic criteria. Whether the mechanistic definition can be applied to patients' care in clinical practice needs to be tested in prospective observational studies (Beyer et al., 2020).

Before 2016, CP was defined using a traditional clinicopathologic approach, according to which CP is a complex fibro-inflammatory disease characterized by pancreatic inflammation with irreversible fibrotic replacement of normal exocrine and endocrine tissue (Braganza & Parr, 2011). The inevitable shortcomings of this and earlier definitions were the delay in years between onset of symptoms and diagnosis, inability to use preventive treatments that can change the course of the disease, and purely symptomatic and supportive care including replacement of the lost pancreatic function.

2.1.2. Epidemiology

The epidemiology of CP is far from perfectly described, data are scarce and the quality of studies is impacted by several difficulties (Lévy et al., 2014). The main challenges of estimating the incidence and prevalence of CP are associated with diagnostic problems:

- There exists no simple and reliable diagnostic test for early CP. Definitive diagnosis can take years (Ge et al., 2021).
- Because histology is usually not available, the diagnosis of CP is primarily based on the demonstration of pancreatic macroscopic ductal or parenchymal morphological changes that typically develop over time in the course of the disease (Banks, 2007).
- Signs of established CP can be highly variable, especially in the case of local complications. In some cases, with the diagnosis of an obvious complication, 'underlying CP' can be missed.
- It is not always possible to differentiate between chronic and acute relapsing pancreatitis, or between CP and other, non-inflammatory diseases of the pancreas.
- Long-term follow-up for obtaining data on survival and prevalence is often problematic, especially when dealing with chronic alcoholics.

These considerations strongly suggest that CP is an under-diagnosed disease. However, the incidence rates reported from Western countries are largely in the same range, varying from 4/100,000 in the United Kingdom and United States to 13.4/100,000 in Finland (Lévy et al., 2014). Xiao et al reported in their meta-analysis a global incidence rate of CP being 9.6 per 100,000 (Xiao et al., 2016).

Assuming a survival of 15–20 years, the prevalence should be between 60 and 160 per 100,000 (Lévy et al., 2014), Olesen et al reported a point prevalence of CP being 153.9 per 100,000 in Denmark (Olesen et al., 2021).

2.1.3. Pathophysiology

It has been stated that 'CP remains an enigmatic process of uncertain pathogenesis, unpredictable clinical course, and unclear treatment' (Steer et al., 1995). Indeed, the pathophysiology of CP is a complex process with many parallel and overlapping disorders.

During recent decades valuable insight into fibrogenesis in CP has been gained. This process is the result of a dynamic cascade of mechanisms beginning with acinar cell injury and necrosis, followed by inflammatory processes and activation of pancreatic stellate cells. The next steps are stimulation of synthesis of the extracellular matrix and reduced matrix degradation with the ultimate consequence of fibrous tissue development (Jin et al., 2020).

Five major mechanisms have been hypothesized to be involved in the pathophysiology of CP. First, the 'necrosis-fibrosis sequence hypothesis' of 1992 (Klöppel & Maillet, 1992) suggests that CP develops through episodes of severe acute pancreatitis, through replacement of damaged tissues by inflammatory cells and pancreatic stellate cells, and over time by fibrotic tissue. Second, according to the 'sentinel acute pancreatitis event' hypothesis, an initiating event is necessary for causing pancreatitis, and anti-inflammatory and pro-fibrotic events enable the ongoing injury and progression to CP (Schneider & Whitcomb, 2002). Third, the 'oxidative stress theory' suggests that chronic exposure to the metabolites of oxidative stress promote acinar cell necrosis,

inflammation and fibrosis (Norton et al., 1998). Fourth, the 'toxic-metabolic theory' suggests a direct toxic effect of environmental factors (alcohol and its metabolites, and tobacco) on acinar cells. Although the main site of alcohol metabolism is in the liver, the pancreas is also capable of oxidative and non-oxidative metabolization causing local glandular damage (Wilson & Apte, 2003). According to the fifth theory, 'ductal dysfunction' leads to the formation of protein plugs with consequent ductal obstruction. Protein plugs in pancreatic ducts (PD) are observed in most forms of CP (Bhanot & Möller, 2009).

Despite the diversity of the pathophysiologic theories of CP and many undiscovered subcellular and molecular events in the pathogenesis of CP, the key pathophysiological feature of CP is loss of functional parenchyma and pancreatic fibrosis with irreversible scarring of the pancreatic parenchyma (DiMagno et al., 1993; Klöppel, 2007).

2.1.4. Classifications

Throughout the modern history of CP, several attempts have been made to provide a clear-cut definition of acute and chronic pancreatitis. The first was the Marseilles classification of 1963, which made differentiation between acute pancreatitis, acute relapsing pancreatitis, chronic pancreatitis, and chronic relapsing pancreatitis (Sarles, 1965). The initial classification was revised and further improved repeatedly (the Cambridge classification of 1984; the second Marseilles classification of 1984; the Marseilles-Rome classification of 1988). The Cambridge classification established explicit criteria for the description of pancreatic duct (PD) by imaging with endoscopic retrograde cholangiography (ERCP). Five situations were distinguished: normal PD, equivocal, mild, moderate, and marked changes of PD (Sarner & Cotton, 1984). Later, similar grading criteria were defined for pancreatic imaging with computed tomography (CT) and abdominal ultrasonography (US) (Catalano et al., 1998; Hoffmeister et al., 2015; Sahai et al., 1998). However, PD abnormalities seen on ERCP have poor sensitivity for diagnosing early or mild CP (Schmitz-Moormann et al., 1985). The same limitations apply to CT and magnetic resonance cholangiopancreatography (MRCP) (Catalano et al., 2009). To address these issues, an international working group defined the endoscopic ultrasonography- (EUS-) based 'standard criteria' for the diagnosis of CP and described nine potentially abnormal features of pancreatic parenchyma and ducts suggestive of CP (Wiersema et al., 1993). Another consensus meeting in Rosemont, defined the EUS-based 'Rosemont criteria' for a more precise diagnosis of CP and classified EUS findings as: normal, indeterminate for CP, suggestive of CP, and consistent with CP, , (Catalano et al., 2009). The ideal threshold number of EUS criteria necessary for the diagnosis has not been firmly established, but presence of ≥ 5 and ≤ 2 strongly suggests or refutes the diagnosis of CP (Conwell et al., 2014).

The Zürich classification of 1997 was dedicated to alcoholic CP and distinguished between 'definitive CP' and 'probable CP' (Ammann, 1997). Besides its clinical importance, the definition of 'definitive CP' allows to more

precisely define clinical study groups in the process of clinical research (Ammann, 2001).

At the turn of the century, the TIGAR-O classification system based on etiological risk factors, was introduced (Etemad & Whitcomb, 2001). The TIGAR-O classification differentiated between toxic-metabolic, idiopathic, genetic, autoimmune, recurrent, and obstructive risk factors.

This was followed by the ABC-classification attempted to distinguish between painless and painful non-complicated and complicated CP (Ramesh, 2002). However, the latter does not clearly differentiate between different degrees of disease severity within a given category, nor does it allow categorization of all possible clinical presentations of CP. An attempt to improve the ABC classification was the Manchester three-stage clinical classification of 2006, which distinguished between mild, moderate and end-stage CP (Bagul & Siriwardena, 2006). Moderate CP was defined through presence of pancreatic functional impairment, and the end-stage disease was defined through accrual of extrapancreatic complications. For all stages, it was stipulated that there must be radiological evidence of CP. However, while the Manchester classification has similarities with the ABC classification, it has unfortunately also the same limitations.

2.1.5. Classifications including complications of chronic pancreatitis

The next important development was the M-ANNHEIM classification of CP, which was elaborated as a product of a critical literature review on clinical courses and all previous classification systems (Schneider et al., 2007). This classification system includes etiology, different stages of the disease, various degrees of clinical severity, and for the first time complications of CP were classified. The classification of complications was based on their clinical reversibility. The authors divided complications into possibly reversible features (such as presence of stenosis of adjacent viscera, e.g. duodenal stenosis, colonic stenosis, common bile duct stenosis; but also gastrointestinal bleeding; development of ascites; occurrence of pleural effusion; osseous lesions; pseudoaneurysms; and pancreatic fistulas) and irreversible complications (portal or splenic vein thrombosis with or without portal hypertension; occurrence of pancreatic cancer).

The Scandinavian Baltic Pancreatic Club has made a further important input to the classification of CP via clustering complications in 2019 (Olesen, Nøjgaard, et al., 2019). Olesen and coworkers aimed to describe the complications of CP using the M-ANNHEIM classification; to investigate the clustering of complications; and to evaluate associations between clusters and etiological risk factors. The authors distinguished between three clusters of complications: inflammatory complications (pseudocysts, ascites, pleural effusion, pancreatic fistula and portal or splenic vein thrombosis), fibrosis related complications (PD lesions, common bile duct stenosis, and duodenal stenosis), and pancreatic

insufficiency (exocrine and endocrine). This was the first attempt to develop a pathophysiological classification of complications of CP. Correlation analysis revealed higher risk of inflammatory complications in alcoholic etiology, while smoking was associated with fibrotic complications.

Although in the earlier history of CP there have been also attempts to classify complications of CP in a number of ways (e.g. functional vs morphological abnormalities; complications located in the pancreatic gland or in surrounding tissues; medically or surgically treated complications), none of them have been widely accepted or used (Prinz & Keith, 2002). Probably was one of the reasons an oversimplification, and another not so obvious practical value, at least in some cases.

2.2. Long-term survival, risk factors and causes of mortality

Several studies have noted that patients with CP have lower survival compared to the general population. Lowenfels and co-authors reported in their multicenter study 3.6 times higher mortality and Nøjgaard et al. in the Copenhagen Pancreatitis Study, 4.3–4.5 times higher mortality compared to the background population (Lowenfels et al., 1994; Nøjgaard et al., 2010).

However, relatively few studies have focused on long-term survival, causes of death and its risk factors in patients with CP. Studies of Pedrazzoli et al. and Bang et al. demonstrated higher mortality rate due to cancers, cerebrovascular diseases, chronic pulmonary diseases, peptic ulcer complications, diabetes, chronic renal disease, and liver cirrhosis (Bang et al., 2014; Pedrazzoli et al., 2008).

Reports on the role of the risk factors of death concern some shared risks (e.g. alcohol consumption). Alcohol consumption as a risk factor for an unfavorable disease course and lower long-term survival has been demonstrated in several studies (Dancour et al., 1993; Hao et al., 2018; Miyake et al., 1989). In patients with alcoholic CP the rate of local complications is also higher compared to other etiologies (Agarwal et al., 2020).

However, reports on the relevance of other risks are in some way dissimilar or even clearly contradictory. For example most studies have found smoking and diabetes to exert a negative impact on survival (Hegyi et al., 2020; Miyake et al., 1989; Seicean et al., 2006). At the same time Pedrazzoli and co-authors did not observe any significant difference in this regard (Pedrazzoli et al., 2008). Furthermore, there are a number of risk factors (e.g. social life associated factors, health-related factors), whose prognostic impact has been assessed in only a few studies and their role remains to be clarified. Study of some of the above factors have revealed lower long-term survival in patients with exocrine and endocrine pancreatic insufficiency (Lévy et al., 2014; Ockenga, 2009; Olesen, Büyükuslu, et al., 2019) and comorbidities (De La Iglesia-Garcia et al., 2018).

Although comparative data about long-term survival in terms of the applied treatment are scanty, it seems to have a significant impact. For example, the Danish Nationwide Matched-Cohort Study based mostly on conservatively managed patients, demonstrated a mortality of 77.4 per 1,000 patient-years (PY) (Bang et al., 2014). At the same time, Rösch and co-authors reported in a large multicenter study a mortality rate of 29 per 1,000 PY for an endoscopically treated cohort, and Tuluvath et al. found a mortality rate of 27 per 1,000 PY for a surgically treated cohort (Rösch et al., 2002; Thuluvath et al., 2003). Sohn et al. and Bühler et al. also reported excellent long-term survival and pain relief after surgical treatment (Bühler et al., 1999; Sohn et al., 2000). Sakorafas with co-authors reported a negative impact of resective surgery versus drainage procedures among surgically treated cohort (Sakorafas, Farnell, et al., 2000).

Relatively few studies have addressed the causes of death from CP. According to Lèvy et al., the main cause were hepatopathy, malignancies and postoperative mortality, while according to Seisean et al., these were pancreatic cancer, perioperative complications and gastrointestinal hemorrhage; De La Iglesia-Garcia and co-authors reported cancers, infections and cardiovascular events (Levy et al., 1989; Seicean et al., 2006; De La Iglesia-Garcia et al., 2018).

2.3. Morphological changes and complications of chronic pancreatitis

CP is characterized by a variety of morphological changes at the subcellular and cellular levels. The term ‘drunkard’s pancreas’ was used to describe characteristic macroscopic changes of the entire pancreatic gland by Nikolaus Friedrich already in 1878 (Navarro, 2018). In complicated cases, numerous abnormalities may occur also in surrounding tissues and organs. Until the latest definition of CP in 2016, the main morphological features of CP have been part of the definition of CP in most cases. In the mechanistic definition of 2016, the morphologic changes of CP are listed separately as signs of established and advanced disease (Whitcomb et al., 2016).

However, despite the fact that the following classification has not been used earlier, from the pragmatic point of view it seems reasonable to distinguish between three groups of the features of CP:

- microscopic features,
- macroscopic features,
- complications of CP.

Microscopic features are always present in established CP. The microscopic hallmarks of CP, the so called ‘triad of CP’, were defined by Klöppel and Esposito as progressive irreversible loss of the acinar tissue, its replacement by the fibrotic tissue, and changes of the PD (atrophic epithelium, protein plugs, distortions) (Esposito et al., 2020; Klöppel & Maillet, 1991).

There are several other microscopic changes, all or any of which may be seen in an individual patient, including areas of focal active chronic inflam-

mation, parenchymal calcifications, enlarged peripheral nerves, fibrous thickening and obliteration of blood vessels, duct wall thickening and periductal fibrosis leading to duct distortion and dilatation (Esposito et al., 2020; Klöppel et al., 2003).

However, clinical decision-making has to be done usually without histological confirmation of CP: given the potential for complications, pancreatic biopsy is not indicated for proving the diagnosis of CP, especially in early stages of the disease (Iglesias García et al., 2018). Thus, the clinical diagnosis is usually based on typical history of CP and radiological finding. The only indication for pancreatic biopsy is in suspected malignancy or autoimmune pancreatitis (Kleeff et al., 2017).

Macroscopic features of CP have been the cornerstones of establishing the diagnosis of CP for decades. As a general rule, the macroscopic characteristics of CP are the consequence of the above mentioned ongoing microscopic tissue damage (Frøkjær et al., 2018).

In clinical practice, the suspicion of CP usually arises in the case of patients with a typical anamnesis of CP, such as long-lasting alcohol consumption and/or smoking, in conjunction with clinical symptoms like chronic abdominal pain and symptoms of pancreatic exo- and endocrine insufficiency (Andersson & Löhr, 2021). This scenario is usually followed, and the diagnosis is made, by cross-sectional imaging, typically by using CT or MRI (Forsmark & Pham, 2018). There are four macroscopic features of the pancreatic gland and ducts commonly detectable in pancreatic imaging:

- calcifications,
- PD dilatation,
- pseudotumor,
- pancreatic atrophy (Figure 1).

The most common are pancreatic calcifications with a prevalence of 35% to almost 70% (Lucendo et al., 2014; Machicado et al., 2018). Higher rate of calcifications (up to 90%) have been reported in the more advanced disease, and in subjects with a long history of smoking and alcohol misuse (Ammann et al., 1988; Olesen, Lisitskaya, et al., 2019). In approximately half of cases it is believed that calcifications within the pancreatic main duct are the consequence of ductal strictures, especially if the strictures are located in the region of the pancreatic head (Dumonceau et al., 2019).

Calcifications within the PD can obstruct drainage of pancreatic secretions and lead to another macroscopic change: pancreatic duct dilation, which is assumed to be an important factor in the development of chronic pain (Jalleh et al., 1991). Bachmann demonstrated in a large retrospective study better pain relief after surgical treatment in patients with a dilated main PD compared to patients without duct enlargement (Bachmann et al., 2021). The changes of the PD seen in ERCP, or nowadays more commonly in MRCP or EUS, serve as the basis for the Cambridge classification of CP (Axon et al., 1984).

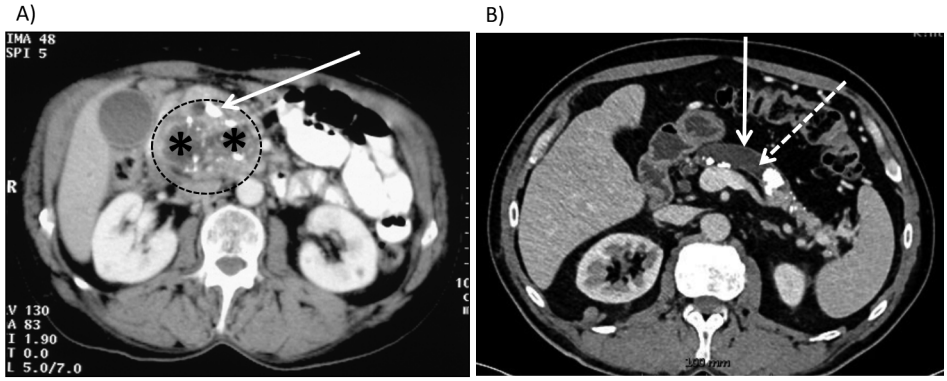


Figure 1. Common macroscopic features of chronic pancreatitis. (Source: clinical cases from the study cohort, figures from Hospital Information System.)
A) Pseudotumor ('inflammatory mass') in the region of pancreatic head. Black dashed line – 65 mm pseudotumor; white arrow – pancreatic calcifications; black stars – pseudocysts within pseudotumor.
B) Pancreatic atrophy and dilated pancreatic duct. White arrow – 2 mm thick pancreatic parenchyma around dilated pancreatic duct; white dashed arrow – pancreatic duct with diameter of 20 mm.

The rate of PD dilatation varies from study to study, as the cut-off value of dilated PD varies in a wide range and the threshold value for surgical PD decompression varies even more. In pancreatic imaging dilated PD is defined as being ≥3.5 mm (Conwell et al., 2014; Dasyam et al., 2019). Usually, a much larger PD diameter has been suggested for PD decompression through PJ. In some centers the indication for decompressive surgery is PD enlargement more than 4 mm (Ceppa & Pappas, 2009), in other centers more than 6 mm (M. W. Büchler & Warshaw, 2008; Schnelldorfer et al., 2007). An even larger PD (≥10 mm) has been reported as an indication for surgical PD decompression (Kurian & Gagner, 1999; Tantia et al., 2004). According to the diameter of PD, Etemad et al distinguished between the 'small duct disease' and the 'large duct disease' (Etemad & Whitcomb, 2001).

However, despite the diverse cut-off value for defining PD dilatation, the reported rates of PD dilatation have been mostly between 50% and 85% (Luetmer et al., 1989; Negi et al., 2010; Talukdar et al., 2021; Tian et al., 2019).

The next macroscopic feature of CP is pancreatic head heterogeneous enlargement ('chronic inflammatory mass' or 'pancreatic pseudotumor') defined as the antero-posterior diameter of the pancreatic head of >35 mm in some studies (Negi et al., 2010), but the cut-off value of >40 mm is more widely accepted (Bachmann et al., 2021; Kempeneers et al., 2022). Development of inflammatory mass is most likely the consequence of chronic active inflammation in the region of the pancreatic head characterized, besides the presence of microscopic 'triad', also by mixed inflammatory infiltrates and by calcifications

and pseudocysts (Farrell, 2005). Among surgically treated patients, the proportion of patients with inflammatory mass in the pancreatic head has been reported to be as high as 84% in German centers and as low as <25% in the United States (Izbicki et al., 1998; Keck et al., 2009). However, a recent study from the Amsterdam University Medical Centers found an equal proportion of patients with the enlarged pancreatic head and those with a dilated main PD, but without pancreatic head enlargement, in a surgical cohort of 140 patients (Kempeneers et al., 2022).

Pancreatic atrophy (defined as a thickness of the pancreas of ≤20 mm in the left vertebral margin) is a feature of CP, that reflects macroscopically advanced microscopic changes (loss of acinar tissue and fibrosis) and is usually characteristic of the end-stage disease (Frøkjær et al., 2018; Tirkes et al., 2019).

Although the magnitude of macroscopic changes may vary significantly, none of them (if asymptomatic) is an indication for any type of treatment, as there is currently no known therapy to reverse or stop the progression of chronic inflammation in the pancreatic gland (Ramsey et al., 2017). Clinical management primarily consists in screening for and treating complications.

Complications of CP, after chronic pain, is the next common indication for active treatment. The natural history of CP is usually characterized by progression of tissue damage: macroscopic changes of the pancreatic gland will become more and more apparent over time, and various complications may occur.

Functional complications with the clinical manifestation of pancreatic exocrine insufficiency (PEI) and diabetes mellitus are more common in the terminal stage of CP (Toskes, 1995). Local complications of CP may develop at any time of the disease; their diversity has been well described throughout the history of CP (Ramsey et al., 2017).

The literature pertaining to the complications of CP is more precisely reviewed in the chapter 5.4.

2.4. Pancreatojejunostomy in treatment of chronic pancreatitis

Chronic debilitating pain is the most common clinical symptom of CP, being reported by 75% of patients at presentation, and by almost 100% over time (Drewes et al., 2020). The pathophysiology of pain is not fully clarified and is probably multifactorial (Majumder & Chari, 2016). There are two dominating hypotheses of generation of pain in CP.

The first is based on PD obstruction which leads to intraductal hypertension, followed by PD dilatation and intraparenchymal hypertension and ischemia of the pancreatic tissue, which induces pain (Jalleh et al., 1991; Varabei et al., 2019). This is supported by the fact that decompression of a dilated PD provides excellent pain relief in the majority of patients (Fernández-Cruz et al., 2015; Sudo et al., 2014).

According to the second hypothesis, the enlarged pancreatic head is the 'pacemaker' of pain, and removal of this 'pancreatic pseudotumor', or 'inflammatory mass', is the most effective method of pain treatment (Beger & Poch, 2016; Köninger et al., 2006).

Systematic literature reviews have concluded that surgical treatment remains the best option for the management of pain in both these settings (Jawad et al., 2017; Kleeff et al., 2016). Although there are several controversies in the surgical treatment of CP, the basic options are:

- drainage operations, most commonly decompression of the PD through side-to-side PJ;
- resection of the chronic inflamed, painful and functionally impaired 'pancreatic pseudotumor';
- in some cases, a combination of these approaches (Kleeff et al., 2016).

The role of partial pancreatic head resection has been a source of controversies for a long time: some surgeons prefer to use resective procedures only in the case of 'inflammatory pseudotumor', while others argue that resection should be routinely performed to stop inflammation. As a result, the preferred surgical method varies widely between surgeons, centers, and countries (Kempeneers et al., 2022).

The indication for decompressive PJ is the presence of a dilated PD and the absence of a 'pancreatic pseudotumor' (Strobel et al., 2009). Various surgical drainage procedures have been employed during more than 60 years of the history of surgery of CP. The Partington-Rochelle modification is the most widely used method owing to its safety and feasibility. It has been emphasized that the standard Partington-Rochelle PJ has to achieve complete drainage of the Wirsung duct along the whole pancreas and has to be at least 10 cm long (Friess et al., 2002; Parekh & Natarajan, 2015; Wani et al., 2007). Recently the term 'extended PJ' has been used to describe the method where the PD is opened in full length, from 1–2 cm from the distal end of the pancreatic tail up to 1 cm from the ampulla of Vateri (Kempeneers et al., 2022).

The obvious advantage of the total opening of the PD is easy clearance of the entire PD of calcifications and full decompression of the duct (Greenlee et al., 1990; Sudo et al., 2014). However, total ductotomy has also its own disadvantages and surgical risks. Unroofing of the PD is especially challenging in the region of the pancreatic head: the gastroduodenal artery (GDA) is usually located in the proximal 1.5–3 cm of the pancreatic head and has to be suture ligated superiorly and inferiorly in front of the ductotomy. Nevertheless, despite ligation of the GDA, the pancreatic head is still very well vascularized and ductotomy in this region is associated with a considerable risk of bleeding. Therefore, some surgeons have suggested performing partial resection of the pancreatic head in this situation (as described by Frey) as a less risky procedure compared to pure ductotomy (Ho & Frey, 2001; Sakorafas & Sarr, 2000).

Due to the surgical risk of 'extended ductotomy', variable suggestions concerning the length of PJ have been proposed. Bradley stated in his review that

the length of PJ should be at least 6 cm to gain long-term success in pain treatment; Yeo et al. reported having attempted to obtain a minimum of 8 cm ductotomy (Bradley III, 1987; Yeo et al., 2012). Prinz et al. suggested ductotomy which is now known as extended: it is carried out to within 1 cm of the ampulla of Vater and to within 1 cm of the tip of the pancreatic tail (Prinz et al., 2008). However, the pioneers of the method, Partington and Rochelle, stated in their original paper in 1960 that 'sacculations of the PD should be opened if possible, but a uniformly dilated duct need not be opened so extensively and the PD split should continue somewhat right to mesenteric vessels, it is rarely necessary to split the distal portion in the tail' (Partington & Rochelle, 1960). Some authors admit that the extent of the ductal incision does not have a fixed length; rather, ductotomy has to ensure full PD decompression.

During past decades there have been used several new intraoperative methods to avoid wide ductotomy. E.g. intraoperative endoscopic visualization of the PD, which has been pioneered by laparoscopic surgeons. Kurian et al. used the choledochoscope for visualization of PD and Fogarty catheters for ductal clearance of calcifications; Tantia et al. used a 30° laparoscope to visualize the lumen of the PD and cleared the unopened part of the PD of calcifications using the graspers – a procedure which the authors called 'pancreaticodochoscopy' (Kurian & Gagner, 1999; Tantia et al., 2004). Sahoo and Kumar suggested using a cystoscope to confirm ductal clearance beyond ductotomy (Sahoo & Kumar, 2014).

3. SUMMARY OF THE LITERATURE REVIEW AND STUDY RATIONALE

Understanding of the pathophysiology, diagnosis and treatment of CP treatment has tremendously improved over time. However, at the same time, the literature review revealed that many questions and problems have remained unanswered and unsolved.

From the point of view of the present PhD thesis, the following issues are the most important:

Previously, relatively few studies have focused on long-term survival, causes of death and its risk factors in patients with CP. There are risks whose negative impact on prognosis has been convincingly demonstrated (e.g. alcohol consumption, tobacco smoking), however, there are also risks with unknown and/or understudied impact (e.g. social life-associated factors, health-related factors). The same applies to the causes of death: there are only a few studies addressing this topic. Another issue in earlier studies has been a significant number of patients lost during follow-up, with the consequently significant number of unknown causes of death. As the present study succeeded in achieving a 100% follow-up rate, the complete dataset could provide a better insight into the real picture of causes of death in patients with CP.

Emphasis has been laid on the need for an accurate classification of complications of CP, as it would help define primary end points for trials in a heterogeneous cohort of patients with CP. As each patient seems to develop a different set of complications, each complication must be isolated and viewed according to the underlying pathophysiological mechanisms of development and progression (Kleeff et al., 2017). A deep understanding of these mechanisms would serve as the foundation for 'personalized medicine' in the future. However, it is noteworthy that up to now there exists no pathophysiological classification of the complications of CP. This circumstance was the driving force behind the attempt to create one within the present PhD thesis and to test it on the study cohort. This classification should allow to more precisely assess the potential of different treatment methods in the management of existing complications, and in the avoidance of new ones.

Decompressive PJ is the most widely employed surgical option in treatment of patients with chronic debilitating pain and dilatation of PD. Still, the required extent of pancreatic ductotomy and the length of pancreatojejunal anastomoses are somewhat disputable. According to the prevailing suggestion, 'long' anastomosis is recommended for all patients with enlarged PD, regardless of other local changes of PD. Although there is some discussion about the necessary length of 'long' anastomosis (L-PJ), the opinion about the need for a 'long' anastomosis is quite unanimous.

However, if the need for 'long' anastomosis in the case of multiple PD strictures and/or calcifications is unequivocal, then the need for it in the case of a uniformly dilated PD is not so well explained. It should be noted that there are

no studies evaluating the possible role of ‘short’ anastomosis in this situation. Within the present study ‘short’ pancreatojejunal anastomosis (S-PJ) was employed in patients with a uniformly dilated PD. Thus, this is the first study introducing the potential of ‘short’ anastomosis.

The goal of the present PhD thesis was to give an input to the enlightening of the above issues.

Besides, the present study is the first to address the topic of CP in Estonia. The surgical cohort treated at Tartu University Hospital during more than 20 years is the largest in the Baltic countries.

4. AIMS OF THE RESEARCH

1. To assess long-term survival, causes of death and impact of risk factors on survival in a cohort of surgically managed patients with CP.
2. To propose a pathophysiological classification of the complications of CP, and application of the proposed classification to evaluate the prevalence of complications of CP in a surgically treated cohort prior to and following surgical treatment.
3. To assess the impact of the type of the used surgical method on the occurrence of new complications of CP during follow-up. To evaluate through this assessment advantages and disadvantages of different surgical methods.
4. To evaluate the possible advantages and disadvantages of S-PJ and L-PJ; and to interpret the perspective of S-PJ in treatment of CP.

5. MATERIALS AND METHODS

5.1. Patients

The Research Ethics Committee of the University of Tartu approved this clinical research (protocols 291/T-1 and 302/M-31). All participants gave their written informed consent.

All adult patients aged 18 years or older, who were operated due to CP and had evidence of definitive CP according to the Zürich criteria (Ammann, 1997), were included in the study. Further, the diagnostic criteria of the American Pancreatic Association, as being more precise, were used (Conwell et al., 2014).

The exclusion criteria were: patients younger than 18 years; patients operated on because of acute or acute recurrent pancreatitis; patients with pancreatic malignancies (confirmed during surgical treatment or after the histological evaluation of the removed specimen).

All patients were operated at the Department of Surgery of Tartu University Hospital between 1997 and 2021.

The first study *'Long-term survival, risk factors and causes of death in surgically treated CP'* was based on the data of 161 consecutive patients' operated due to CP between 1997 and 2020.

The second study *'Complications of CP in surgically treated cohort'* was based on the same database, but with 5 accrued patients in 2021 (166 patients in total).

The third study *'Pancreatojejunostomy in the treatment of CP'* was based on the data of a subgroup of 91 consecutive patients, treated via pancreatojejunostomy, from the same database.

5.2. Preoperative data and follow-up visits

The study database comprises questionnaires completed by the patients before and after surgical treatment (one, three and five years after operation, and subsequently at every 5 years). The questionnaires used were:

- For assessment of pain, 11-point numerical rating scale (NRS) was used ranging from 0 (no pain at all) to 10 (worst imaginable pain) (Hartrick et al., 2003; Price et al., 1994; Williamson & Hoggart, 2005).
- Pain-associated role limitations were assessed using the pain disability index (PDI) (Chibnall & Tait, 1994). The PDI reflects the degree of interference with normal role functioning caused by chronic pain, based on an 11-point scale ranging from 0 to 10, in seven areas of activities, with a maximum score of 70.
- QOL was evaluated using the RAND 36-item short form (SF-36) health survey (Hays et al., 1993; Hays & Morales, 2001).
- For evaluation of the patients' satisfaction with surgical treatment, Likert's five-level scale was used (Joshi et al., 2015; Likert, 1932) ranging from 1 –

not satisfied at all, to 5 – very much satisfied, or pain assessment from 1 – much worse, to 5 – much better.
- The questionnaires contained also data on psychosocial and behavioral risks (patterns of alcohol and tobacco consumption, educational level, marital and employment status), as well as clinical complaints.

Additional data, recorded at baseline, at surgery, and during follow-up, were:
- Demographics (age, gender, nationality).
- Co-morbidities according to Charlson's comorbidity index (Charlson et al., 1987). Further health-related data, as well as the causes of death were obtained from hospital case files, the Estonian Electronic Health Record (E-health) and general practitioners' reports. In the case of death, all efforts were made to trace the patients' status during the last months before death; some additional information was also obtained from the patients' relatives. Finally, we double-checked all causes of death using the National Causes of Death Register's database. As a result, we managed to gain reliable information about the causes of death, comorbidities and the patients' risk behavior before death in all cases.
- Disability was defined as reduced working capability as assessed and documented by the National Unemployment Insurance Fund.
- CP-associated data (duration, etiology, exacerbations, number of hospital admissions, earlier endoscopic, endovascular, percutaneous or surgical procedures).
- Local changes in the pancreatic gland and surrounding tissues (diameter of PD, calcifications, pseudocysts, biliary, duodenal or vascular complications). This dataset was obtained from pancreatic imaging (CT scan was used routinely), and further information was obtained and recorded during surgery.
- Pancreatic exo- and endocrine function. For assessment of PEI, we used an original set of five simple signs (weight loss, diarrhea, steatorrhea, flatulence and foul-smelling stool) that the patients assessed in a questionnaire. PEI was defined as the presence of two or more of the above-mentioned symptoms or as the need for supplementary treatment with pancreatic enzymes. Additionally, patients' loss of body weight during the year before surgery and body mass index (BMI) as possible markers of PEI were recorded. Pancreatic endocrine function was evaluated by presence of DM.
- Medications (e.g. medical pain treatment, pancreatic exocrine replacement therapy, treatment of diabetes).
- Characteristics of surgical treatment (type of surgical procedure, technical aspects, duration of the operation, morbidity, mortality, need for blood transfusion and/or for intensive care, length of stay). For assessment of morbidity, the Clavien-Dindo classification and comprehensive complication index (CCI) were used (Dindo et al., 2004; Slankamenac et al., 2013).

The patients were followed up from surgical treatment until the end of the study (August 31, 2021) or until death. No patients were lost during follow-up.

5.3. Methods

5.3.1. Long-term survival, risk factors and causes of death in surgically treated chronic pancreatitis

The study cohort's (surgically treated patients with CP) long-term survival analysis was performed using the method of Kaplan-Meier, and the corresponding curves were presented.

The impact of the following risk factors on survival were evaluated:

- Demography-, social life- and health-related factors (age, gender, nationality, marital status, educational level, employment status, working ability, co-morbidities).
- Behavioral factors (history of and continuous alcohol consumption, history of and continuous smoking).

  The patients were divided into two groups according to the patterns of alcohol consumption. The first group consisted of non-users and those who used alcohol rarely in small amounts. This group was comparable to type I users according Bobashev; light users according to Cahalan; and low-frequency users according to Chaiyasong (Bobashev et al., 2014; Cahalan et al., 1969; Chaiyasong et al., 2018). The second group consisted of patients with moderate and heavy alcohol consumption.

  The impact of the history of smoking on survival was analyzed by comparing three groups: non-smokers; patients with a history of smoking <30 pack-years; and those with a history of smoking ≥30 pack-years.

  The impact of postoperative smoking habits on survival was also evaluated by comparing three groups. The first group was formed of non-smokers and those who had stopped smoking after the surgical treatment of CP. The second group consisted of patients who smoked continuously less than 1 pack per day and the third group consisted of patients who smoked at least one (or more) pack(s) per day.
- CP-associated factors (duration of symptomatic CP, etiology of CP, presence of PEI and/or DM, predominant indication for surgical treatment, type of surgery, and pain relief after surgical treatment).

The impact of the above risk factors was reported as HR.

The SMR (standardized mortality ratio) for the study cohort was compared with mortality for the age- and sex-matched background population.

The causes of death were analyzed and presented in four groups, according to the main characteristics of the causes of death:

- Alcohol consumption-associated deaths were defined as the deaths caused by complications of chronic alcoholic liver disease, including cirrhosis, intoxication with alcohol and its surrogates, and alcoholic cardiomyopathy.
- Smoking-associated deaths were defined as the deaths due to cancers of the respiratory tract and due to other smoking related cancers, as well as death due to complications of ischemic heart disease and cerebrovascular disease.

– CP-associated deaths were defined as the deaths due to secondary complications of CP (e.g. biliary sepsis, vascular complications etc.).
– Deaths due to other causes.

5.3.2. Complications of chronic pancreatitis in surgically treated cohort

This study consisted of three parts:
– Proposal for a pathophysiological classification of complications of CP (Chapter 5.4.).
– Evaluation of the prevalence of complications of CP in a surgical cohort prior to, and following surgical treatment.
– Assessment of the impact of different surgical methods on the occurrence of new complications of CP during follow-up. Based on this assessment, evaluation of the advantages and disadvantages of different surgical methods.

The development of the proposed pathophysiological classification of complications of CP was based on a literature review on the pathophysiology of CP, on the clinical presentation and course of complications of CP, as well as on a review of previous classification systems of CP.

The prevalence of complications of CP prior to and following surgery was evaluated using the method of Kaplan-Meier, and the corresponding curves of complication-free survival were presented.

Assessment of the impact of the surgical method on the occurrence of new complications was made according to proposed pathophysiological classification and grouping of complications of CP (pancreatic duct complications; peripancreatic complications; pancreatic hemorrhages, pancreatic insufficiency, and pancreatic cancer).

The assessment of the impact of surgical method on the occurrence of new peripancreatic complications was made in three subgroups:
– Pancreatoduodenal (‘Whipple’) resections,
– Pancreatic resections (excluding pancreatoduodanal resections),
– Pancreatic drainage operations.

The assessment of the impact of surgical method on the occurrence of new cases of pancreatic insufficiency comparison was made between:
– Pancreatic head resections (all modifications),
– Pancreatic distal resections,
– Pancreatic drainage operations.

5.3.3. Pancreatojejunostomy in treatment of chronic pancreatitis

For evaluation of the clinical effects of two types of PJ (S-PJ and L-PJ), comparison of preoperative and 1-year follow-up data was made. The assessed characteristics were: QOL, intensity of chronic pancreatic pain, pain-associated role limitations, changes in pain treatment, BMI, hospital admissions because of CP, and patients' satisfaction with surgical treatment.

Complete pain relief was defined as freedom of chronic abdominal pain and absence of the need for pain medications; partial pain relief was defined as pain reduction by 50% or more according to NRS.

For assessment of the effect of surgical pain treatment, a comparative analysis of preoperative and 1-year follow-up use of pain medications was made. The patients were divided into three groups: opioid users, users of non-opioid painkillers, and patients without the need for any pain medications.

The impact of surgical treatment on the exacerbations of CP requiring hospital admissions was calculated using the number of admissions per patient year (PY). Preoperative PY was calculated as the period from the first admission due to CP to the time of surgery; postoperative PY was calculated as the period starting from surgical treatment. The effect of surgical treatment was assessed as the proportion of preoperative and postoperative admissions due to CP per PY.

For evaluation of the patients' satisfaction with surgical treatment, Likert's five-level scale was used. All patients were asked to evaluate satisfaction with the results of surgical treatment in general, changes in pain characteristics after surgical treatment, and changes in QOL after surgery.

Surgical methods

The choice of the surgical method (S-PJ or L-PJ) was based on the anatomical characteristics of PD. Patients with a uniformly dilated PD and significant strictures or calcifications in only a single location of the duct were treated using S-PJ (Figure 2). On patients with multiple PD strictures, calcifications and dilatations, L-PJ was performed. S-PJ was defined as the anastomosis with a length of 30 to 50 mm; in the case of L-PJ, the length of the anastomosis was 50 mm or more (up to 10 cm).

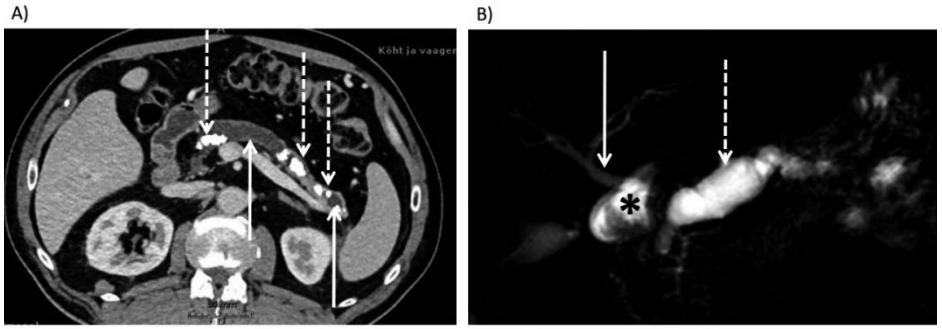


Figure 2. Pancreatic duct dilatation. (Source: clinical cases from the study cohort, figures from Hospital Information System.)
A) Multiple calcifications and strictures. White arrow – pancreatic duct dilatations; white dashed arrow – calcifications in pancreatic duct.
B) Uniformly dilated pancreatic duct. White dashed arrow – pancreatic duct with diameter of 20 mm; white arrow – normal common bile duct; black star – duodenal bulb.

As a standardized approach, the dilated PD was opened distal to strictures or calcifications, usually in the region of the pancreatic body, after which ductotomy was extended proximally to overcome the stricture and/or to remove calcifications.

The initial length of ductotomy was usually 35–40 mm. All discovered calcifications were removed with the graspers. This was followed by testing the adequacy of drainage along the entire PD. For this, a 3 mm (9 french) metallic probe was used, a length of 100 mm of successful probing (proximal and distal duct together) was judged sufficient to ensure free outflow of pancreatic juice (Figure 3). If probing was successful (there were no more strictures or calcifications), a single-layer continuous PJ anastomosis with slowly absorbable suture material (4-0 polydiaxanone) was done, involving a small portion of the transected pancreatic parenchyma (Figure 4).

If probing was unsuccessful due to multiple PD strictures, initial ductotomy was extended beyond the last detected stricture. All calcifications were removed with the graspers, and when necessary, additional ductotomy was carried out. The total length of L-PJ was dependent on the number and location of strictures and was somewhat variable (50 mm to 100 mm). However, the basic principle was in all cases the same: ductotomy has to be long enough to ensure complete decompression of the PD, which was tested by probing.

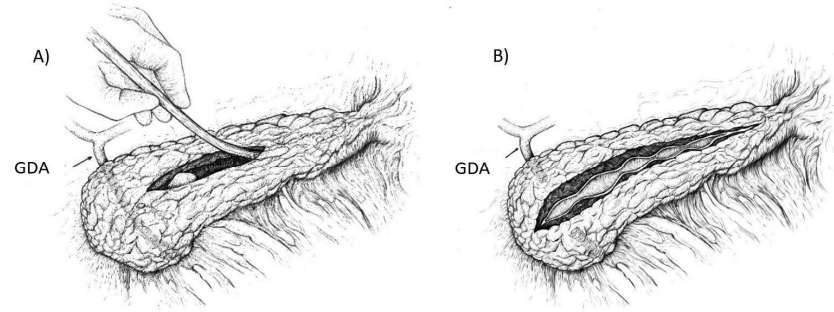


Figure 3. Two variants of pancreatic ductotomy. (Figure by T. Veršinina)
A) Short ductotomy, probing of the pancreatic duct,
B) Long ductotomy (up to 100 mm). GDA – gastroduodenal artery.

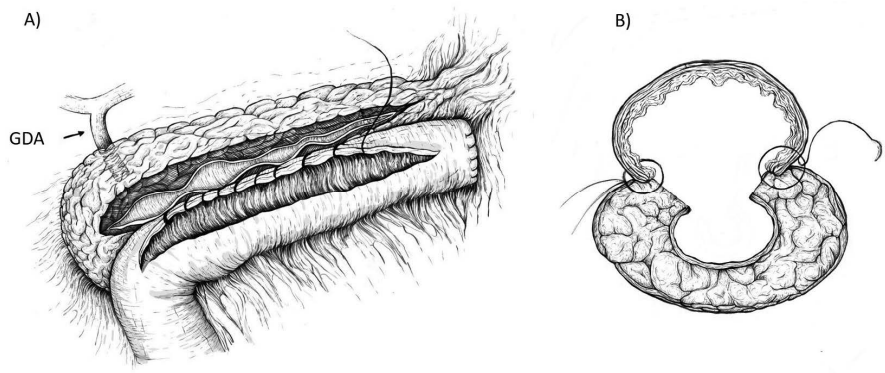


Figure 4. Technique of pancreatojejunostomy. (Figure by T. Veršinina)
A) Long pancreatojejunostomy (up to 100 mm).
B) Cross-section of view of the suturing technique.

5.4. Proposal for a pathophysiological classification of complications of CP

The need for a pathophysiological classification of complications of CP arose from the great number of diverse complications, on the one hand, and from the lack of such a classification on the other. The use of a pathophysiological classification would allow to group different complications pathophysiologically, and to more precisely assess the potential of different treatment methods in the management of existing complications, as well as in the avoidance of new ones. An accurate classification would be helpful in clinical decision making, and in defining end points for trials in such a heterogeneous cohort of patients (Kleeff et al., 2017).

The development of the pathophysiological classification of complications of CP was based on a literature review on the pathophysiology of CP, on the clinical presentation and course of complications of CP, as well as on a review of previous classification systems of CP.

5.4.1. Definition

Complications of CP were defined through the presence of following criteria:
- development of a new clinical problem or condition during the course of CP,
- need for a change of existing treatment with a need for escalation in most cases,
- negative impact on the patients prognosis.

Although being more characteristic for the advanced disease, complications may appear at any stage during the course of the disease (Ramsey et al., 2017).
From the clinical point of view, it is advisable to distinguish between functional ('pancreatic insufficiency') and morphological (also the terms 'local', 'anatomical' and 'structural' have been used) complications. Functional complications usually need only medication use (replacement therapy), while local anatomical complications, if clinically relevant, usually need some kind of invasion (whether minimally invasive methods or surgical treatment).

5.4.2. Pathophysiology

The pathophysiology of complications of CP is a complex process with many parallel and overlapping disorders. The processes in CP involve primarily the acinar cells, the predominant site of initial injury, leading to an inflammatory cascade and resulting ultimately in pancreatic fibrosis (Singh et al., 2019).

The extent of primary acinar cell injury, as well as the extent of the subsequent inflammatory process can be highly variable, from minimal necrosis and subclinical cases of pancreatitis to extended pancreonecrosis and massive inflammation associated with shock. However, activation of the pancreatic stellate cells in the process of inflammation seems to have a crucial role in development of chronic inflammation and pancreatic fibrosis. In response to oxidative stress, cytokine growth factors, and inflammation-associated toxins, pancreatic stellate cells are activated into myofibroblast-like cells (Mann et al., 2021). The next important steps are stimulation of the synthesis of the extracellular matrix proteins and reduced matrix degradation with the ultimate consequence of collagen deposition and fibrous tissue development (Jin et al., 2020). CP develops slowly, the preclinical period of the disease is usually reported to be several years.

The main process involved in development of functional complications of CP, is:
- Progressive *parenchymal damage*, leading to *pancreatic atrophy* and critical impairment of the pancreatic function: pancreatic exocrine and/or endocrine insufficiency.

The following processes are mainly associated with development of morphologic ('local') complications:

- *Extensive fibrosis and scarring* within and around the pancreatic gland as a consequence of recurrent inflammatory episodes, and replacement of the pancreatic parenchyma by the fibrous connective tissue. The scarring of the fibrotic tissue has a potential for narrowing the lumen of any tubular organ in the region. As a result, there can occur, clinically relevant strictures of the main pancreatic duct, and of the peripancreatic tubular structures (common bile duct, duodenum, and peripancreatic major veins). The occlusion of any of the listed structures can lead to severe complications requiring urgent treatment.

  The strictures of the pancreatic duct predispose pancreatic gland to recurrent attacks of acute pancreatitis (Bhanot & Möller, 2009). They also can provoke development of the pancreatic fistulas and pseudocysts. The latter can lead through mechanical pressure to the further narrowing of the lumens of tubular structures.
- *Edema of the pancreatic gland and surrounding tissues* as a result of exacerbation of chronic pancreatitis can be a contributing factor to development of the obstruction of tubular organs.
- *Increased level of inflammatory mediators and tissue factors* can trigger activation of the coagulation system and induce thrombosis of peripancreatic veins (Qi et al., 2020; Rebours et al., 2012).
- *Erosive damage of intra- and peripancreatic vessels* due to local release of pancreatic digestive enzymes, possibly combined with *local inflammation* and *pressure necrosis* from ductal calcifications and pancreatic pseudocysts may result in pancreatic hemorrhages, in the form of either contained or ruptured pseudoaneurysm formation (Eckhauser et al., 1980; Sakorafas, Sarr, et al., 2000).
- *Inflammation and fibrosis with epithelial to mesenchymal transition* are critical factors in pancreatic carcinogenesis (Hemanth et al., 2020). Mechanistically ongoing pancreatic chronic inflammation is related to the acquisition of somatic KRAS mutations in the pancreatic ductal cells and development of pancreatic intraepithelial neoplasms, progressing to pancreatic ductal adenocarcinoma (Logsdon & Ji, 2009). CP can also promote acinar-to-ductal *metaplasia*, which has been linked to development of pancreatic ductal adenocarcinoma (Guerra et al., 2011).

Local complications of CP may develop at any time of the disease (Ramsey et al., 2017). Due to the complexity of complications of CP and parallel processes in its pathogenesis, many patients have more than one complication. Particularly in advanced CP, pancreatic functional complications (exo- or endocrine insufficiency) can be relatively often combined with local structural complications.

According to the predominant pathophysiology and clinical presentation, five groups of complications were distinguished (Figure 5, the schematic presentation Figure 6):

1. Pancreatic duct complications.
2. Peripancreatic complications.
3. Pancreatic hemorrhages.
4. Pancreatic insufficiency.
5. Pancreatic cancer.

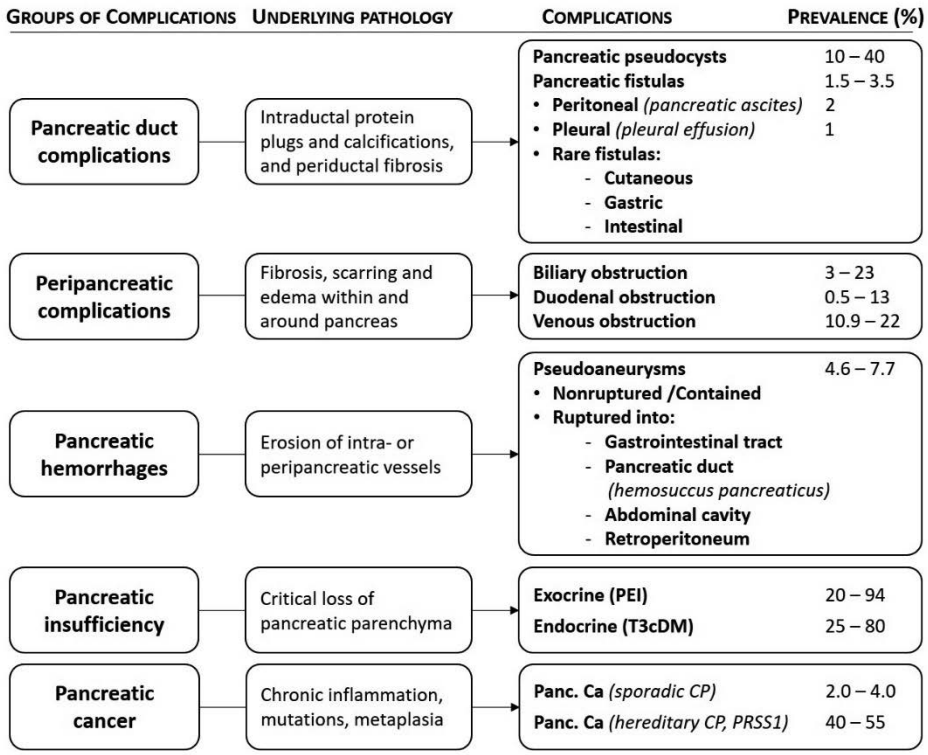


Figure 5. Pathophysiological classification of complications of chronic pancreatitis.
PEI – pancreatic exocrine insufficiency; T3cDM – type 3c diabetes mellitus; CP – chronic pancreatitis; PRSS1 – serine protease 1.

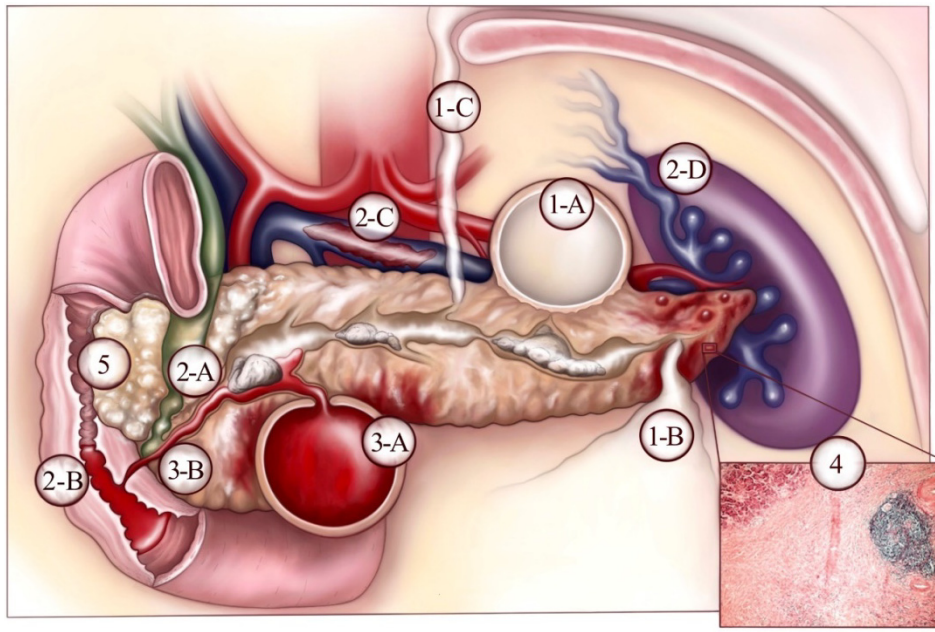


Figure 6. Main complications of chronic pancreatitis. (Figure by T. Veršinina)
1) Pancreatic duct complications – 1-A: pancreatic pseudocyst; 1-B: pancreatic ascites; 1-C: pancreatic pleural effusion.
2) Peripancreatic complications – 2-A: common bile duct stenosis; 2-B: duodenal stenosis; 2-C: venous thrombosis (splenic vein); 2-D: 'left-side' portal hypertension due to splenic vein thrombosis.
3) Pancreatic hemorrhages – 3-A: peripancreatic pseudoaneurysm; 3-B: ruptured pseudoaneurysm (into pancreatic duct – *hemosuccus pancreaticus*).
4) Pancreatic exocrine and endocrine insufficiency due to extensive loss of functional pancreatic parenchyma (acinar atrophy, fibrosis, inflammatory infiltrates).
5) Pancreatic cancer.

5.4.3. Pancreatic duct complications

Common pathophysiological denominator: This particular group of complications consists of complications due to the obstruction of the PD by calcifications, protein plugs and/or periductal fibrosis, followed by intraductal hypertension and disruption of the main PD or its branches (Banks et al., 2013; Howell et al., 1998). PD disruption results in development of pancreatic pseudocysts (PPC) or leakage of pancreatic secretions, and hence in development of various types of pancreatic fistulas (PF) (Tringali et al., 2008). The source of PF can be leakage directly from a rupture of the PD or, more frequently, leakage from a ruptured PPC (Dhar et al., 1996). In the case of pancreaticopleural fistula, pancreatic secretion flows through the retroperitoenum via the area of least resistance into the pleural cavity, usually through the esophageal hiatus. The direct tract of fistula through the diaphragm has also been described (Sachs et al., 1991).

PPC are relatively common complications of CP, with reported prevalence as high as 10%–40% (Dumonceau et al., 2019; Klöppel, 2000). Most of the small PPC are typically asymptomatic and do not need any treatment.

Clinical presentation tends to occur if some of the secondary complications of PPC, such as bleeding, rupture or infection, evolve (Zerem et al., 2015). Additionally, large PPC can alone, through compression, or in conjunction with underlying CP, lead to the obstruction of the lumen of adjacent organs (biliary tract, gastric outlet and peripancreatic veins) (Gouyon et al., 1997). All secondary complications can occur throughout the clinical course and, if present, usually do need active treatment (Dumonceau et al., 2019). Although the complications of PPC and related clinical presentation can be diverse and dependent of the localization and size of PPC, patients most frequently present with abdominal pain (Gumaste & Pitchumoni, 1996).

Despite the fact that PF are relatively rare, the gross prevalence of various types of PF has been reported as high as 3.5 % (Da Cunha et al., 1995; Kaman et al., 2001). Pancreaticoperitoneal fistulas (leading to pancreatic ascites) with a prevalence of 2% and pancreaticopleural fistulas (leading to pancreatic pleural effusions, Figure 7) with a prevalence of 1% are more common (Bintcliffe et al., 2016). Both need PD decompression, in most cases endoscopic stenting of PD is sufficient (Dumonceau et al., 2019).

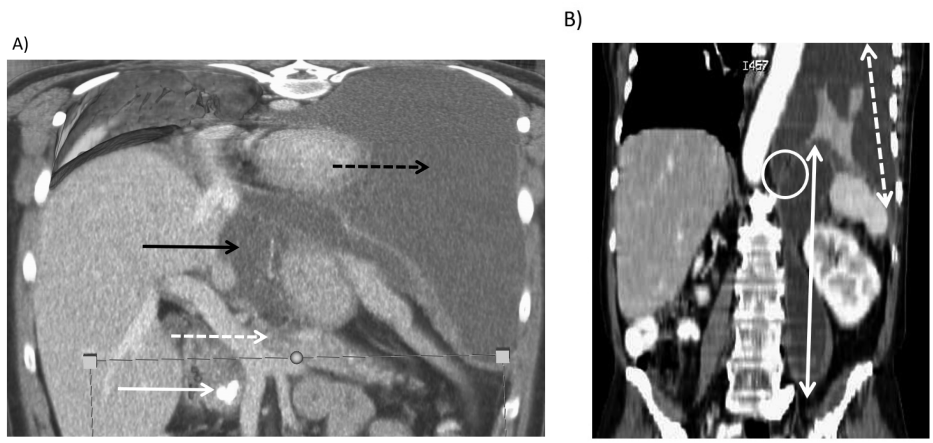


Figure 7. Pancreatic duct complications. (Source: clinical cases from the study cohort, figures from Hospital Information System.)

A) CT-scan of a pancreaticopleural fistula due to the rupture of the pancreatic duct. White arrow – calcification in the region of pancreatic head; white dashed arrow – rupture of the pancreatic duct; black arrow – pancreatic fluid in subphrenic region; black dashed arrow – massive pancreatic pleural effusion.

B) CT-scan of a retroperitoneal leakage of pancreatic fluid and pleural effusion. White arrow – retroperitoneal leakage; white dashed arrow – pancreatic pleural effusion; white ring – leakage through the diaphragmatic hiatus.

Other types of PF, pancreaticogastric or – intestinal fistulas, which may appear as symptomless findings at endoscopic evaluation, are rare. Pancreaticocutaneous fistulas are usually the consequence of previous percutaneous drainage of PPC or pancreatic fluid collections, and may lead to significant loss of pancreatic juice and local skin problems.

Pancreaticopericardial fistulas (leading to pancreatic pericardial effusion) and pancreaticoportal fistulas (leading to portal thrombosis with following consequences) are casuistic (Clark & Gross, 2019; Raza et al., 2013).

5.4.4. Peripancreatic complications

Common pathophysiological denominator: This group of complications comprises obstructive complications of the organs adjacent to the pancreas (biliary tract, duodenum and major peripancreatic veins). Although the details of the process of the development of these obstructions are slightly different, it is hypothesized that obstructive complications occur mainly as a consequence of recurrent episodes of pancreatitis, which may ultimately result in fibrosis and scarring within and around the pancreatic gland (Mallick & Winslet, 2004; Sarles & Sahel, 1978). An additional contributing factor to obstruction can be PPC, especially in the region of the pancreatic head (Bernades et al., 1992).

Biliary strictures in patients with CP are relatively common with a prevalence of 3% to 23% with a mean of 6% (Vijungco & Prinz, 2003). Some patients with biliary obstruction may be asymptomatic and have only modestly deranged liver function tests (Abdallah et al., 2007).

However, common bile duct obstruction may lead to jaundice, persistent cholestasis (Figure 8A), acute cholangitis and secondary biliary cirrhosis (Costamagna & Boškoski, 2013). Timely treatment of symptomatic strictures is required to prevent these secondary complications.

Duodenal obstruction is usually reported to occur in the second or third part of the duodenum (Figure 8B) (Bradley & Clements, 1981).

It has been suggested that an underlying mechanism in its evolution is duodenal ischemia caused by arterial narrowing and thrombosis in the region of inflammatory mass in the pancreatic head (Satake & Umeyama, 1984). An uncommon form of CP is groove pancreatitis or paraduodenal pancreatitis characterized by inflammation in the ‘groove’ between the duodenal wall and the pancreatic head (Latham et al., 2013). The pathophysiology of this particular condition remains unclear, despite many suggested theories (Shin et al., 2016).

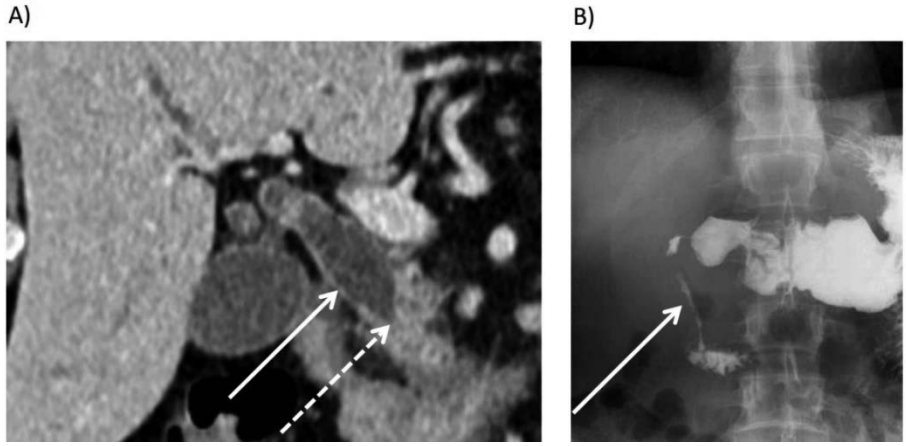


Figure 8. Peripancreatic complications. (Source: clinical cases from the study cohort, figures from Hospital Information System.)
A) CT-scan of a biliary stenosis. White arrow – dilated common bile duct; white dotted arrow – stenosis of distal common bile duct.
B) Abdominal x-ray image, with per oral contrast media, of a duodenal stenosis. White arrow – stenosis of the second part of duodenum.

Among the various pathological findings of groove pancreatitis, the fibro-inflammatory process in the pancreatoduodenal groove has been described as the only consistent finding in this disease (Patel et al., 2020). Groove pancreatitis is more common in middle-aged men and is strongly associated with history of alcohol consumption and tobacco smoking (Arvanitakis et al., 2014).

Duodenal obstruction is relatively rare with a reported prevalence of 0.5% to 13% with a mean of 1.2% (Vijungco & Prinz, 2003). Patients usually present with symptoms of gastric outlet obstruction such as vomiting, fluid and electrolytes imbalance, and weight loss.

Among the peripancreatic veins thrombosis is mainly involved the splenic vein (up to 80.6%, Figure 9A), followed by the portal vein. Splenic vein thrombosis leads to left-side portal hypertension; these patients are at risk of development of gastric varices, splenomegaly and ultimately severe variceal bleeding (Figure 9B), which has been reported to occur in 4%-17% of all cases (Ru et al., 2020). The prevalence of the thrombosis of the major peripancreatic vein had varied from 10.9% to 22.0% with a pooled prevalence of 11.6% (Gabrielli et al., 2017; Gorsi et al., 2021). Several other splenic complications such as spontaneous splenic rupture, intrasplenic PPC, and splenic infarction have also been reported, but their prevalence remains well below 1% (Jain et al., 2020).

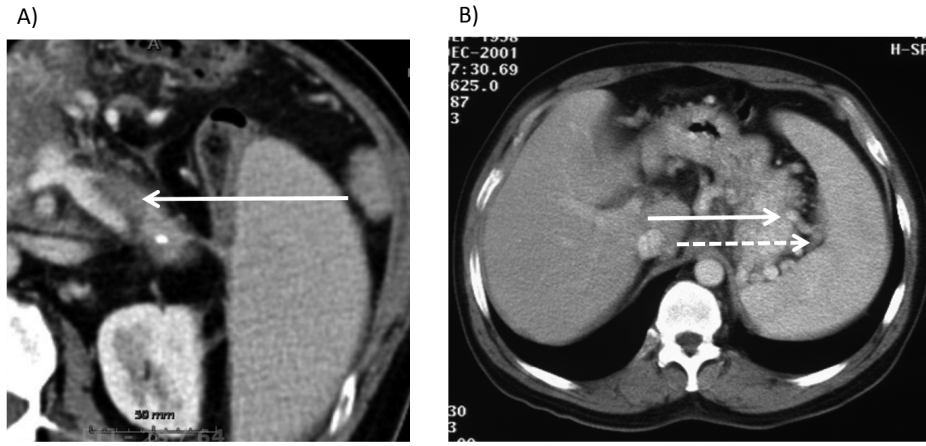


Figure 9. Peripancreatic complications. (Source: clinical cases from the study cohort, figures from Hospital Information System.)
A) CT-scan of a splenic vein thrombosis. White arrow – thrombus in lienal vein.
B) CT-scan of a left-side portal hypertension. White arrow – dilated gastric veins; white dashed arrow – splenic enlargement.

5.4.5. Pancreatic hemorrhages

Common pathophysiological denominator: This group of complications encompasses all pancreatic hemorrhages due to the erosion of major intra- and peripancreatic vessels, mainly arteries. Local inflammation, possibly combined with local release of pancreatic digestive enzymes, pressure necrosis from ductal calcifications, and PPC may result in either pseudoaneurysm (PA) formation or bleeding into pre-existing PPC, which transforms PPC into PA (Eckhauser et al., 1980; Sakorafas, Sarr, et al., 2000).

Although pancreatic bleeding in patients with CP is considered uncommon, the prevalence among in-patient cohorts is reported to be 4.6% to 7.7% (Bergert et al., 2004; Nagarajan et al., 2021). Splenic artery is the commonest involved vessel, followed by gastroduodenal and pancreaticoduodenal arteries (Kalva et al., 2011; Mallick & Winslet, 2004). As severity of blood loss and patients' hemodynamic status depend on the rupture of PA, it is important from the clinical point of view to distinguish between non-ruptured ('contained PA') and ruptured PA. Patients with non-ruptured PA have better prognosis, as blood loss is relatively small and the effect of self-tamponade can provide spontaneous hemostasis (Vanlangenhove et al., 1999). Usually, these patients present with abdominal pain combined with symptoms of moderate blood loss, or sometimes even without the latter. Radiological imaging is essential to establish the diagnosis. The diagnosis of PA is usually made on the basis of abdominal contrast-enhanced CT-scan done for evaluation of the etiology of abdominal pain (Gorsi et al., 2021).

Almost two thirds of the patients with PA have ruptured PA that is associated with much more severe hemorrhage and often with shock (Bergert et al., 2004). The most common site of rupture is the gastrointestinal tract (GIT), presenting as an upper GIT bleeding with hematemesis and/or melena (Balachandra & Siriwardena, 2005). Rarely, PA can rupture into the pancreatic duct and further into the GIT through the papilla of Vater, leading to *hemosuccus pancreaticus* (Figure 10B) (Sandblom, 1970). This condition is in most cases associated with diagnostic difficulties because of the concealed source of bleeding. Correct diagnosis is commonly made only after many episodes of bleeding and numerous endoscopic evaluations and contrast enhanced CT scans. High index of suspicion should arise if the triad of symptoms i.e. GIT bleeding, abdominal pain and hyperamylasemia, is present (Sakorafas, Sarr, et al., 2000). The two possible sites of PA rupture are the abdominal cavity, presenting as massive intra-abdominal hemorrhage, and the retroperitoneum, presenting as retroperitoneal hematoma (Figure 10A) (Hsu et al., 2006; Yamakado et al., 2000).

Acute GIT hemorrhages in patients with CP, which are directly not associated with CP (e.g. peptic ulcer bleedings, Mallory-Weiss syndrome, variceal bleedings etc.), are not included in this group of complications.

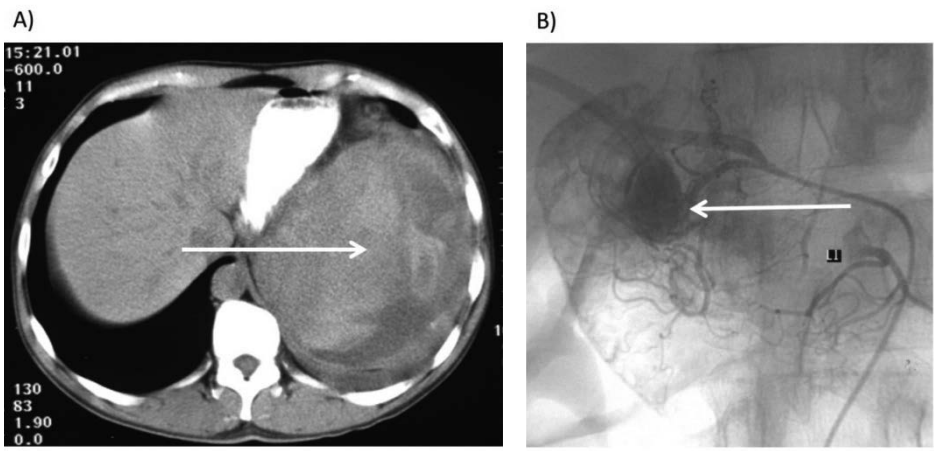


Figure 10. Pancreatic hemorrhages. (Source: clinical cases from the study cohort, figures from Hospital Information System.)

A) CT-scan of a pancreatic ruptured pseudoaneurysm. White arrow – 20cm peripancreatic hematoma.

B) Angiography image of a pseudoaneurysm in the region of pancreatic head, the patient presenting with *hemosuccus pancreaticus*. White arrow – 3 cm pseudoaneurysm.

5.4.6. Pancreatic insufficiency

Common pathophysiological denominator: The fourth group represents complications due to extensive loss of the functioning pancreatic parenchyma, leading to pancreatic exocrine (PEI) and endocrine insufficiency.

As damage to the pancreatic tissue is a continuous process throughout the course of the disease, the prevalence of PEI in patients with CP increases steadily over time, from 20% in early CP to 94% in the end-stage of the disease (Dumasy et al., 2004; Li et al., 2016). Long duration of CP (>30 years) is associated with a prevalence of PEI higher than 80% (Kempeneers, Ahmed Ali, et al., 2020). Patients' main complaints are steatorrhea, weight loss, flatulence and abdominal discomfort (Figure 11). If untreated, the deficit of fat-soluble vitamins may lead to secondary complications (e.g. osteoporosis, fractures, immunodeficiency and infections) (Sikkens et al., 2013).

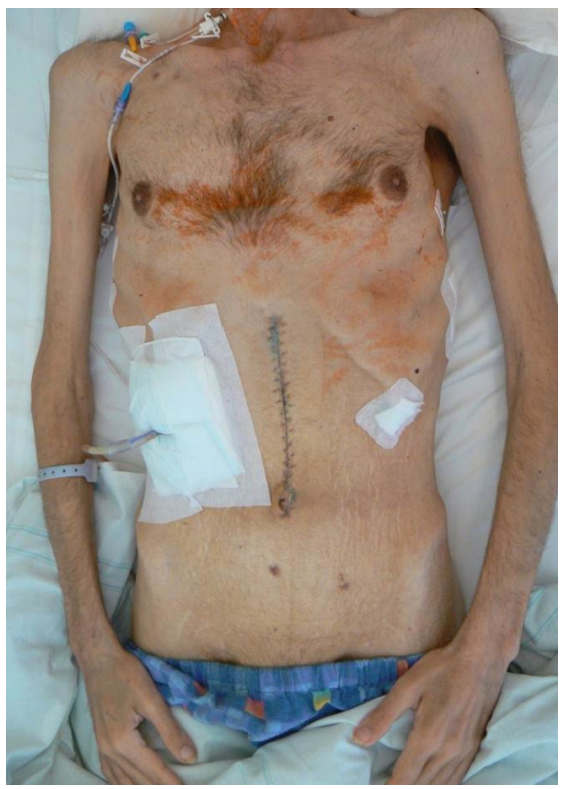


Figure 11. Image of a patient with severe pancreatic exocrine insufficiency (body mass index 14.5 kg/m^2). (Source: clinical cases from the study cohort)

Diabetes mellitus (DM) secondary to pancreatic diseases or pancreatic surgery is classified as pancreatogenic diabetes or type 3c diabetes (T3cDM) or post-pancreatitis DM according to the current classifications of DM (Bhattamisra et al., 2019; Petrov & Basina, 2021). The prevalence of DM in CP has been

reported to be between 25% and 80% (Hart et al., 2016; Olesen et al., 2020). Like PEI, T3cDM shows clear correlation with duration of CP. In CP patients with associated T3cDM, blood glucose control may be complicated due to the loss of glucagon response to hyperglycemia, food malabsorption, and irregular eating patterns because of debilitating pain and/or continuous alcohol abuse (Larsen, 1993).

5.4.7. Pancreatic cancer

Common pathophysiological denominator: chronic inflammation of pancreatic parenchyma is related to the acquisition of somatic KRAS mutations in the pancreatic ductal cells and development of pancreatic intraepithelial neoplasms, progressing to pancreatic ductal adenocarcinoma (Logsdon & Ji, 2009). CP can also promote acinar-to-ductal *metaplasia*, which has been linked to development of pancreatic ductal adenocarcinoma (Guerra et al., 2011).

Several observational studies have found association between CP and pancreatic cancer (Kudo et al., 2011; Raimondi et al., 2010). After the diagnosis of CP, about 1.3% of patients progressed into pancreatic cancer during an 8-year follow- up (Hao et al., 2017). The cumulative risk of pancreatic cancer in patients with CP after 10 years and 20 years is 2% and 4%, respectively (Malka et al., 2002).

According to a meta-analysis of 13 studies reported that patients with CP have an eight-fold increase in the risk of pancreatic cancer at the end of five-year follow-up. However, the risk decreased with the increasing time from the diagnosis of CP, and was 3.5 at 9 years (Kirkegård et al., 2017). The prognosis of pancreatic adenocarcinoma remains poor with a reported 5-year disease-specific survival of 5% (Yadav et al., 2018).

5.5. Statistical analysis

All perioperative and follow-up data were entered in a computerized database (Microsoft Access 2016). The software package Statistica version 13.3 (TIBCO Software, California, USA) was used for statistical calculations.

The main characteristics are presented as arithmetical means with standard deviation (SD) in the case of normally distributed variables, or medians with 25% and 75% percentiles in the case of non-normal distribution of variables. The dichotomous variables are given as counts and percentages.

Comparison between the study groups was made using the following tests:

- Fisher's exact test in the case of percentages,
- Unpaired t-test in the case of samples' means for independent groups,
- Non-parametric Mann-Whitney U-test in the case of medians for non-normally distributed variables.

Survival analysis was performed using the method of Kaplan-Meier (publications N° I and II).

Cox proportional univariate and multivariate hazard regression was used to assess the impact of different risk factors on mortality. The results are reported as hazard ratios (HR) with the 95% confidence interval (CI). The log-rank test was used to test for the difference in survival between the groups. The factors of univariate analysis that were correlated with some other factor (e.g. age and DM that are incorporated in Charlson's index), were excluded from multivariate analysis.

SMR for the surgically treated CP cohort was calculated comparing mortality rate for the study cohort with mortality for the age- and sex-matched background population.

The prevalence of complications of CP was evaluated according to the proposed pathophysiological classification. Complications prior to and following surgery were recorded and analyzed.

Evaluation of the clinical effects of the two types of PJ (S-PJ and L-PJ) was performed by comparing the preoperative and 1-year follow-up data for both groups.

All statistical tests were two-sided and $p<0.05$ was considered statistically significant.

6. RESULTS

6.1. Long-term survival, risk factors and causes of death

6.1.1. Long-term survival and risk factors of death

Patients

This study comprises the data of 161 consecutive patients operated for CP from the beginning of 1997 until March 31, 2019 at the Department of Surgery of Tartu University Hospital. The mean age of the patients at the time of surgical treatment was 49.0 years (SD 9.7); there were 135 male (83.9%) and 26 female patients. In 143 patients (88.8%) CP was alcohol induced, in the rest of the cases the etiology was idiopathic or rare causes.

Chronic abdominal pain was the most common (68.3%) indication for surgical treatment. Pancreatic resection was performed in 58 cases (36.0%), pancreatic drainage operation in 91 cases (56.5%), and extrapancreatic palliative procedures in 12 cases (7.5%). There was no perioperative mortality. During follow-up 12 patients required secondary surgery, mostly due to emerged complications of CP. The follow-up period was 0.4–19.6 years (median 6.3 years, IQR 3.1–10.1 years).

Mortality

Forty-eight out of the 161 patients (29.8%) died during follow-up. Median survival after surgical treatment of CP was 13.3 years (Table 1A).

Table 1A. Univariate Cox regression analysis of risk factors with impact on mortality (HR, 95%CI, p-value), ten-year survival rate (95% CI) and median survival of patients with surgically treated CP.

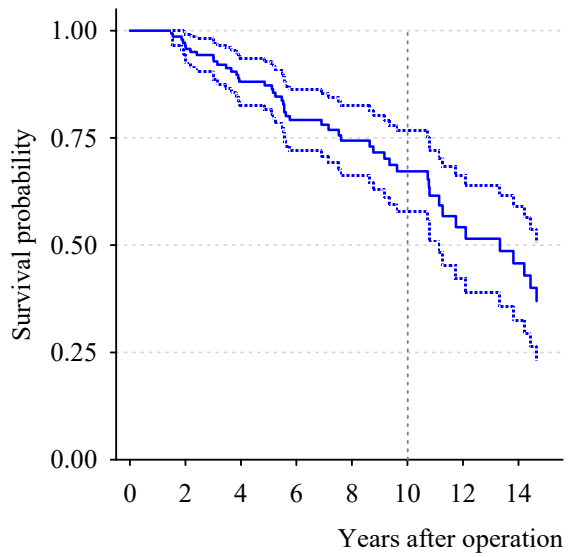
Risk factors	N^0 (%)	HR (95% CI)	p-value	10 y survival (95% CI)	Median survival
Surgically treated CP	161	-	-	67.2 (57.8–76.6)	13.3
Demography-, social life- and health-related factors					
Age					
<50 y	85 (52.8)	1		75.9 (65.8–86.0)	14.4
≥50 y	76 (47.2)	2.22 (1.24–3.98)	**0.007**	54.2 (39.5–68.8)	10.8
Gender					
Female	26 (16.1)	1		81.5 (64.9–98.2)	NA
Male	135 (83.9)	2.13 (0.76–5.93)	0.150	64.7 (54.6–74.9)	12.1
Nationality					
Estonian	132 (82.0)	1		69.4 (59.5–79.4)	13.8
Non-Estonian	29 (18.0)	1.44 (0.75–2.80)	0.270	59.0 (40.5–77.5)	11.1
Marital status					
Married or cohabitees	98 (60.9)	1		72.6 (61.8–83.4)	14.4
Single	63 (39.1)	1.56 (0.88–2.76)	0.126	60.6 (47.4–73.9)	11.3
Educational level					
Higher education	45 (28.0)	1		75.3 (60.4–90.2)	14.7
Secondary education	65 (40.4)	1.25 (0.56–2.77)	0.582	70.1 (57.8–82.5)	13.8
Basic education	51 (31.6)	1.89 (0.85–4.18)	0.116	58.5 (43.5–73.5)	11.1
Employment					
Employed	87 (54.0)	1		83.0 (74.0–92.0)	18.4
Unemployed	74 (46.0)	3.70 (1.96–6.97)	**<0.0001**	50.3 (36.5–64.0)	10.7
Working-capability					
Normal	60 (37.3)	1		80.4 (68.3–92.4)	NA
Disabled	101 (62.7)	2.22 (1.08–4.60)	**0.031**	61.5 (50.2–72.8)	11.3
Comorbidities – Charlson's index					
0–1	62 (38.5)	1		88.0 (80.0–96.0)	NA
2–3	68 (42.2)	3.43 (1.55–7.59)	**0.002**	64.4 (50.0–78.9)	11.7
≥4	31 (19.3)	9.12 (4.00–20.75)	**<0.0001**	31.1 (13.7–48.6)	6.9

Risk factors	N^0 (%)	HR (95% CI)	p-value	10 y survival (95% CI)	Median survival
Behavioral factors					
History of alcohol consumption					
Non/minimal (during last 5 years)	37 (23.0)	1		94.9 (85.1–100.0)	NA
Long-lasting moderate/heavy	124 (77.0)	8.87 (1.22–64.58)	**0.031**	62.6 (52.3–72.8)	11.7
Alcohol consumption (follow-up)*					
Non/minimal	68 (46.3)	1		86.8 (78.2–95.4)	NA
Moderate/heavy	79 (53.7)	4.44 (2.14–9.20)	**<0.0001**	53.3 (40.5–66.1)	10.8
History of smoking					
Non-smokers	17 (10.6)	1		95.2 (86.1–100.0)	NA
Smoking <30 pack-years	66 (41.0)	2.06 (0.25–16.76)	0.500	90.4 (83.1–97.8)	NA
Smoking ≥30 pack-years	78 (48.4)	16.16 (2.19–119.41)	**0.006**	45.4 (32.2–58.7)	9.2
Smoking (follow-up)*					
Non-smokers	31 (21.1)	1		96.7 (90.4–100.0)	NA
Smoking <1 pack per day	30 (20.4)	4.95 (0.60–41.2)	0.139	84.7 (72.6–96.9)	18.4
Smoking ≥1 pack per day	86 (58.5)	18.89 (2.59–137.8)	**0.004**	53.1 (40.9–65.4)	10.8

* Patients followed up for at least 1 year (147 patients).

Mean age at death was 56.6 years. Cumulative Kaplan-Meier 1-, 3-, 5-, 10- and 15-year survival for the entire group was 100%, 93.6%, 87.2%, 67.2% and 37.0%, respectively (Figure 12).

Mortality rate was 32.8 per 1,000 PY since the diagnosis of CP. The SMR for the surgically treated CP cohort was 1.8. A more detailed analysis of SMR revealed the role of the patients' risk behavior during follow-up. Mortality for the group of patients with non/minimal alcohol consumption did not significantly differ from that for the background population, but it was significantly increased in patients with moderate/severe alcohol consumption (SMR 2.7).



Year	1	5	10	15
N^0 at risk	147	103	44	12
Survival	100.0	87.2	67.2	37.0

Figure 12. Kaplan-Meier cumulative survival of patients with surgically treated CP – 161 patients (solid line represents the rate of actual events, dashed lines represent 95% CI).

Risk factors

The impact of risk factors on mortality was assessed in three groups using univariate logistic regression models.

Evaluation of demographic, psychosocial and health related factors revealed lower survival in patients aged 50 years or older, compared to patients aged under 50 years, their HR of death being 2.22. To evaluate the impact of comorbidities, Charlson's comorbidity index was employed. Patients with index 0–1 were compared to patients with index 2–3 and ≥4. Patients with Charlson's index 2–3 and ≥4 had a HR of death of 3.43 and 9.12, respectively. Ten-year Kaplan-Maier cumulative survival rate for these groups was 88.0%, 64.4% and 31.1%, respectively (Figure 13).

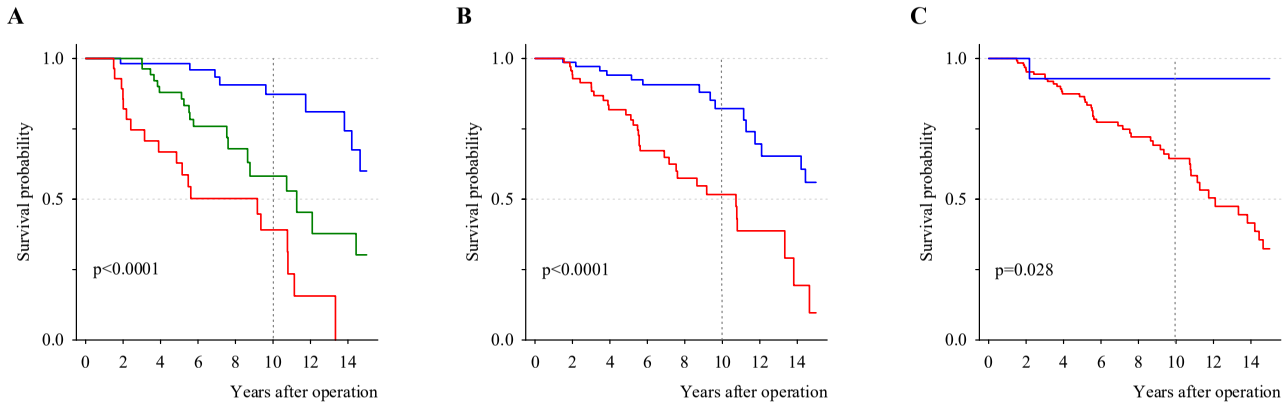


Figure 13. Kaplan-Meier curves according to the impact of different risk factors for patients with surgically treated CP.
A) Charlson's comorbidity index (0–1 – blue line; 2–3 – green line; ≥4 – red line). B) Employment status (employed – blue line; unemployed – red line).
C) Etiology of CP (non-alcoholic CP – blue line; alcoholic CP – red line).

The HR of death for unemployed patients was 3.70 compared to that for employed patients. Ten-year survival for unemployed persons was 50.3% versus 83.0% for employed patients. The HR of death for disabled patients was 2.22, compared to those without disability. Ten-year survival for disabled persons was 61.5% versus 80.4% for nondisabled persons.

Under behavioral risks, were evaluated the impact of the patients' history of alcohol consumption and smoking, as well as their continuous alcohol and tobacco use after surgical treatment of CP. The HR of death for persons with history of moderate/heavy drinking was 8.87, compared to no- or minimal alcohol users. The HR of death for patients who resumed moderate or heavy drinking after surgical treatment of CP, was 4.44 compared to no- or minimal alcohol users. Ten-year survival was 86.8% for no- or minimal alcohol users, and 53.3% for second group (Figure 14).

The HR of death for patients with history of smoking <30 pack-years and ≥30 pack-years was 2.06 and 16.16, respectively compared to non-smokers. Ten-year survival for these groups was 90.4% and 45.4%, respectively and 95.2% for non-smokers.

Assessment of the impact of postoperative smoking revealed a HR of death of 4.95 for patients smoking less than one pack per day and 18.89 for patients smoking more, compared to non-smokers. Ten-year survival for these groups was 84.7% and 53.1%, respectively, and 96.7% for non-smokers.

Among the CP-associated factors, higher HR of death (6.48) characterized the alcoholic etiology of CP (88.8% of the patients) compared to non-alcoholic CP.

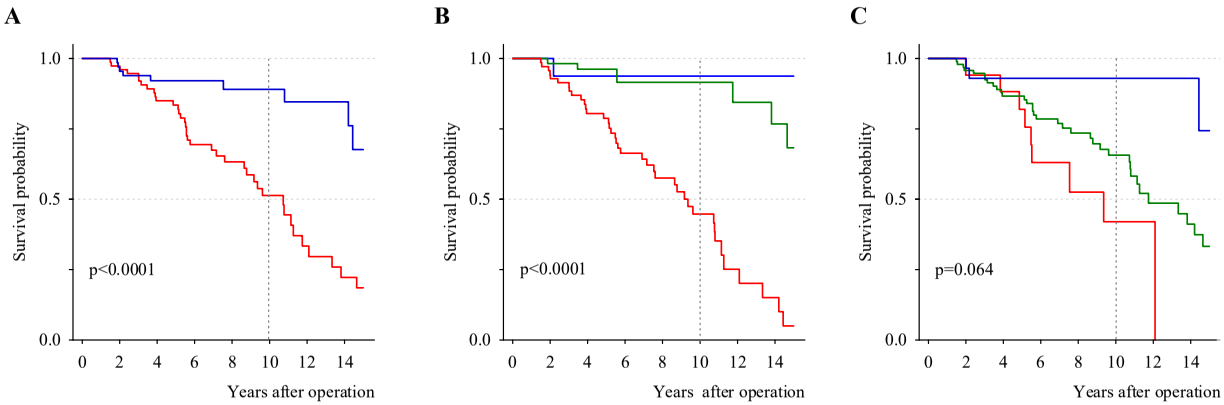


Figure 14. Kaplan-Meier curves according to the impact of different risk factors for patients with surgically treated CP.
A) Postoperative alcohol consumption (non or minimal – blue line; moderate or heavy – red line). B) Preoperative smoking (non-smokers – blue line; <30 pack-years – green line; ≥30 pack-years – red line). C) BMI (≥25 kg/m^2 – blue line; 18.5–24.9 kg/m^2 – green line; <18.5 kg/m^2 – red line).

However, due to the relatively small group of non-alcoholic CP, this difference did not reach statistical significance (Table 1B). The duration of the disease had no significant impact on survival.

Impairment of pancreatic function showed a significant impact on survival. The HR of death for diabetic patients requiring insulin treatment was 2.01 compared to those without DM. Ten-year survival rate for these groups was 72.2% and 52.0%, respectively.

The HR of death for patients with two or more signs of PEI was 2.77 compared to those who had one or no signs of PEI. Ten-year survival rate for these groups was 61.1% and 83.7%, respectively. Among the signs of PEI, the most common sign was weight loss more than 10% of body mass during the last 12 months (116 patients, 72.0%). The most excessive weight loss, measured as weight loss >20% during the last year before surgery, was seen in 35 patients. Of these, 20 patients (12.4%) had a body mass index (BMI) of <18.5 kg/m^2, which was significantly correlated with lower survival, with a HR of death of 5.92, compared to patients with light overweight (BMI ≥25 kg/m^2). Light overweight showed some protective effect, while patients with normal BMI (18.5–24.9 kg/m^2) had also lower survival compared to those with light overweight, with a HR of death of 2.99. Ten-year survival rate for patients with underweight, normal weight and light overweight was 44.5%, 66.5% and 87.2%, respectively.

Evaluation of the factors associated with surgical treatment of CP showed no differences in survival between the different indications for surgery (pain vs complications of CP) or different types of surgery (pancreatic resections vs drainage procedures vs palliative measures). Nor did the analysis of the effectiveness of surgical pain treatment show differences in survival between patients with complete pain relief and those with partial or no pain relief. However, this can be explained by the relatively small group of patients with partial or no pain relief (the difference between the groups, although present, remains non-significant).

Table 1B. Univariate Cox regression analysis of risk factors with impact on mortality (HR, 95%CI, p-value), ten-year survival rate (95% CI) and median survival of patients with surgically treated CP.

Risk factors	N^0 (%)	HR (95% CI)	p-value	10 y survival (95% CI)	Median survival
Surgically treated CP	161	-	-	67.2 (57.8–76.6)	13.3
CP-associated factors					
Duration of intense symptoms of CP					
≤1 year	74 (46.0)	1		69.3 (56.8–81.8)	13.8
1–2 years	41 (25.5)	1.40 (0.73–2.69)	0.315	59.9 (44.0–75.7)	11.3
>2 years	46 (28.5)	0.90 (0.44–1.88)	0.788	71.8 (57.1–86.4)	14.2
Etiology					
Non-alcoholic	18 (11.2)	1		93.5 (81.1–100.0)	NA
Alcoholic	143 (88.8)	6.49 (0.89–47.15)	0.065	64.5 (54.5–74.5)	12.1
Diabetes with insulin treatment					
No	123 (76.4)	1		72.2 (62.5–82.0)	14.2
Yes	38 (23.6)	2.01 (1.09–3.71)	**0.025**	52.0 (34.1–69.8)	10.7
Pancreatic exocrine insufficiency					
0–1 symptoms	56 (34.8)	1		83.7 (72.4–94.9)	18.4
≥2 symptoms	105 (65.2)	2.77 (1.27–6.01)	**0.010**	61.1 (50.0–72.1)	11.3
Body mass index					
≥25	34 (21.1)	1		87.2 (75.1–99.3)	NA
<18.5	20 (12.4)	5.92 (1.78–19.69)	**0.004**	44.5 (20.4–68.7)	9.2
18.5–24.9	107 (66.5)	2.99 (1.06–8.44)	**0.039**	66.5 (55.6–77.5)	12.1
Indication for surgery					
Pain	141 (87.6)	1		67.3 (46.8–87.8)	13.3
Complications of CP without pain	20 (12.4)	1.00 (0.45–2.24)	0.993	67.2 (57.3–77.1)	13.3
Type of surgery					
Pancreatic resection	58 (36.0)	1		62.2 (48.6–75.9)	11.7
Pancreatojejunostomy	91 (56.5)	0.74 (0.41–1.32)	0.307	70.5 (59.0–82.0)	14.2
Palliative (biliary anastomosis)	12 (7.5)	0.70 (0.21–2.32)	0.555	71.9 (44.7–99.1)	14.2
Surgical pain treatment[#]					
Effective	95 (76.6)	1		67.0 (55.8–78.3)	14.2
Partially effective or ineffective	29 (23.4)	1.38 (0.70–2.71)	0.348	57.5 (38.4–76.7)	11.1

[#] Patients operated on because of pain and followed up for at least 1 year (124 patients).

In multivariate regression analysis lower survival was associated with continuous moderate or heavy alcohol consumption (HR 2.27); history of heavy smoking (HR 4.40); unemployment (HR 2.49); Charlson's comorbidity index 2–3 and ≥4 (HR 2.53 and HR 3.16, respectively) and BMI <18.5 kg/m^2 (HR 4.01) (Table 2).

Table 2. Multivariate Cox regression analysis of risk factors with impact on mortality (HR, 95%CI, p-value), of patients with surgically treated CP.

Risk factors	HR (95% CI)	p-value
Alcohol consumption (follow-up)		
Non/minimal	1	
Moderate/heavy	2.27 (1.04–4.96)	**0.040**
History of smoking		
Smoking <30 Pack-Y	1	
Smoking ≥30 Pack-Y	4.40 (1.62–11.99)	**0.004**
Employment		
Employed	1	
Unemployed	2.49 (1.20–5.17)	**0.014**
Comorbidities – Charlson's index		
0–1	1	
2–3	2.53 (1.00–6.39)	**0.050**
≥4	3.16 (1.18–8.40)	**0.021**
Body mass index		
≥25	1	
<18.5	4.01 (1.00–15.99)	**0.049**
18.5–24.9	2.60 (0.73–9.22)	0.139

Pack-Y – pack-years

For more detailed assessment of the impact of continuous smoking on survival, with and without continuous alcohol consumption, an additional analysis of these risks in a Cox multivariate model was performed (adjusted for Charlson's index and BMI). Among patients with non/minimal alcohol consumption, the subgroup of non-smokers had the best prognosis; moderate smokers had a HR of death of 2.77 and heavy smokers 8.30, compared to non-smokers. Ten-year survival rate for these groups was 84.0% and 59.3%, respectively, and for non-smokers 94.0% (Figure 15).

An analogous, but even more prominent, correlation was seen for patients with moderate/heavy alcohol consumption: in this group, non-smokers had a HR of death of 1.78, moderate smokers 4.93, and heavy smokers 14.78. Ten-year survival rate for these groups was 89.0%, 73.3% and 39.7%, respectively.

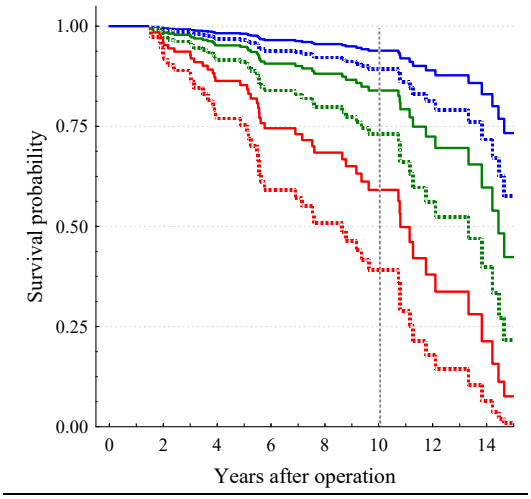


Figure 15. Kaplan-Meier curves of the combined impact of smoking and alcohol consumption during follow-up for patients with surgically treated CP.

Solid lines represent non/minimal alcohol users and dashed lines represent moderate/heavy alcohol users. Blue line – non-smokers; green line – moderate smokers; red line – heavy smokers.

6.1.2. Causes of death

During 19.6 years of follow-up, there occurred 48 deaths (29.8% of the patients). There was no postoperative mortality. According to the main characteristics of the causes of death, the patients were divided into three groups:

1. Causes associated with behavioral factors (alcohol and tobacco consumption).
2. CP-related causes,
3. All other causes.

Alcohol consumption related mortality formed the largest group with 17 cases. Although not directly, at least four more cases were associated with excessive alcohol consumption. In two cases, patients had severe insulin requiring DM, which had remained untreated for some period because of continuous drinking and which resulted in death from severe metabolic disturbances. In two other cases, continuous drinking was the predominant cause of suicide (excessive alcohol abuse led first to family separation and ended then up in suicide). As alcohol consumption is well-known suicide risk factor, the last two cases were also included in alcohol related deaths, which makes 21 cases the cumulative number (43.7%, Table 3).

Table 3. Causes of deaths in patients with surgically treated CP and the distribution of patients according to their post-operative risk behavior. The patients were followed up for at least 1 year (147 patients).

			Alcohol consumption[#]		Smoking[Δ]		
			Group I	Group II	Group I	Group II	Group III
Causes of death	N[0] (%)		68 (46.3)	79 (53.7)	31 (21.1)	30 (20.4)	86 (58.5)
Alcohol-related causes	21 (43.7)						
Liver cirrhosis		11	-	11	-	-	11
Intoxications *(alcohol, surrogates)*		3	-	3	-	-	3
Alcoholic cardiomyopathy		3	-	3	-	-	3
Diabetes*		2	-	2	-	1	1
Suicide*		2	-	2	-	-	2
Smoking-related causes	15 (31.3)						
Malignancies *(5 pulmonary)*		8	3	5	-	1	7
Myocardial infarction		3	1	2	-	1	2
Cerebrovascular diseases		4	3	1	-	1	3
Complications of CP	2 (4.2)	2	-	2	-	1	1
Other causes	10 (20.8)						
Pneumonia		6	1	5	-	1	5
Malignancies		1	1	-	1	-	-
Other		3	-	3	-	-	3
Deaths – N[0], mortality (%)	**48 (100)**		**9 (13.2)**	**39 (46.8)**	**1 (3.2)**	**6 (20.0)**	**41 (47.7)**

[#] Alcohol consumption: Group I – non and minimal; Group II – moderate or severe.

[Δ] Smoking: Group I – non-smokers; Group II – moderate smoking (<1 pack/day); Group III – heavy smoking (≥1 pack/day).

* Comments in the article.

The critical impact of smoking on survival was reflected by the high number of smoking related deaths (15 cases, 31.3%).

CP-associated complications were seldom the cause of death (two cases, 4.2%). One patient died from biliary sepsis caused by intrapancreatic common bile duct stricture and cholangitis, and the other patient died from portal thrombosis with consequent complications.

Among the other lethal cases (ten patients, 20.8%), the predominant cause of death was pneumonia with six cases. All these patients had severe accompanying diseases, as a rule, more than one disease (e.g. liver cirrhosis, chronic obstructive pulmonary disease, HIV-infection, cardiac insufficiency, candida infection etc.).

6.2. Complications of chronic pancreatitis

The natural history of CP is usually characterized by progression of tissue damage: macroscopic changes of the pancreatic gland become more and more apparent over time, and various complications, whether functional or morphological, may occur at any stage during the course of the disease. Due to the association with more or less severe clinical signs and symptoms, the common denominator of complications of CP is the need for some kind of treatment in most cases.

This study consisted of three parts:

1. Proposal for a pathophysiological classification of complications of CP (Chapter 5.4.).
2. Evaluation of the prevalence of complications of CP in a surgical cohort prior to and following surgical treatment.
3. Assessment of the impact of the surgical method on the occurrence of new complications of CP during follow-up. Based on this assessment, evaluation of the advantages and disadvantages of different surgical methods.

6.2.1. Prevalence of complications of CP in a surgical cohort

Patients

All surgically treated CP patients (166 patients), who were operated at the Department of General Surgery of Tartu University Hospital between 1997 and 2021 were prospectively enrolled. The mean age of the patients was 49.8±9.9 years, there were 140 male (84.3%) and 26 female patients (Table 4). In 148 patients (89.2%) CP was alcohol-induced, in the rest of the cases the etiology was idiopathic or rare causes.

Table 4. Characteristics of the surgically treated patients with chronic pancreatitis.

Characteristic	Patients (166)
Age (y), mean±SD	49.8±9.9
Duration of CP before surgery, median (IQR)	1.5 (0.5–3.0)
Male gender, n (%)	140 (84.3)
Etiology of CP, n (%)	
Alcocholic	148 (89.2)
Other	18 (10.8)
Predominant indication for surgery, n (%)	
Chronic pain	112 (67.5)
Complications of CP[#]	54 (32.5)
Follow-up (y), median (IQR)	7.2 (3.8–10.8)
Long-term survival (Kaplan-Meier), % (95%CI)	
1-year	100
5-year	88.2 (83.0–93.5)
10-year	70.4 (61.7–79.1)
15-year	41.2 (27.4–55.1)
Median survival (y)	13.9

[#] in many cases patients had also more or less intense abdominal pain. y – years; SD – standard deviation; CP – chronic pancreatitis; IQR – interquartile range; n – number; CI – confidence interval

The most common indication for surgical treatment was chronic abdominal pain, being the predominant indication in 112 cases (67.5%). Local complications of CP were the predominant indication for surgical treatment in 54 cases (32.5%).

Surgical treatment was pancreatic resection in 60 cases (36.2%), pancreatic drainage operation in 93 cases (56.0%), and extrapancreatic palliative procedure in 13 cases (7.8%). There was no perioperative mortality (Table 5). Cumulative Kaplan-Meier 10-year survival and median survival were 70.4% and 13.9 years, respectively. Median follow-up was 7.2 years. During follow-up 12 patients required secondary surgery, mostly due to emerged new local complications of CP (predominantly biliary stenosis).

Table 5. Surgical treatment of 166 patients with chronic pancreatitis.

Type of surgery	N (%)	
Pancreatic resection	60 (36.2)	
Pancreatoduodenal resection (Whipple procedure)		*11*
DPPHR (Beger or Berne or Frey procedure)		*34*
Pancreatic distal resection		*15*
Pancreatic drainage operation	93 (56.0)	
Pancreatojejunostomy (Partington-Rochelle)		*93*
Palliative procedures	13 (7.8)	
Biliodigestive anastomosis		*11*
Gastrointestinal anastomosis		*2*

*DPPHR – duodenum-preserving pancreatic head resection

Prevalence of complications of CP prior to and following surgical treatment
Although abdominal pain was the predominant indication for surgical treatment, almost half of the patients (81 patients, 48.8%) had at least one local complication of CP before surgical treatment. Their clinical relevance was highly varying (from asymptomatic PPC to ruptured PA). Ten patients (6.0%) had had more than one local complication.

Besides local anatomical complications, 52 patients (31.3%) had PEI and 45 patients (27.1%) had T3cDM prior to surgical treatment.

The prevalence of 'PD complications' at baseline (before surgical treatment of CP) was 20.5% (Figure 16). 10.8% of the patients had PPC, and 9.6% had various types of PF (Table 6). Endoscopic attempts to resolve these complications via PD stenting preceded to surgical therapy in two out of 16 patients (12.5%) with PF. Further surgical treatment was undertaken due to continuous PD leakage.

Surgical PD decompression was highly effective in the treatment of 'PD complications', with very a low risk of new complications during follow-up (only one new PPC developed).

'Peripancreatic complications' showed a baseline prevalence of 23.5% (39 patients); three patients had concurrent biliary tract and duodenal or venous obstruction. The most common complication was biliary tract obstruction with 29 cases (17.5%), eight patients had duodenal obstruction (4.8%) and venous occlusion was seen in five patients (3.0%). Endoscopic common bile stenting preceded surgical therapy in 18 out of 29 cases (62.1%) in patients with common bile duct strictures. Further surgical treatment was indicated because of unsuccessful endoscopic treatment (defined as inconsistent effect of endoscopic stenting).

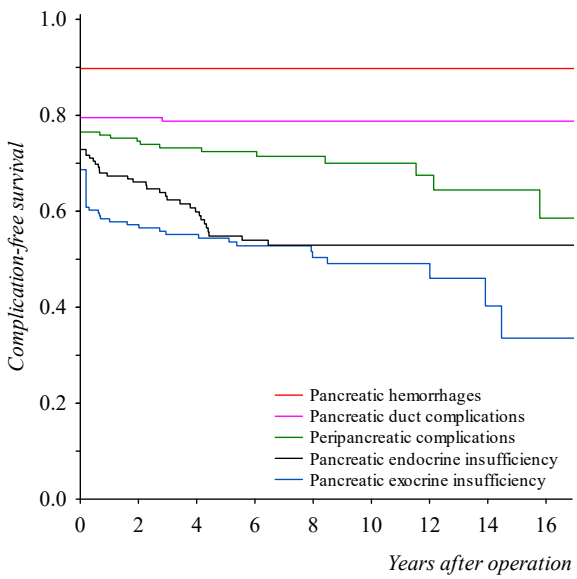


Figure 16. Kaplan-Meier curves of complication-free survival of pathophysiologically grouped complications prior to, and following surgical management of chronic pancreatitis in a cohort of 166 patients.

Table 6. Baseline and 15-year Kaplan-Meier prevalence of complications of chronic pancreatitis in a surgically treated cohort of 166 patients.

Complications	Baseline n	Baseline %	15-year Kaplan-Meier, %
Pancreatic duct complications:	**34**	**20.5**	**21.2**
Pancreatic pseudocysts	18	10.8	
Pancreatic fistulas:	16	9.6	
Pancreaticoperitoneal ('pancreatic ascites')	*4*	*2.4*	
Pancreaticopleural ('pancreatic pleural effusion')	*5*	*3.0*	
Other (mostly pancreaticocutaneous)	*7*	*4.2*	
Peripancreatic complications:	**39**[#]	**23.5**	**35.6**
Bile duct obstruction	29	17.5	
Duodenal obstruction	8	4.8	
Venous thrombosis (splenic or portal vein)	5	3.0	
Pancreatic hemorrhages:	**17**	**10.2**	**10.2**
Contained pseudoaneurysms	7	4.2	
Ruptured pseudoaneurysms into:	10	6.0	
Abdominal cavity	*2*	*1.2*	
Gastrointestinal tract	*6*	*3.6*	
Pancreatic duct	*2*	*1.2*	
Pancreatic exocrine insufficiency – PEI	**52**	**31.3**	**66.4**
Pancreatic endocrine insufficiency – T3cDM	**45**	**27.1**	**47.1**

[#]3 patients had two concurrent complications at baseline
T3cDM – type 3c diabetes mellitus

During follow-up 13 new complications were documented in 11 patients, which resulted in a 15-year Kaplan-Meier prevalence of 12.1% for new 'Peripancreatic complications'. The total 15-year prevalence of 'Peripancreatic complications' was 35.6%. The most common among new complications was biliary tract obstruction (eight patients), followed by venous thrombosis (four patients) and duodenal obstruction (one case). Five patients with biliary strictures were managed *via* endoscopic stenting, the remaining three patients needed secondary surgery.

The baseline prevalence of 'Pancreatic hemorrhages' was 10.2% (17 patients). There were 10 cases (58.8%) of ruptured pancreatic PA and 7 cases of contained PA. Ruptured PA presented as an acute life-threatening intraabdominal hemorrhage in two cases and as an acute recurrent gastrointestinal hemorrhage in eight cases: fistulation into the GIT occurred in six cases and into PD, in two cases ('*hemosuccus pancreaticus'*). All patients with ruptured PA were treated *via* pancreatic resection. All but one patient with contained PA underwent intraaneurysmatic hemostasis and a pancreatic drainage procedure. In one case, the affected part of the pancreas was resected. Surgical treatment of pancreatic hemorrhages was highly effective: there were no recurring hemorrhages among patients with PA, nor were there new hemorrhages among the entire surgically treated cohort, regardless of the indication for surgical treatment of CP.

'Pancreatic insufficiency' was evaluated for two subgroups: PEI and T3cDM. Prior to surgical treatment 73 patients (44.0%) had one of these or

both. The prevalence of PEI was 31.3% (52 patients) and the prevalence of T3cDM was 27.1% (45 patients). During follow-up, a steady and almost synchronous increase in both complications was evident, resulting in a 15-year Kaplan-Meier prevalence of 66.4% and 47.1%, respectively. The 15-year Kaplan-Meier prevalence of either exo- or endocrine insufficiency was 74.5%.

As all patients with pancreatic malignant tumors were excluded from the study, and there occurred no new pancreatic cancers during follow-up in the study cohort, this subgroup of complications was not further analyzed.

6.2.2. Impact of surgical treatment on the occurrence of new complications

The impact of surgical treatment on the occurrence of the *de novo* complications of CP during postoperative years was assessed according to the above proposed pathophysiological classification and grouping of complications of CP (Figure 5).

As in the group of 'PD complications' there occurred just one new complication during follow-up, and in the group of 'Pancreatic hemorrhages' there was none, we excluded these groups from additional analysis.

In the group of 'Peripancreatic complications' there developed 13 new complications. As the occurrence of new complications requiring retreatment is a major drawback, we re-evaluated the distribution of these complications by the surgical subgroups depending on the type of the surgical procedure applied. Analysis was performed for three subgroups: 1) pancreatic drainage operations, 2) pancreatic resections (excluding Whipple's procedure), and 3) Whipple's pancreatoduodenal resection as the only procedure incorporating new biliary and gastric bypasses (Table 7).

The analysis revealed differences in the occurrence of new 'Peripancreatic complications'. There appeared no new complications in the group of Whipple's procedure (11 patients); among the other types of pancreatic resections (49 patients), there occurred five complications and in the group of pancreatic drainage operations (93 patients), there occurred eight complications. The 15-year Kaplan-Meier prevalence of 'Peripancreatic complications' following surgical treatment of CP was 0%, 11.4% and 16.5%, respectively (Figure 17A).

Development of pancreatic insufficiency was re-evaluated for the surgical subgroups depending on the type of surgical procedure. The highest rate of new cases of PEI was seen in patients undergoing Whipple's pancreatoduodenal resection (Figure 17B). According to Cox regression analysis, HR for developement of new cases of PEI was 9.3 (95%CI 3.6–24.2) in this group and 1.9 (95%CI 0.8–4.2) in the group of other resections, compared to pancreatic drainage operations.

Development of endocrine insufficiency did not show any significant dependency on the type of surgery. However, the rate of T3cDM was slightly higher for patients undergoing distal pancreatectomy (Figure 17C).

Table 7. Distribution of complications of chronic pancreatitis according to the used type of surgical procedure prior to surgical treatment, and appearance of new complications during follow-up, in 166 surgically treated patients.

	Type of surgical procedure (n)					
	PD resection (11)	DPPHR (34)	Distal resection (15)	Drainage procedure (93)	Palliative procedures (13)	Total (166)
Complications, n (%)						
Pancreatic duct complications	**1 (9.1)**	**1 (2.9)**	**4 (26.7)**	**29 (31.2)**	**-**	**35 (21.1)**
Preoperative cases	*1*	*1*	*4*	*28*	-	*34*
New cases during follow-up	-	-	-	*1*	-	*1*
Peripancreatic complications	**6 (54.5)**	**9 (26.5)**	**-**	**25 (26.9)**	**13 (100)¤**	**55 (33.1)**
Preoperative cases	*6*	*4*	-	*17*	*13*	*42*
New cases during follow-up	-	*5*	-	*8*	-	*13*
Pancreatic hemorrhages	**1 (9.1)**	**1 (2.9)**	**9 (60.0)**	**6 (6.5)**	**-**	**17 (10.2)**
Preoperative cases	*1*	*1*	*9*	*6*	-	*17*
New cases during follow-up	-	-	-	-	-	-
PEI	**8 (72.7)**	**15 (44.1)**	**5 (33.3)**	**46 (49.5)**	**9 (69.2)**	**83 (50.0)**
Preoperative cases	*1*	*6*	*3*	*33*	*9*	*52*
New cases during follow-up	*7*	*9*	*2*	*13*	-	*31*
T3c-DM	**3 (27.3)**	**12 (35.3)**	**8 (53.3)**	**39 (41.9)**	**11 (84.6)**	**73 (44.0)**
Preoperative cases	*1*	*7*	*2*	*25*	*10*	*45*
New cases during follow-up	*2*	*5*	*6*	*14*	*1*	*28*

¤ Three patients had two simultaneous peripancreatic complications.

PD – pancreatoduodenal resection; DPPHR – duodenum-preserving pancreatic head resection; PEI – pancreatic exocrine insufficiency; T3c-DM – type 3c diabetes mellitus.

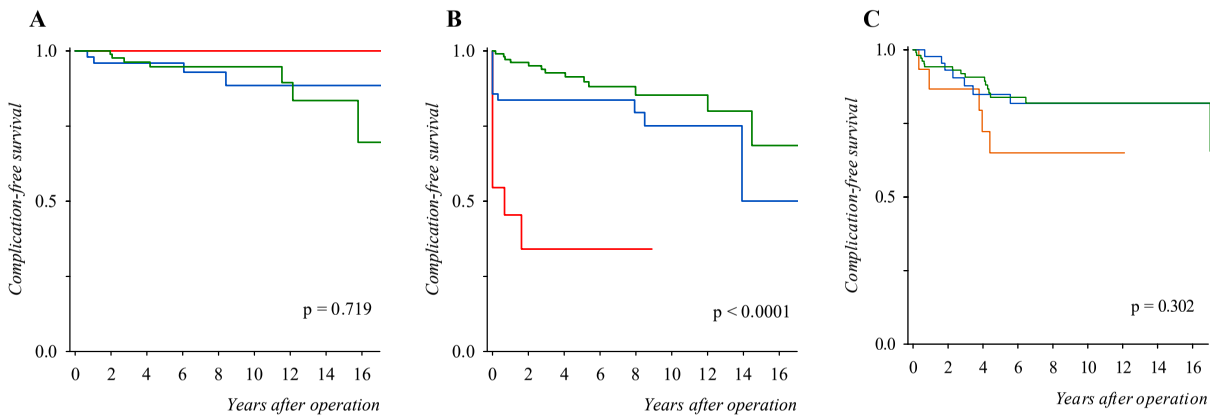


Figure 17. Kaplan-Meier curves of complication-free survival characterizing the impact of the type of surgery on the occurrence of new complications of chronic pancreatitis.

A) Peripancreatic complications (Whipple's pancreatoduodenal resection – red line; other pancreatic resections – blue line; pancreatic drainage operations – green line).

B) Pancreatic exocrine insufficiency (Whipple's pancreatoduodenal resection – red line; other pancreatic resections – blue line; pancreatic drainage operations – green line).

C) Pancreatic endocrine insufficiency (pancreatic distal resection – orange line; other pancreatic resections – blue line; pancreatic drainage operations – green line).

6.3.Pancreatojejunostomy in treatment of chronic pancreatitis

Between 10/1997 and 12/2020, 91 patients underwent side-to-side PJ: S-PJ in 46 patients and L-PJ in 45 patients.

A comparison of the preoperative data in these two groups revealed some anatomical and clinical differences (Table 8). The most important anatomical characteristic of the L-PJ group was the presence of multiple strictures or calcifications in the PD: the outflow of pancreatic juice was compromised in several locations, which was decisive for carrying out L-PJ.

Table 8. Comparison of the S-PJ and L-PJ patients. Preoperative characteristics and characteristics of surgery (mean ± SD or median values with IQR or percentages as appropriate, *P* values).

Characteristics	S-PJ (*n* = 46)	L-PJ (*n* = 45)	*P* value
Preoperative data			
Age (yr)	52.6 ± 9.7	45.6 ± 7.6	**< 0.001**
Male (%)	73.9	88.9	0.116
Co-morbidity (Charlson's index)	2 (1–3)	1 (1–3)	0.066
Disabled persons (%)	45.6	73.3	0.013
Chronic pancreatitis			
Alcoholic etiology (%)	82.6	95.6	0.096
Time from onset of pain (mo)	18 (6–36)	24 (10–36)	0.420
N^0 of admissions due to CP	4 (2–5)	5 (3–7)	**0.002**
Rate of admissions per PY[1]	1.8 (1.5–2.1)	2.0 (1.8–2.3)	0.240
Anatomical changes in CP			
PD diameter (mm)	6 (5–7)	8 (7–9)	**0.002**
Pancreatic calcifications (%)	58.7	77.8	0.082
Pseudocysts (%)	58.7	53.3	0.760
Pancreatic endo- and exocrine function			
DM (%)	28.3	28.9	0.999
BMI (kg/m^2)	23.6 ± 5.0	22.3 ± 3.3	0.161
Loss of body weight (kg)[2]	9 (6–12)	9 (5–17)	0.366
≥ 2 symptoms of PEI (%)	47.8	73.3	**0.022**
Characteristics of surgery			
Length of anastomosis (mm)	40 (35–45)	65 (60–70)	**< 0.0001**
Duration of surgery (min)	107.5 (85.0–139.0)	134.0 (110.0–155.0)	**0.006**
IO PRC transfusion (%)	0	15.6	**0.011**
PRC transfusion in total (%)	2.2	31.1	**0.001**
Length of stay (d)	8.5 (8.0–11.0)	9.0 (8.0–11.0)	0.668
Morbidity (%)	6.5	17.8	0.182
CCI[3]	26.6 (20.9–29.6)	20.9 (20.9–34.6)	0.919
Mortality (%)	0	0	

[1]Preoperative patient year was defined as the time from onset of chronic pain requiring first admission.
[2]During one year before surgery.
[3]Median comprehensive complications index for complicated cases (S-PJ *n* = 3, L-PJ *n* = 8).
S-PJ: Short pancreatojejunostomy; L-PJ: Long pancreatojejunostomy; IQR: Interquartile range; CP: Chronic pancreatitis; PY: Patient year; PD: Pancreatic duct; DM: Diabetes mellitus; BMI: Body mass index; PEI: Pancreatic exocrine insufficiency; IO: Intraoperative; PRC: Packed red cells; CCI: Comprehensive complications index.

The patients of the L-PJ group, compared to those of the S-PJ group, were significantly younger (45.6 years *vs* 52.6 years), had more previous admissions due to CP (5 *vs* 4), and had a larger main PD (8.0 mm *vs* 6.0 mm). This group also had higher proportion of disabled persons (73.3% *vs* 45.7%), as well as the proportion of patients with ≥ 2 symptoms of PEI (73.3% *vs* 47.8%). In addition, the proportion of patients with alcoholic etiology (95.6% *vs* 82.6%) and pancreatic calcifications (77.8% *vs* 58.7%) was higher in this group, but these differences were not significant.

There were no differences between the groups regarding patients' gender, time from onset of chronic pain, endocrine insufficiency, BMI, loss of body weight or proportion of patients with pancreatic pseudocysts. Pain characteristics (NRS and PDI) did not differ between the groups before surgery (Figures 18 and 19).

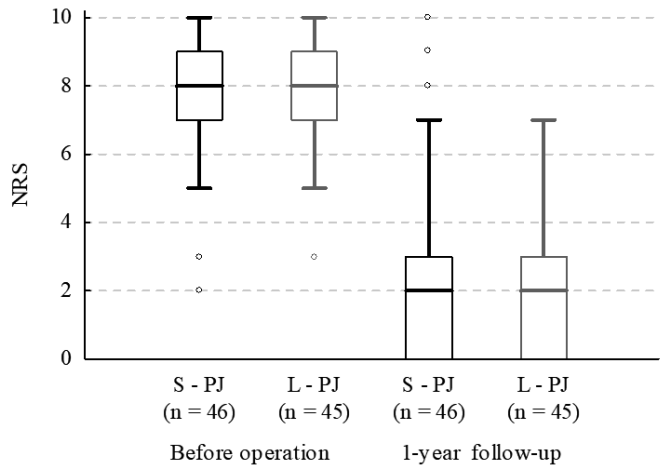


Figure 18. Box plot of the intensity of pain according to the numerical rating scale (0–10) before surgery and 1 year after surgical treatment of chronic pancreatitis.
NRS – Numerical rating scale; S-PJ – Short pancreatojejunostomy; L-PJ – Long pancreatojejunostomy.

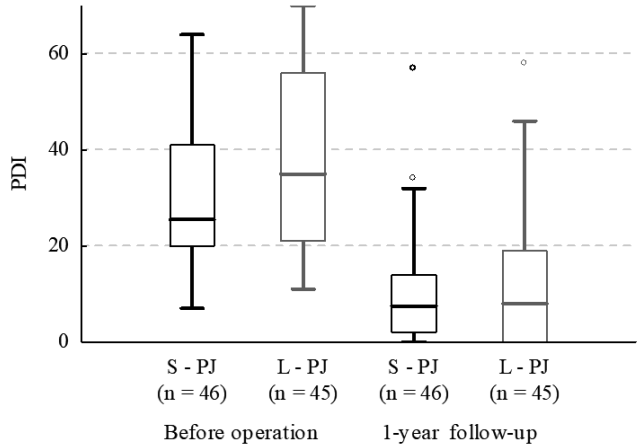


Figure 19. Box plot of the pain disability index (0–70) before surgery and 1 year after surgical treatment of chronic pancreatitis.
PDI – Pain disability index; S-PJ – Short pancreatojejunostomy; L-PJ – Long pancreatojejunostomy.

Approximately half of the patients required pain treatment with opioids (45.7% in the S-PJ group and 57.8% in the L-PJ group, Figure 20). The preoperative characteristics of QOL were similar for both groups (Figure 21).

The indications for surgical treatment were chronic intractable pain in 79 cases (86.8%) and complications of CP associated with pancreatic intraductal hypertension in 12 cases (13.2%). There were no differences in the indications between the groups.

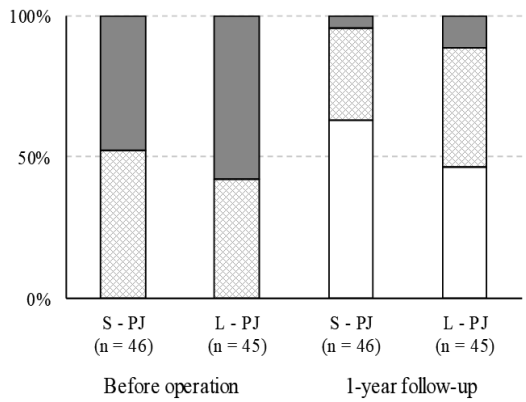


Figure 20. Data on pain treatment before surgery and 1 year after surgical treatment of chronic pancreatitis.
Gray bars – opioid users; diamond-filled bars – users of non-opioid painkillers; white bars – non-users of any painkillers.
S-PJ – Short pancreatojejunostomy; L-PJ – Long pancreatojejunostomy.

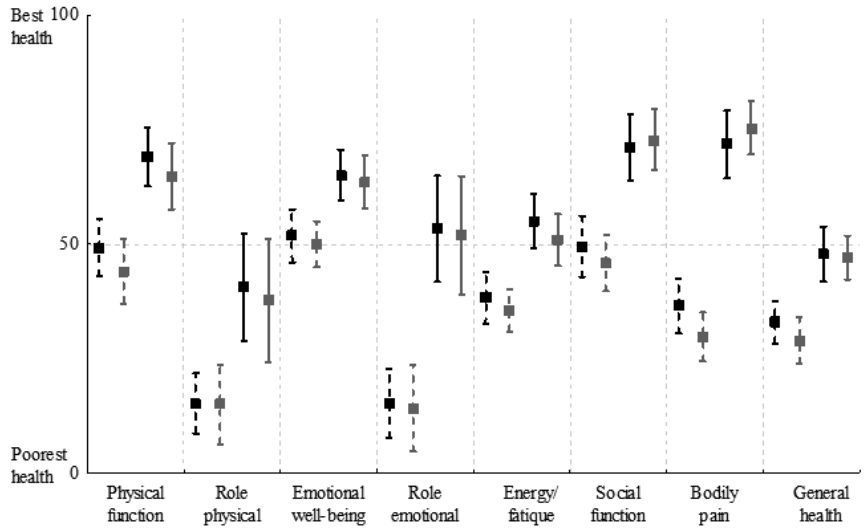


Figure 21. Quality of life RAND SF-36 mean scores, with 95% confidence interval, before surgery and 1 year after surgical treatment of chronic pancreatitis.
Black – Short pancreatojejunostomy (n=46); gray – Long pancreatojejunostomy (n=45).
Dashed lines – before surgery; solid lines – 1 year after surgical treatment.

Pancreatojejunostomy: characteristics of surgery

Assessment of the surgical characteristics of PJ revealed significantly shorter operating time (107.5 min *vs* 134.0 min), lower need for intraoperative packed red cells (PRC) transfusion (0% *vs* 15.6%), as well as for total PRC transfusion in the perioperative period (2.2% *vs* 31.1%) in the S-PJ group (Table 8).

In addition, morbidity was lower in the S-PJ group (6.5% *vs* 17.8%), but this difference was not significant. The total number of complications was 11; most of them were mild according to the Clavien-Dindo classification (grades I–II). There were only three grade III complications: in the S-PJ group there was one case of peripancreatic fluid collection (grade IIIa), which was percutaneously drained. In the L-PJ group there were two cases of postoperative intra-abdominal hemorrhage (associated with pancreatic ductotomy) both of which required relaparotomy (grade IIIb). Use of CCI for evaluation of severity of complicated cases revealed no difference between the groups: median CCI was 26.6 for the S-PJ group and 20.9 for the L-PJ group. Perioperative mortality was zero in both groups.

There was no difference in the median length of hospital stay between the groups (8.5 days for S-PJ and 9.0 days for L-PJ).

Clinical effects of surgical treatment

All clinical effects were assessed before surgery and one year after surgery. Pain assessment revealed significant pain reduction in both study groups without differences between them. Median decrease in NRS was 6 points (8 to 2) in

both groups (Figure 16). Analogously, a significant decrease in median PDI was seen in both groups, without a significant difference between them: 18.0 points (25.5 to 7.5) in the S-PJ group and 27.0 points (35.0 to 8.0) in the L-PJ group (Figure 17). Complete or partial pain relief was seen in 84.8% and 88.9% of patients, respectively.

Pain relief was correlated with marked changes in pain treatment: when before surgery all patients needed some kind of pain treatment, then one year after surgery almost two thirds of the patients in the S-PJ group (63.0%) and almost half of the patients in the L-PJ group (46.7%) did not need any pain treatment (Figure 18).

The proportion of patients with the occasional need for opioids was 4.4% (two patients) in the S-PJ group and 11.1% (5 patients) in the L-PJ group; the difference between the groups was not significant. Changes in QOL were measured using the RAND SF-36 scale. All eight assessed aspects of QOL showed significant improvement in both study groups, with the most notable positive effect regarding the impact of pain on QOL and role limitations due to emotional problems (Figure 21).

Patients' BMI increased during the first year after surgery in most cases: 75.6% in the S-PJ group and 55.8% in the L-PJ group. However, despite the high proportion of patients with weight gain, the average increase in BMI was modest, being only 1.1 and 0.4 kg/m^2, respectively.

PJ showed high effectiveness in preventing new hospital admissions due to exacerbations or complications of CP in both groups. There were 1.8 (S-PJ group) and 2.0 (L-PJ group) hospital admissions because of CP per PY before surgery, which dropped to 0.1 admissions per PY in both groups after surgery.

Patients' general satisfaction with the results of the surgical treatment of CP according to the Likert 5-point scale was very high: 4.7 in the S-PJ group and 4.9 in the L-PJ group. Changes in chronic abdominal pain were rated as much less intense, at 4.9 points compared to the baseline in both groups (1 – much more intense, to 5 – much less intense).

7. DISCUSSION

The current research was conducted with the aim to evaluate long-term results of surgical treatment of CP.

First, long-term survival in a surgically treated cohort, and the impact of different risk factors on survival was assessed. This was followed by evaluation of the causes of death.

The second topic of interest was complications of CP. Their prevalence prior to and following surgical treatment was evaluated. The next aim was to assess the impact of the type of the surgical method on the occurrence of new complications. For this purpose, a consistent pathophysiological classification of complications of CP was essential. As no such classification was available, a relevant proposal for one, based on a literature review, was made.

The third part of the research comprised assessment of the possible advantages and disadvantages of 'short' and 'long' pancreatojejunostomy in the treatment of CP in the case of a dilated pancreatic duct.

7.1. Long-term survival, risk factors and causes of mortality

Long-term survival

The first study reports long-term survival after surgical treatment of CP with a prospective follow-up period of 19.6 years, identifies risk factors for survival and the causes of death.

Several studies have noted that patients with CP have lower survival compared to the background population. Lowenfels et al reported in their multicenter study 3.6 times higher mortality and Nøjgaard et al. reported 4.3–4.5 times higher mortality compared to the background population (Lowenfels et al., 1994; Nøjgaard et al., 2010). According to our study, SMR was 1.8. In further evaluation, we found a significant correlation with patients' risk behavior after surgical treatment: for non/minimal alcohol users mortality did not differ significantly from that for the age-and sex-matched background population, while for moderate/heavy users SMR was 2.7.

There has been reported a mortality rate of 27 per 1,000 PY for a surgically treated cohort by Thuluvath et al, and excellent long-term survival and pain relief after surgical treatment in several other studies (Bühler et al., 1999; Sohn et al., 2000; Thuluvath et al., 2003). In the present study, the mortality rate was 32.8 per 1,000 PY. Hence, based on these data it seems that surgical treatment is associated with more favorable long-term outcome and lower mortality compared to conservative treatment (the Danish Nationwide Matched Cohort study reported a mortality rate of 77.4 per 1,000 PY among predominantly conservatively treated patients) (Bang et al., 2014).

The slightly higher mortality (compared to that reported by Thuluvath et al) in our study can be explained by two circumstances. Firstly, in our study group the proportion of patients with alcoholic CP was extremely high (88.8%). Several studies have shown that alcoholic CP is associated with an unfavorable disease course and lower long-term survival compared to other etiologies (Dancour et al., 1993; Hao et al., 2018; Miyake et al., 1989). Secondly, also the proportion of patients with local complications of CP and with endo- and exocrine insufficiency in our cohort was relatively high. According to the classification of Lèvy et al, patients with local complications have at least the middle-phase CP and those with exocrine and endocrine insufficiency have the late-phase CP with lower survival and higher rate of complications, as noted previously by Ockenga et al (Lévy et al., 2014; Ockenga, 2009). The high proportion of patients with local complications and pancreatic insufficiency indicates that the patients of our study cohort may have had a more advanced disease.

Risk factors for mortality

Demography-, psychosocial life- and health-associated factors

Analysis of the patients' age showed, as expected, lower survival among older patients. However, we found that comorbidities, rather than patients' age, played a critical role, which we evaluated using Charlson's comorbidity index. Patients with Charlson's index 4 or higher showed a HR of death of 9.12 compared to index 0–1. For this subgroup of patients, ten-year Kaplan-Meier cumulative survival rate was 31.1% and median survival was 6.9 years. This low survival among patients with high Charlson's index indicates poor prognosis for surgical management. Yet, on the other hand, all these cases were almost exclusively patients with complications of CP, in whom interventional or endoscopic treatment had been unsuccessful and surgical treatment was therefore unavoidable. Despite the relatively low life expectancy in this special subgroup of patients, surgical treatment was not only indicated, but was clearly lifesaving in many cases. Certainly, for patients with high Charlson's index, endoscopic measures should be the first line treatment in elective situations.

Both unemployment and disability had a strong negative impact on survival. There was significant correlation between disability and unemployment, since intractable pain often renders persons disabled, which in turn may lead to unemployment. According to Mullady et al, one-third of the patients with CP are unable to work (Mullady et al., 2011). In our study the rate of disability for the surgically treated cohort was undesirably high, at 62.7% (101 patients), which is not easy to explain. On the one hand, as noted above, CP is known to be a disease with a substantial impact on the employment status because of chronic disabling pain (Gardner et al., 2010). Hard physical work was reported as one of the provokers of abdominal pain in 44.6% of the disabled patients in our study. However, although more than half of the patients did not report association with physical work as a provoker of pain, they were categorized as persons with reduced working capability. This can be explained by the socio-

economic background: during the study period the rate of unemployment in the service area of our hospital was relatively high (7–16%). On the other hand, documented disability granted constant support for disabled people, which was often their only income and so they were highly motivated to have the disabled status. Thus, we cannot underestimate the psychosocial and socioeconomic issues pertaining to patients with CP.

Alcohol

Alcohol consumption is the most common cause of CP. In their systematic review, Irving et al found monotonically increasing dose-response relationship between average alcohol consumption and pancreatitis (Irving et al., 2009), Jeon et al showed that heavy alcohol consumption (median almost 35,000 units) is usually needed for evoking CP (Jeon et al., 2019). Miyake et al demonstrated a negative impact of alcohol consumption on survival. In our survival analysis, we divided the patients into only two groups: 1) non- and minimal consumption and 2) moderate and heavy consumption. We did not analyze patients with moderate and heavy drinking separately because obtaining reliable data in this case would have been highly questionable: heavy drinkers tended to report a lower than actual amount of alcohol used. Sand et al has also noted this problem (Sand et al., 2007). In our cohort alcoholic CP accounted for 88.8%; however, as absolute abstinence from alcohol was the strict prerequisite for surgical treatment, we assumed that all our patients were alcohol abstainers in the peri-operative period. Still, the patients' risk behavior during follow-up was varying. Less than half (44.1%) of the patients remained abstainers. The remaining cohort soon discovered that postoperative drinking was not followed by severe abdominal pain as before surgery. The outcome for this subgroup of patients proved unfavorable and their ten-year survival was 53.3%.

Smoking

The detrimental effects of tobacco consumption on CP have been studied in recent decades. Cigarette smoking as an independent risk factor for development of CP has been identified in many studies (Lai et al., 2017; X. Ye et al., 2015). Maisonneuve et al reported in their multicenter study that smoking also contributes to deterioration of CP through development of calcification and diabetes (Maisonneuve et al., 2005). Our study demonstrated that cigarette smoking is an independent risk factor for mortality in surgically treated CP patients. Both the preoperative history of heavy smoking, measured in pack-years (≥30), and continuous heavy smoking during follow-up (≥1 pack per day), were significant risk factors. Continuous smoking showed intensity-dependent correlation: heavy smokers had lower survival compared to moderate smokers and non-smokers. An additional analysis of the impact of smoking in association with alcohol consumption demonstrated that the co-existence of these risks was associated with analogous, but even more prominent, impact on survival. Heavily smoking patients with moderate/heavy alcohol consumption had the highest HR of death (14.78), compared to non-smokers and non- or minimal

alcohol users. Ten-year survival rate for these groups was 39.7% and 94.0%, respectively.

Through counseling during surgical treatment of CP, we succeeded in motivating some patients to quit smoking. The survival of these patients was higher than that of continuous smokers and was comparable to that of non-smokers. These results support the data by Thun et al, who reported a dramatic reduction in mortality from all major smoking-related diseases after quitting smoking at any age (Thun et al., 2013).

CP-associated factors

The duration and etiology of CP did not show a significant effect on survival. Although alcoholic etiology was associated with elevated risk of death (HR 6.46), this increase did not reach statistical significance because of the relatively small group of non-alcoholic CP.

Impairment of pancreatic endo- and exocrine functions has been referred to as a sign of late-phase CP and has a negative impact on survival (K. J. Roberts et al., 2019; Sohn et al., 2000). This was evident in our surgical cohort of CP as well: insulin therapy-requiring diabetes and PEI was associated with significantly lower long-term survival. Among other signs, the impact of the patients' nutritional status on survival was impressive: the highest survival was seen for patients with mild overweight (BMI ≥25) whose ten-year survival rate was 87.2%, whereas for patients with normal BMI (18.5–24.9) and low BMI (<18.5), ten-year survival rate was 66.5% and 44.5%, respectively. Among those with low BMI, there were some extreme cases (BMI 13–15) where the patients were hospitalized in ICU because of severe metabolic disturbances. In all these cases, we managed to prepare the patients for surgery and provided appropriate surgical treatment without postoperative mortality.

The different aspects of surgical treatment of CP did not have significant influence on long-term survival. There were no differences in survival between the different indications for surgical treatment (pain vs complications of CP) or the type of surgery (pancreatic resections vs drainage operations vs palliative measures). We believe that successful elimination of the main clinical problem, regardless of its entity, is paramount and gives patients a chance for favorable outcome and long-term survival. Generally, pancreatic resections are indicated in cases of pancreatic pseudotumor (inflammatory enlargement), and drainage operations are indicated in cases of a dilated pancreatic duct (Kleeff et al., 2016).

As an advantage of drainage operations, it has been emphasized that pancreatic exocrine and endocrine functions are well preserved, since the loss of the functional pancreatic tissue is minimal. However, as a disadvantage, according to long-term follow-up, there is a risk of pain recurrence and biliary duct strictures over time (Warshaw, 1985). On the contrary, pancreatic resections have shown excellent long-term pain relief (70%–95%), but somewhat higher perioperative morbidity and mortality, as well as higher rate of exocrine insufficiency and new onset of endocrine insufficiency (Van Der Gaag et al.,

2012). Still, owing to effective pain treatment shown in large surgical studies, pancreatic resection is the most widely recommended option of surgical management (Bachmann et al., 2014; Beger & Mayer, 2018; Strobel et al., 2009).

Although it is mandatory to consider the above aspects when choosing the type of operation, surgical method had no impact on long-term survival in our study. To find a possible explanation for this, we performed an additional assessment of patients in the resection and drainage groups. When the patients of the resection group had higher rate of severe peripancreatic complications (e.g. vascular complications and duodenal stenosis) prior to surgery, then the patients of the drainage group had a high rate (13.2%) of PD disruptions (with pancreatic ascites or pleural effusions) and a significantly lower rate of severe complications. It seems that the patients of the resection group had a more advanced disease, which could explain the absence of survival difference compared to the drainage group.

It has been shown that the type of operation in treatment of CP has to be personalized, since there is much heterogeneity in clinical problems, anatomical features and complications in patients with CP (Van Der Gaag et al., 2012). We believe that in the case of successful pancreatic surgery, after elimination of clinical problems, prognosis is mainly determined by other health problems associated largely with the patients' risk behavior.

Causes of death

In this study, we analyzed the causes of death in a surgical cohort and attempted to find their common denominator. One clearly distinguishable group comprised the deaths caused by diseases associated with the risk behavior: alcohol consumption and smoking. The second group consisted of all CP-related deaths and the third group comprised all other causes.

During follow-up, there were 48 deaths. The conditions associated with alcohol consumption were clearly dominating among the causes of death, at 43.7% (the most common cause of death was complicated alcoholic liver cirrhosis). This proportion is higher than that reported in other studies (De La Iglesia-Garcia et al., 2018; Nøjgaard et al., 2010). The most probable reasons for this are the high proportion of alcoholic CP among our patients (88.8%) and the fact that more than half of the patients with alcoholic CP resumed moderate or heavy alcohol consumption, usually 1–2 years after surgery. Our geographical neighbors from Finland reported a similar problem: 58% of the patients continued alcohol consumption even after the diagnosis of CP (Parhiala et al., 2020). Such continuous drinking leads to the impairment of other organs, alcoholic liver disease occupying the first place among them.

The rate of deaths from smoking-associated diseases was also high (31.3%). Although we managed, through counseling, to reduce smoking among patients from preoperative 89.4% to postoperatively 78.3%, it remained a serious problem and increased mortality due to cancers, ischemic heart disease, cerebrovascular disease and chronic obstructive pulmonary disease.

Assessment of the causes of death showed that the vast majority of lethal outcomes (36 patients, 75.0%) were associated with extrapancreatic consequences of the risk behavior – alcohol consumption and smoking. Here lies probably one of the keys to improvement of patients' long-term survival. It is of paramount importance to achieve patients' permanent cessation of alcohol and tobacco consumption. A complex approach to proactive implementation of preventive strategies, psychological and social support and rehabilitation programs, counseling, and restoration of working ability in some cases, can be successful, saving the lives of many patients as well as improving the quality of life of their family members.

7.2. Complications of chronic pancreatitis

Our second study was dedicated to complications of CP. We evaluated their prevalence in a surgically treated cohort prior to and following surgical treatment. We also assessed the impact of the type of the surgical method on the occurrence of new complications during the further course of the disease. For this, we used a novel pathophysiological classification of complications of CP.

As there is currently no treatment to reverse or delay disease progression in CP, clinical management consists primarily in screening for and treating of complications (Ramsey et al., 2017). The most effective treatment of complications is pathophysiological treatment.

The proposed classification defines the common denominator for each pathophysiological group and distinguishes between 'PD complications', 'Peripancreatic complications', 'Pancreatic hemorrhages', 'Pancreatic insufficiency' and 'Pancreatic cancer'.

This kind grouping of complications allows to easily determine both the predominant pathophysiologic mechanism and the clinical problem. The ultimate goal was to develop a simple tool that could be beneficial for clinical decision making, providing a better understanding of the pros and cons of the treatment under consideration, on the one hand, and on the patient's needs, on the other. Moreover, this classification could be used as an instrument for quality improvement in the treatment of CP. We strongly believe that the potential of any treatment to avoid further complications of CP would serve, besides the known indicators of quality of treatment (pain relief, quality of life *etc.*), an additional relevant indicator.

The goal of the surgical treatment of CP is usually to decompress the PD or to resect the nidus of chronic inflammation, and to eliminate local complications of CP. In our study, the clinical impact of surgical treatment on different complications of CP was highly variable and clearly dependent on the underlying predominant pathophysiological mechanism.

The first group of complications ('PD complications') were effectively treated by pancreatic drainage operations, as well as by PJ created during pancreatic resection. The achieved effect was long-lasting over time: only one

PPC developed during follow-up *vs* 34 preoperative complications. Unfortunately, we failed to find previous data about the recurrence rate of PPC or PF after pancreatic duct drainage for comparison. Less radical treatment modalities, *e.g.* anastomoses between GIT and PPC, and endoscopic drainage, have shown a relatively high rate of recurrence. According to Ye *et al*, the recurrence rate of PPC was 11.2% after pseudocystojejunostomy and 7.5% after pseudocystogastrostomy, with an average follow-up of 42.7 months (J. Ye et al., 2021). However, these authors did not provide data about the etiology of PPC (acute or chronic pancreatitis). Endoscopic treatment seems to be associated with higher recurrence rate: Rückert *et al* reported a recurrence rate of 23.3% after endoscopic drainage during 42.2 months of follow-up and underlined the high recurrence risk of CP-associated PPC (Rückert et al., 2017). Farias *et al* compared endoscopic and surgical drainage (mainly *via* pseudocystogastrostomy) of PPC in a meta-analysis and found no significant difference in their recurrence rates (Farias et al., 2019). Our data support the surgical decompression of PD in the case of CP-provoked PPC and PF. High effectiveness of surgical decompression is attributable to the most radical relief of the main pathology (PD obstruction and intraductal hypertension).

The impact of surgical treatment on 'Peripancreatic complications' revealed significant dependency on the surgical method used. During follow-up, there were no new complications in the group of Whipple's procedure, which can be explained by the nature of this procedure (creation of a new bilioenteric and gastroenteric anastomosis). Following the other surgical procedures (pancreatic drainage operations and non-Whipple's pancreatic resections: mostly the Beger or the Berne modifications of pancreatic head resection, and pancreatic tail resection) there developed new 'Peripancreatic complications', which necessitated readmissions and reoperations. In most cases there were biliary strictures (eight patients) and venous thrombosis of SV or PV (four patients); one patient developed duodenal obstruction. The causes of new 'Peripancreatic complications' in the postoperative period can be variable. It seems that among the predominant causes are further development of the fibrotic tissue and the process of scarring within and around the pancreas. This theory is indirectly supported by the results of endoscopic stenting of CP-associated biliary strictures. Several studies have found that long-lasting stenting (10–12 months) is more effective than short-term therapy (3–6 months), indicating persistent fibrosis and scarring (Lakhtakia et al., 2020; Ramchandani et al., 2021). The present study showed that biliary strictures can occur even many years after surgical treatment of CP. In these cases, exacerbations of CP, whether clinical or subclinical, might be responsible, as they are associated with additional extrinsic compression due to edema or development of PPC in the region of the pancreatic head (Adler & Gardner, 2017). The ability to avoid new 'Peripancreatic complications' is one of the obvious advantages of Whipple's procedure in the treatment of CP, as reported earlier by Diener *et al* in the ChroPac trial and by Müller *et al* (Diener et al., 2017; Müller et al., 2008). Whether this advantage of Whipple's procedure is sufficient to prefer this operation to other

surgical options remains a subject of discussion. In fact, Whipple's operation has also clear disadvantages, such as longer operating time and, according to most studies, higher perioperative morbidity and mortality, and higher rate of postoperative PEI.

The third group of complications ('Pancreatic hemorrhages') are associated with the poorest prognosis. Even with prompt diagnosis and immediate therapy, the mortality rate reported in earlier studies is 15% to 50% (Chiang et al., 2014). In the past two decades, owing to the enormous progress in radiological techniques and instrumentation, angiographic treatment as the first-line therapy has been widely employed to stop bleeding from visceral PA in hemodynamically stable patients. In a recent meta-analysis Sagar *et al* reported a technical success rate of 88%, a clinical success rate of 86%, a re-bleeding rate of 16.3%, and a morality rate of 8% for endovascular therapy (Sagar et al., 2021).

Surgical treatment is reserved for patients for whom vascular interventional therapy has failed or is not accessible, as well as for those with unstable vital signs; during the study period, we had 17 such patients. Our surgical approach was relatively radical: in cases of recurrent GIT bleeding from the fistulation of PA and ineffective endovascular therapy, or in cases of ongoing bleeding in an unstable patient, surgical treatment consisted in the resection of the affected area of the pancreas in all cases. In most such cases pancreatic tail resection was performed (eight cases), as hemorrhages emerged from the splenic artery, but in two cases pancreatic head resection was required. In cases of contained PA, the treatment of choice was intra-aneurysmatic hemostasis followed by pancreatic drainage operation. This approach resulted in a highly effective treatment result: there were no recurrent pancreatic hemorrhages in our cohort during follow-up (median 7.2 years). As there occurred no re-bleedings after surgery in our cohort and we managed to achieve zero perioperative mortality, we are convinced that surgical therapy remains an important highly effective treatment modality for patients with pancreatic hemorrhage. In unstable patients, surgery should be the first-line therapy; in hemodynamically stable patients, surgery should be indicated in cases of unsuccessful endovascular therapy, as the next step of treatment.

Besides effective treatment of pancreatic hemorrhages, surgical therapy demonstrated also the potential to avoid pancreatic hemorrhages: there were no episodes of pancreatic hemorrhage during follow-up in the entire surgically treated cohort. One explanation for this might be the beneficial effect of PD decompression. Regarding the occurrence of chronic PPC, which usually precedes PD obstruction and intraductal hypertension (Adrén-Sandberg & Dervenis, 2004), surgical PD decompression has a preventive effect on development of PPC, and there by on its transformation into PA. A study of Anand et al supported this theory and established PPC as the most important risk factor for development of PA and pancreatic hemorrhage (Anand et al., 2020).

The fourth group of complications ('Pancreatic insufficiency') showed continuous steady deterioration of pancreatic function. A similar result, i.e. impairment of pancreatic function over time, has been repeatedly demonstrated earlier,

most recently by Kempeneers *et al*, on the basis of data from the Dutch Chronic Pancreatitis Registry (Kempeneers, Ahmed Ali, et al., 2020).

Comparison of the surgical options in the present study revealed higher rate of PEI after Whipple's pancreatoduodenal resection (compared to the other types of surgery), which can be explained by further reduction in exocrine pancreatic secretion due to a considerable portion of the removed pancreatic parenchyma in patients with already impaired pancreatic function (Domínguez-Muñoz, 2009).

The postsurgical rate of T3cDM did not differ significantly between pancreatic resections and drainage operations. The slightly higher rate of T3cDM observed in the group of pancreatic tail resection is attributable to the relative deficiency of insulin production due to the removed pancreatic tail (Slezak & Andersen, 2001; Wu et al., 2020).

The fifth group of complications ('Pancreatic cancer') was not analyzed within the present study, as all patients with pancreatic malignant tumors were excluded, and there occurred no new pancreatic cancers during follow-up in the study cohort. However, this group should not be underestimated, as the reported cumulative risk of pancreatic cancer in patients with CP after 10 years and 20 years was 2% and 4%, respectively (Malka et al., 2002). For patients with sporadic CP, despite the presence of the risk of pancreatic carcinoma, it is still too low to recommend active screening (Greenhalf et al., 2020). All patients with CP should be advised to lead a healthy lifestyle aimed at avoiding risk factors for progression of CP and pancreatic cancer.

According to 'The international consensus guidelines on surveillance for pancreatic cancer in chronic pancreatitis', in the subgroup of patients with hereditary pancreatitis due to inherited PRSS1 mutations, the risk of pancreatic cancer is high enough (lifetime risk of 40%-55%) to justify surveillance (Greenhalf et al., 2020). According to 'The International consensus guidelines on surgery in CP', even prophylactic pancreatic resection can be considered for these patients (Kempeneers, Issa, et al., 2020).

Although several earlier studies have found that early surgery could be beneficial in terms of slowing down the impairment of the pancreatic function (Lamme et al., 2007; Yang et al., 2014), the latest randomized study revealed no difference between early surgery compared to endoscopy first approach (Issa et al., 2020). The data of the present study are insufficient to provide any additional information regarding this effect, as our patients were clearly not 'early cases' of CP.

Based on the proposed pathophysiological classification of complications of CP, our analysis of surgical treatment shows that there exist no ideal surgical options suitable for all cases of CP. Nevertheless, despite the lack of evidence supporting the universal superiority of any available surgical procedure, it is obvious that each of them has its own specific advantages. Thus, the choice of the surgical procedure should proceed from at least four aspects (Table 9):

1. Presence of chronic pain due to CP.
2. Anatomical changes of the pancreatic gland.

3. Presence and nature of local complications of CP.
4. Procedure-specific risks of surgery.

Thus the treatment under consideration should harmonize best with each patient's individual needs, while the presence and nature of complications of CP are of extreme importance. This is consistent with the conclusion by Frola *et al* according to which a tailored approach to CP patients is mandatory (Frola et al., 2019).

Table 9. Surgical options and clinical aspects requiring consideration by the choice of the surgical procedure in treatment of chronic pancreatitis.

Clinical aspects	Pancreatic drainage operation	Non-Whipple's pancreatic resections[1]	Whipple's pancreato-duodenal resection	Palliative operations[2]
Chronic pain[3]	🟢	🟢	🟢	🟡
Anatomical features:				
- Pseudotumor	🟡	🟢	🟢	🟡
- Dilated PD	🟢	🟢	🟢	🟡
Complications of CP:				
- Pancreatic duct complications	🟢	🟢	🟢	🟡
- Peripancreatic complications[4]	🟡	🟡	🟢	🟢
- Pancreatic hemorrhage[5]	🟢	🟢	🟢	🟡
- Pancreatic insufficiency	🟡	🔴	🔴	🟡
- Pancreatic cancer[6]	🟡	🟡	🟢	🟡
Surgical risks[7]	⚫	⚫⚫	⚫⚫⚫	⚫

🟢 – positive impact on current aspect

🟡 – no impact on current aspect

🔴 – negative impact on current aspect

⚫ – surgical risk

[1] – pancreatic head resections according to Beger, Bern or Frey; pancreatic distal resection

[2] – biliodigestive or gastroenteric bypass

[3] – reported long-term pain relief has been slightly higher after pancreatic resections compared to pancreatic drainage procedures

[4] – as pancreatic drainage operations and non-Whipple's resections do not solve biliary or duodenal obstruction, it has been suggested to combine these procedures with a palliative biliodigestive or gastroenteric bypass if needed (and if Whipple's procedure is not possible)

[5] – in the case of ongoing hemorrhage pancreatic resection is the most widely suggested option; for contained pseudoaneurysm. Intraaneurysmatic hemostasis in combination with pancreatic drainage operation is also an effective treatment

[6] – Whipple's resection is the only effective surgical treatment in the case of pancreatic head cancer; for pancreatic distal cancers, distal or subtotal pancreatectomy is indicated

[7] – surgical risks are relatively low in the case of pancreatic drainage operations and palliative procedures; Whipple's procedure is associated with the highest surgical risk

7.3. Pancreatojejunostomy in treatment of chronic pancreatitis

This retrospective study provides comparative data on some aspects of surgical treatment of CP and clinical effects of surgery, when either S-PJ or traditional L-PJ was used. The S-PJ was applied in cases of an almost uniformly dilated PD and L-PJ was applied in cases with multiple ductal changes: strictures, dilatations and calcifications. According to the study, S-PJ showed better perioperative results: shorter operating time, lower need for PRC transfusion and lower rate of perioperative complications. There was no significant difference in the clinical results regarding pain relief, improvement in QOL, weight gain, patients' satisfaction with surgical treatment, and decrease in the rate of postoperative hospital admissions per PY due to CP.

Thus, the main outcome of the study is that for patients with a uniformly dilated PD and strictures or calcifications in a single region, S-PJ shows better operative characteristics, while the subsequent clinical effects are not inferior to those of L-PJ.

Study groups

Assessment of the preoperative data showed that study groups were similar regarding the patients' main complaints (intensity of pain, time from onset of pain, pain medications) and QOL. At the same time, the groups were dissimilar regarding some other important aspects. The L-PJ group was characterized by a higher rate of alcoholic CP, and the patients of this group had more admissions due to CP in the history of the disease. According to several studies, alcoholic CP is associated with a more aggressive disease course and a higher rate of complications compared to other etiologies (Dancour et al., 1993; Hao et al., 2018; Miyake et al., 1989). In support of these findings, the patients of the L-PJ group had more pronounced local changes in the pancreatic gland: multiple ductal changes (strictures, dilatations and calcifications) and a larger diameter of PD.

Pancreatojejunostomy – characteristics of surgery

Longitudinal PJ, also known as the Partington-Rochelle or modified Puestow procedure, was performed for the first time in 1960 (Partington & Rochelle, 1960). This procedure is indicated for the treatment of patients with a dilated PD ('large duct disease')(Braganza & Parr, 2011). The method offers a series of advantages such as the low incidence of endocrine and exocrine pancreatic insufficiency, rapid symptom improvement in at least 80% of cases, low morbidity and low postoperative mortality (Isaji, 2010).

According to the predominant statement, 'standard PJ' necessitates the full-length anastomosis with total opening of the PD. However, the term 'extended PJ' has been recently introduced to describe the method where the PD is opened in full length, from 1–2 cm from the distal end of the pancreatic tail up to 1 cm from the ampulla of Vateri (Kempeneers et al., 2022). The use of this new term

is slightly confusing, as the earlier term for the same procedure was ‘standard PJ’.

The obvious technical advantage of this approach is easy clearance of the entire PD of calcifications and full decompression of the duct (Greenlee et al., 1990; Sudo et al., 2014). However, regarding the extent of ductotomy, the pioneers of the method, Partington and Rochelle, stated in 1960: ‘uniformly dilated duct need not be opened extensively’, ‘PD split should continue somewhat right to mesenteric vessels’ and ‘it is rarely necessary to split distal portion in the tail’ (Partington & Rochelle, 1960). Some authors admit that the extent of the ductal incision does not have a fixed length; rather, ductotomy has to ensure full PD decompression (Frey & Amikura, 1994; Julianov & Saroglu, 2021). Thus, instead of the widely accepted ‘standard’, there exist slightly different opinions and practices. Despite the fact that there are dozens of reports on the surgical technique, morbidity, mortality and the clinical effects of the Partington-Rochelle modification of PJ, no comparative studies are available on the impact of the anastomotic length of PJ on the outcome of surgical treatment, especially in terms of pain relief and QOL.

Regardless of the obvious advantages, total ductotomy has also some disadvantages and surgical risks. Unroofing of the PD is especially challenging in the region of the pancreatic head: The gastroduodenal artery (GDA) is usually located in the proximal 1.5–3 cm of the pancreatic head and has to be suture ligated superiorly and inferiorly in front of the ductotomy. Yet, despite the ligation of the GDA, the pancreatic head is still very well vascularized and ductotomy in this region is associated with a considerable risk of bleeding. Therefore, some surgeons have suggested partial resection of the pancreatic head in this situation (as described by Frey) as a less risky procedure compared to ductotomy (Ho & Frey, 2001; Sakorafas & Sarr, 2000).

There are several options to avoid long ductotomy, especially in the region of the pancreatic head. One of them is to replace long ductotomy with intraoperative instrumental exploration of the PD. In the present study was used intraoperative PD probing, and in the case of detected additional calcifications or strictures, further ductotomy was performed. An alternative would be endoscopic visualization of the PD, which has been pioneered mainly by laparoscopic surgeons. Kurian and Gagner used a choledochoscope for visualization of PD and Fogarty catheters for ductal clearance of calcifications; Tantia *et al* used a 30° laparoscope to visualize the lumen of the PD and cleared the unopened part of the pancreatic head of calcifications using the graspers – a procedure which the authors called ‘pancreaticodochoscopy’ (Kurian & Gagner, 1999; Tantia et al., 2004). Bhandarwar *et al* suggested using a 5 mm zero-degree laparoscope to confirm ductal clearance beyond the ductotomy, while Sahoo and Kumar used a cystoscope for this purpose (Bhandarwar et al., 2019; Sahoo & Kumar, 2014). In a recently published study, Julianov *et al* employed intraoperative pancreaticoscopy for assessment of the PD, and the length of ductotomy was tailored according to discovered strictures or calcifications. A full-length ductotomy was required in 52% of the patients; short ductotomy was

required in 34%; in 14% the initial small incision did not require any additional ductotomy (Julianov & Saroglu, 2021).

The value of ductotomy in the region of the pancreatic tail is also debatable: in the splenic hilum the PD is not well accessible and is narrowing anyway, so the effect of the extensive distal PD incision (up to within 1 cm of the tip of the pancreatic tail) for allowing better pancreatic juice drainage can be quite modest. Considering the above mentioned aspects, several surgeons have abandoned opening the PD in the region of the pancreatic tail and have replaced it with intraoperative exploration of the PD (Ceppa & Pappas, 2009; Julianov & Saroglu, 2021; Sahoo & Kumar, 2014).

According to the present study, avoiding total ductotomy provided significant benefits in terms of operating time, need for PRC transfusion, and morbidity. However, the rate of severe complications was low in both groups: only two patients in the L-PJ group needed relaparotomy due to postoperative hemorrhage, both cases being due to ductotomy in the region of the pancreatic head.

Clinical effects

The clinical effects of the two types of PJ were evaluated one year after surgery. Both surgical options, S-PJ in the treatment of patients with a uniformly dilated PD and L-PJ in the treatment of patients with multiple ductal changes (strictures, dilatations and calcifications) were effective in resolving the main clinical problems without significant differences in the results.

The proportion of patients with pain relief was comparable to that reported in previous studies (D'Haese et al., 2014; Tian et al., 2019). The median decrease in NRS was 6 points (8 to 2) in both groups, an analogous significant decrease in the median PDI was seen in both groups. Complete or partial pain relief was seen in more than 80% of patients in both groups. Pain relief was correlated with notable reduction in the need for pain treatment. Interestingly, despite the fact that 4.4% (S-PJ) and 11.1% (L-PJ) of the patients occasionally used opioids, they rated (according to the Likert 5-point scale) abdominal pain as much less intense compared to the baseline. Some patients reported that 'they were used to take opioids even in the case of mild pain because of effectiveness of this medication, and because they used to'. Patients' general satisfaction with the results of the surgical treatment of CP was high, being on average 4.7 in the S-PJ group and 4.9 in the L-PJ group (Likert's 5 point scale).

Significant improvement in QOL was evident in all eight aspects of the RAND SF-36 tool. The most marked changes were seen in pain associated QOL and in role limitations because of emotional problems. The importance of pain in predicting QOL is well known (Machicado et al., 2017). Hence, a greater than 30-point improvement in pain associated QOL was to be expected.

One of the anticipated effects of the surgical treatment of CP is prevention of new admissions due to pain and exacerbations or complications of CP (Diener et al., 2017). In this study, the effectiveness of surgical treatment in preventing new admissions was higher than 95%: there were 1.8 (in the S-PJ group) and

2.0 (in the L-PJ group) hospital admissions because of CP per PY before surgery; after surgery this indicator dropped to 0.1 admissions per PY in both groups. This effect cannot be underestimated, as it translates into a decrease of the health care burden for patients with CP. Hall *et al* found in their systematic review that most treatment costs for patients with CP are associated with pain management (Hall et al., 2014). Hence effective surgical pain treatment leads to a considerable economic effect.

8. CONCLUSIONS

1. SMR for surgically treated CP cohort was 1.8. A subgroup of patients resuming moderate/heavy alcohol consumption after surgical treatment of CP had SMR of 2.7.
2. The major risk factors for death in the surgically treated cohort of CP were alcohol consumption and smoking; high co-morbidity index; unemployment; and low BMI.
3. Alcohol-related and smoking-related non-pancreatic diseases caused the vast majority of deaths. Thus, surgery provides the best results in patients, preventing postsurgical relapse of original behavioral risks. Long-term outcomes of surgically treated CP was associated with low CP-related mortality.
4. Defining common pathophysiological mechanisms, a novel pathophysiological classification of complications of CP is proposed. Five groups of complications were distinguished: 'PD complications', 'Peripancreatic complications', 'Pancreatic hemorrhages', 'Pancreatic insufficiency', and 'Pancreatic cancer'.
5. The proposed classification allows grouping of different complications and generalized analysis. It also demonstrated pros and cons of different surgical methods in the treatment of CP and revealed the impact of the type of the surgical method on the occurrence of new complications.
6. The presence and pathophysiological nature of complications should be among the main determinants in clinical decision making and in surgical choice.
7. In the treatment of patients with CP and a dilated PD, in the setting of a uniformly dilated PD, S-PJ provides adequate decompression of PD, as the clinical outcomes following S-PJ are not inferior to those of L-PJ. While the perioperative characteristics of S-PJ surpass those of L-PJ, S-PJ should be preferred as the surgical option in the case of a uniformly dilated PD.

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10. SUMMARY IN ESTONIAN

Kroonilise pankreatiidi kirurgilise ravi lühi- ja kaugtulemused

10.1. Sissejuhatus

Krooniline pankreatiit (KP) on kõhunäärme krooniline põletik, millele on iseloomulik aeglaselt progresseeruv kulg. KP patsientide peamisteks kliinilisteks probleemideks on krooniline kõhuvalu ja kõhunäärme kahjustusest tekkivad tüsistused. Suurel osal patsientidest on haiguse tekke põhjuseks alkoholi liigtarvitamine ja/või suitsetamine.

Tänaseni ei ole avastatud ravivõtteid, mille abil õnnestuks haiguse arengut aeglustada või tagasi pöörata. Seetõttu on ravi suunatud eelkõige kroonilisest põletikust tingitud valu ja tüsistuste kõrvaldamisele.

Ehkki KP iseloomulikke muutusi kõhunäärmes (sidekoestumist ja kaltsifikaate) on kirjeldatud esmakordselt juba sajandeid tagasi, ei teatud nende muutuste olemust, põhjust ega tagajärgi. Alles 1946. aastal kirjeldas Mandred Comfort (Mayo Kliinikust Ameerika Ühendriikides) põhjalikult selle haiguse puhul esinevaid vaevusi, muutusi kõhunäärmes, kulgu ja tüsistusi (Comfort et al., 1946).

Pärast seda on selgitatud paljud KP tekkeriskid ja mehhanismid, tohutult on arenenud diagnostika ja ravivõimalused, välja on töötatud põhilised ravi seisukohad ja algoritmid. Lisaks algsele, peaaegu eranditult konservatiivsele ravile, on KP lokaalsete tüsistuste ravis laialdaselt kasutusele võetud kirurgiline ravi ja erinevad ‘vähe-invasiivsed’ ravivõtted (perkutaansed ja endoskoopilised drenaažid, stentimised; pankrease litotripsia; angiograafilised meetodid pankrease verejooksude korral jne).

Ometi on siiani mitmeid ebaselgeid aspekte, mille osas on täpsustavad uuringud äärmiselt vajalikud. Antud dissertatsiooni peamised uuringu suunad olid: kirurgiliselt ravitud KP patsientide elulemus ja surma põhjused; KP tüsistused; KP drenaaž-operatsiooni tehnilised aspektid.

10.2. Eesmärgid

1. Selgitada KP patsientide kirurgilise ravi kaugtulemused: elulemus, seda mõjutavad riskifaktorid ja surma põhjused.
2. Erinevate KP tüsistuste üldistavaks analüüsiks on vajalik nende patofüsioloogiline klassifitseerimine ja grupeerimine. Kuna selline klassifikatsioon puudub, oli eesmärk see luua.
3. Selgitada KP tüsistuste osakaal ja olemus kirurgiliselt ravitud kohordil. Analüüsida erinevate operatsioonide mõju uute tüsistuste tekkele operatsioonijärgsete aastate jooksul.

4. Selgitada võrdlevalt pankrease juha dreeniva operatsiooni (ehk pankrease ja peensoole anastomoosi) kahe variandi: ‘lühikese’ ja ‘pika’ anastomoosi eelised ja puudused.

10.3. Meetodid

Patsiendid

Uuringu kiitis heaks Tartu Ülikooli inimuuringute eetika komitee (protokollid 291/T-1 ja 302/M-31). Kõik uuritavad allkirjastasid ‘Uuritava informeerimise ja teadliku nõusoleku vormi’.

Uuringusse olid kaasatud kõik >18 aastased patsiendid, kellel esines kindel KP Zürichi kriteeriumide järgi (Ammann, 1997), ja kes olid opereeritud Tartu Ülikooli Kliinikumi kirurgiakliinikus üldkirurgia ja plastikakirurgia osakonnas.

I uuringusse (‘Pikaaegne elulemus, surma riskifaktorid ja põhjused kirurgiliselt ravitud KP kohordil’) olid kaasatud 161 järjestikust patsienti, kes olid opereeritud aastatel 1997.–2019.

II uuring (‘KP tüsistused kirurgiliselt ravitud kohordil’) põhines samal andmebaasil, ent lisandusid 2020. a opereeritud viis patsienti (seega kokku 166 patsienti).

III uuringus (‘Pankreatikojejunostoomia vajalik pikkus KP ravis’) kasutati samast andmebaasist 91 patsiendi andmeid, kellel oli rajatud pankrease-peensoole anastomoos.

Uuringu andmebaas

Andmebaasi koosseis:

- Demograafilised andmed,
- Andmed KP haiguse anamneesi, tüsistuste, hospitaliseerimiste ja senise ravi kohta,
- Valu ja sellest tingitud vaegurluse ja valuravi karakteristikud,
- Elukvaliteedi hinnangud,
- Informatsioon KP lokaalsete muutuste kohta, mis saadi kompuuter-uuringu ja operatsiooni leiu alusel,
- Andmed pankrease funktsionaalse seisundi kohta (endo- ja eksokriinse puudulikkuse olemasolu),
- Kirurgilise ravi karakteristikud (operatsiooni tüüp, kestus, tüsistused, vereülekande vajadus, intensiivravi ja haiglaravi kestus),
- Patsiendi rahulolu hinnangud,
- Andmed patsiendi tervisliku seisundi, kaasuvate haiguste, töövõime ja töötamise kohta.
- Informatsioon riskikäitumise kohta (alkoholi tarvitamine ja suitsetamine).
- Surmaandmed (lahangu korral informatsioon selle leiust, Eesti Surmaregistri andmed, täiendavad andmed lähedastelt).

Loetletud andmed dokumenteeriti enne operatsiooni, üks, kolm ja viis aastat pärast operatsiooni ning hiljem 5 aastaste intervallidega. Patsiente jälgiti kas

uuringu lõpuni (31. august 2021) või surmani. Andmed saadi kõikide patsientide kohta.

Alkoholi tarvitamise ja suitsetamise klassifitseerimine

Vastavalt alkoholi tarvitamise harjumustele operatsioonieelses ja -järgses perioodis jaotati patsiendid kahte riskigruppi: alkoholi mitte/minimaalselt tarvitajad ja mõõdukalt/rohkelt tarvitajad. Täpsemast grupeerimisest loobuti kuna patsientide jaoks läheks täpsemate andmete raporteerimine erinevatel põhjustel keeruliseks ja see viiks ebausaldusväärsete andmete tekkele.

Suitsetamise riski hindamisel jaotati patsiendid nii operatsioonieelses kui ka -järgses perioodis kolme gruppi. Operatsioonieelsed grupid olid: mittesuitsetajad, <30 ja ≥30 pakk-aastat suitsetanud. Operatsioonijärgsed grupid olid: mittesuitsetajad/suitsetamisest loobunud, <1 paki ja ≥1 paki päevas suitsetajad.

Surmapõhjuste klassifitseerimine

Surmapõhjuste analüüs toimus juhtude üksikanalüüsina ja gruppides. Eristati nelja gruppi:

- surmad alkoholi liigtarvitamisest põhjustatud haiguste tüsistustest,
- surmad nende haiguste tüsistustest, kus suitsetamine on üks peamistest etioloogilistest faktoritest,
- KP tüsistustest tingitud surmad,
- surmad muudel põhjustel.

Pankreatikojejunostoomia uuringugrupid

Pankreatikojejunostoomia (PJ) uuringus jaotati patsiendid kahte võrdlusgruppi: 'lühikese' ja 'pika' anastomoosi grupp.

Lühikest anastomoosi kasutati ühtlaselt laienenud pankrease juha korral ja pikka anastomoosi mitmete juha ahenemiste, laienemiste ja kaltsifikaatide korral. Lühikese anastomoosi pikkuse kriteerium oli 30 kuni 50 mm, pika anastomoosi korral 50–100 mm.

KP tüsistuste klassifitseerimine

KP tüsistuste klassifikatsiooni loomisel lähtuti teaduskirjanduses tüsistuste seni toodud loeteludest, ülevaadetest nende olemuse, sageduse ja arvatavate tekkemehhanismide kohta. Selle alusel kirjeldati tüsistuste tekke patofüsioloogilised mehhanismid ja grupeeriti need vastavalt.

Kliiniliselt on otstarbekas eristada funktsionaalseid ('pankrease endo- ja eksokriinset puudulikkust') ja morfoloogilisi ('lokaalseid', 'anatoomilisi' või 'struktuurseid') tüsistusi.

Tulenevalt juhtivast patofüsioloogilisest mehhanismist, võib eristada 5 gruppi tüsistusi:

1. 'Pankrease juha tüsistused' – tekivad pankrease juha sulgusest ja rõhu tõusust juhas (pankrease fistulid ja pseudotsüstid).
2. 'Peripankreaatilised tüsistused' – valendike ahenemised või sulgused pankreast ümbritsevates tubulaarsetes struktuurides (sapiteed, duodeenum, vere-

sooned). Tekivad sidekoestumise, sidekoe kootumise ja põletikulise turse tagajärjel. Täiendavat valendiku ahenemist võib soodustada pankrease pseudotsüstist tingitud kompressioon.
3. 'Pankrease verejooksud' – tekivad pankrease või teda ümbritsevate veresoonte erosiivsest kahjustusest (rebendita ja rebenenud pseudoaneurüsmide teke).
4. 'Pankrease puudulikkus' (endo- ja/või eksokriinne) – tekib parenhüümi ulatusliku hävimise tagajärjel.
5. 'Pankrease pahaloomuline kasvaja' – tekib kroonilise põletiku mutageense toime tõttu.

Antud klassifikatsiooni on kasutatud II uuringu ('KP tüsistused kirurgiliselt ravitud kohordil') kõikide tüsistuste ja tüsistuste kirurgilise ravi mõju analüüsimisel.

10.4. Tulemused

'Pikaaegne elulemus, surma riskifaktorid ja põhjused kirurgiliselt ravitud KP kohordil'

Elulemus

KP patsientide elulemuse uuring tõi välja patsientide operatsioonijärgse riskikäitumise (jätkuva alkoholi tarvitamise ja/või suitsetamise) olulisuse. Kõikide opereeritud KP haigete osas oli standarditud suremuse kordaja 1.8. Operatsioonijärgse jätkuva alkoholi tarvitamise korral oli see 2.7. Mediaan-elulemus pärast KP kirurgilist ravi oli 13.3 aastat.

Surma riskifaktorid

Multivariantse analüüsi tulemusel oli surma suhteline risk (SR, ingl kl *Hazard ratio*) oluliselt suurem järgmiste faktorite korral:

- mõõduka/rohke alkoholi tarvitamise korral oli surma SR 2.27 (võrrelduna mitte/minimaalse alkoholi tarvitamisega),
- operatsioonieelse suitsetamise korral ≥30 pakk-aasta oli see 4.40 (võrrelduna <30 pakk-aasta suitsetajatega),
- Charlsoni kaasuvate haiguste indeksi korral ≥4 oli surma SR 3.16 ja indeksi 2-3 korral 2.53 (võrrelduna Charlsoni indeksiga 0-1),
- kehamassi indeksi korral <18.5 kg/m^2 oli surma SR 4.01 ja indeksi 18.5–24.9 korral 2.60 (võrrelduna indeksiga ≥25 kg/m^2),
- töötutel oli surma SR 2.49 (võrrelduna töötavate patsientidega).

Alkoholi ja suitsetamise koostoime analüüsil vaadeldi suitsetamise toimet kahes alkoholi tarvitamise grupis (mitte/minimaalselt ja mõõdukalt/rohkelt tarvitajatel).

Parim prognoos (10-aasta elulemus oli 94.0%) oli neil alkoholi mitte/minimaalselt tarvitajatel, kes ei suitsetanud. Sellest võrdlusgrupist oli mõõduka suitsetamise korral surma SR 2.77 ja rohke suitsetamise korral 8.30 korda suurem, ning 10-aasta elulemus vastavalt 84.0% ja 59.3%.

Sarnane seos, ent veel enam väljendunud, esines alkoholi mõõduka/rohke tarvitamise grupis. Mittesuitsetajatel oli surma SR 1.78, mõõdukalt suitsetajatel 4.93 ja rohkelt suitsetajatel 14.78 korda suurem võrdlusgrupist. 10-aasta elulemus oli vastavalt 89.0%, 73.3% ja 39.7%.

Surmapõhjused

Surmlõppeid oli jälgimisperioodil kokku 48 (29.8%). Surma põhjuste seas olid juhtivad alkoholi liigtarvitamise (21 pt) ja suitsetamisega (15 pt) seonduvate haiguste tüsistused.

Kaks patsienti (4.2%) suri KP tüsistustesse ja 10 patsienti (20.8%) muude põhjuste tõttu. Viimati nimetatud grupis oli juhtival kohal kopsupõletik (6 patsienti), kõikidel neil patsientidel esines vähemalt kaks või enam rasket kaasuvat haigust (nt maksa tsirroos, krooniline obstruktiivne kopsuhaigus, HIV-infektsioon, südamepuudulikkus, seeninfektsioon jms).

'KP tüsistused kirurgiliselt ravitud kohordil'

Tüsistuste osakaal

Kogu kirurgiliselt ravitud kohordist (166 pt) opereeriti KP lokaalsete tüsistuste tõttu 54 (32.5%). Lisaks esines lokaalseid tüsistusi veel 27 kroonilise valu tõttu opereeritud patsiendil, seega kokku oli lokaalseid tüsistusi 81 patsiendil (48.8%).

Tüsistuste analüüsimisel kasutati originaalset patofüsioloogilist klassifikatsiooni, kus tüsistused olid jagatud 5 gruppi. Preoperatiivselt esines tüsistusi järgnevalt:

- 'Pankrease juha tüsistusi' 34 (20.5%), neist 18 oli tegemist pankrease pseudotsüstiga ja 16 juhul pankrease fistulitega.
- 'Peripankreaatilisi tüsistusi' 39 (23.5%), neist kolmel patsiendil oli tegemist korraga kahe peripankreaatilise tüsistusega. Sagedaseim tüsistus oli sapiteede sulgus (29 juhtu), järgnesid duodenaalstenoos (8 juhtu) ja peripankreaatiliste veenide tromboos (5 juhtu).
- 'Pankrease verejookse' 17 (10.2%), neist 7 juhul oli tegemist rebendita ja 10 juhul rebenenud pseudoaneurüsmiga. Viimastest 6 juhul esinesid korduvad ägeda verejooksu episoodid fistuli kaudu seedetrakti, 2 juhul pankrease juhasse ja sealt duodeenumisse, 2 juhul oli tegemist pseudoaneurüsmi rebendiga *bursa omentalis'*esse.
- 'Pankrease puudulikkust' analüüsiti kahes grupis: pankrease eksokriinne puudulikkus oli 52 patsiendil (31.3%) ja suhkurdiabeet 45 patsiendil (27.1%). Vähemalt üks või mõlemad esinesid 73 patsiendil (44.0%).
- 'Pankrease pahaloomuliste kasvajate' esinemist ei analüüsitud, kuna nende esinemine enne operatsiooni oli patsientide uuringust välja lülitamise kriteerium ja uusi juhte jälgimisperioodil ei tekkinud.

Kirurgilise ravi mõju uute tüsistuste tekkele jälgimisperioodil
Mediaan jälgimisperiood oli 7.2 aastat (minimaalne 1 aasta, maksimaalne 20.6 aastat).

Kuna 'pankrease juha tüsistuste' grupis lisandus jälgimisperioodil vaid üks tüsistus ja 'pankrease verejooksude' grupis mitte ühtegi, siis nendes gruppides uute tüsistuste tekke statistilisest analüüsist loobuti. Võis tõdeda, et mõlema lokaalse tüsistuse kirurgiline ravi oli äärmiselt efektiivne ja püsiva efektiga.

'Peripankreaatiliste tüsistuste' grupis tekkis 11 patsiendil kokku 13 uut tüsistust: 8 juhul sapiteede kliiniliselt oluline ahenemine, mis vajas aktiivset ravi; 4 juhul peripankreaatiliste veenide tromboos ja ühel juhul duodenaalstenoos. Uute 'peripankreaatiliste tüsistuste' kumulatiivne 15-aasta esinemine Kaplan-Meieri järgi oli 12.1% ja summaarne esinemine koos preoperatiivselt esinenud tüsistustega 35.6%.

Uute 'peripankreaatiliste tüsistuste' suhteliselt suure osakaalu tõttu analüüsiti nende tekkimist erinevate operatsiooni meetodite kasutamise korral. Analüüs tehti kolmes operatsioonigrupis:

- pankrease drenaaž-operatsioonid,
- pankrease resektsioonid (välja arvatud Whipple'i operatsioon),
- pankreatoduodenaalne resektsioon Whipple'i järgi.

Whipple'i operatsioon eristub teistest meetoditest, kuna rajatakse sapiteede-peensoole ja mao-peensoole anastomoosid, mis võiksid aidata ennetada uusi 'peripankreaatilisi tüsistusi'. Tõepoolest, Whipple'i operatsiooni järel (11 patsienti), ei tekkinud ühtki uut 'peripankreaatilist tüsistust'. Mitte-Whipple'i resektsioonide järel (49) tekkis viis uut tüsistust ja drenaaž-operatsioonide järel (93) tekkis 8 uut tüsistust. Uute 'peripankreaatiliste tüsistuste' 15-aasta esinemine Kaplan-Meieri järgi oli vastavalt 0%, 11.4% ja 16.5%.

'Pankrease puudulikkuse' osakaal suurenes jälgimisperioodil pidevalt nii ekso- kui ka endokriinse puudulikkuse osas. Nende kumulatiivne 15-aasta esinemine Kaplan-Meieri järgi oli vastavalt 66.4% ja 47.1%. Vähemalt üks või mõlemad puudulikkused esinesid 74.5% patsientidest.

Coxi regressiooni analüüs näitas, et pankrease eksokriinse puudulikkuse tekke SR oli suurim Whipple'i operatsiooni järel, olles 9.3, mitte-Whipple'i resektsioonide järel oli SR 1.9, võrreldуna pankrease drenaaž-operatsioonidega.

Pankrease endokriinse puudulikkuse uute juhtude teke ei sõltunud oluliselt kasutatud operatsiooni meetodist. Mõnevõrra suurem diabeedi teke pankrease distaalsete resektsioonide korral ei olnud statistiliselt oluline.

'Pankreatikojejunostoomia vajalik pikkus KP ravis'
Dekomprimeeriva pankreatikojejunostoomia uuring.
Lühikese PJ korral (46 patsienti) oli anastomoosi mediaan pikkus 40 mm ja pika PJ korral (45 patsienti) 65 mm.

Lühikese PJ eelised võrreldes pikaga olid: lühem operatsiooni kestus (107.5 vs 134 min) ja väiksem patsienti osakaal, kes vajasid erütrotsüütide transfusiooni operatsioonil (0 vs 15.6%) ning kogu haiglaravi vältel (2.2 vs 31.1%).

Tüsistusi esines lühikese PJ korral 6.5% ja pika korral 17.8%, ent see vahe jäi siiski statistiliselt ebaoluliseks.

Teised kirurgilise ravi tulemuste kajastajad olid statistiliselt olulise erinevuseta:

- efektiivsus valu ja valust tingitud igapäevase elu funktsionaalsete häirete kõrvaldamisel oli suur,
- valu medikamentoosse ravi vajadus vähenes oluliselt,
- KP tõttu hospitaliseerimiste arv vähenes 95%,
- patsientide rahulolu operatsiooniga oli suur (4.9 Likerti viie astmelisel skaalal),
- muutused elukvaliteedis näitasid paranemist kõigis hinnatud kategooriates,
- haiglaravi kestuses vahet ei olnud.

10.5. Järeldused

1. Kirurgiliselt ravitud KP patsientidel oli standarditud suremuse kordaja 1.8. Patsientidel, kes ei loobunud alkoholi tarvitamisest pärast operatsiooni, oli see 2.7.
2. Oluliste surma riskifaktoritena selgusid: alkoholi tarvitamine, suitsetamine, kaasuvate haiguste esinemine, töötus ja madal kehamassi indeks.
3. KP tingitud surmade osakaal oli väike.

   Enamus surmadest olid tingitud alkoholi tarvitamise ja suitsetamisega seonduvatest haigustest ja nende tüsistustest. Seega kirurgilise ravi tulemuste parandamisel on üks olulistest võimalustest mõjutada patsiente alkoholist ja suitsetamisest jäädavalt loobuma.
4. Tuginedes senisele teaduskirjandusele defineeriti KP tüsistuste tekke peamised patofüsioloogilised mehhanismid ja selle alusel koostati uuenduslik tüsistuste klassifikatsioon. Eristati 5 gruppi tüsistusi: ‘Pankrease juha tüsistused’, ‘Peripankreaatilised tüsistused’, ‘Pankrease verejooksud’, ‘Pankrease puudulikkus’ ja ‘Pankrease pahaloomulised kasvajad’.
5. KP tüsistuste analüüsil kasutatud patofüsioloogiline tüsistuste grupeerimine võimaldas teha erinevate tüsistuste osas üldistavaid grupipõhiseid analüüse ja järeldusi, mis senises teaduskirjanduses praktiliselt puudusid.
6. Grupipõhine tüsistuste analüüs näitas ära erinevate operatsioonimeetodite eelised ja puudused tüsistuste ravis. See omakorda on abiks raviotsuste tegemisel ja operatsioonimeetodi valikul – tüsistuste olemus ja planeeritava ravi oodatavad efektid peavad olema kooskõlas.
7. Nende KP patsientide kirurgilises ravis, kellel on tegemist ühtlaselt laienenud pankrease juhaga, tagab lühike PJ küllaldase juha dekompressiooni. Kuna lühikese PJ kirurgilise ravi karakteristikud on paremad pika PJ omadest, on lühikese anastomoosi kasutamine eelistatud ühtlaselt laienenud pankrease juha korral.

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12. PUBLICATIONS

13. CURRICULUM VITAE

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Education

2018–2022	University of Tartu, Faculty of Medicine, PhD studies
1990–1991	University of Tartu, Faculty of Medicine, Internship in general surgery
1984–1990	University of Tartu, Faculty of Medicine, MD degree *cum laude*
1973–1984	Türi Secondary School

Professional employment

2000–…	Tartu University Hospital, Surgery Clinic, Department of General Surgery and Plastic Surgery, senior surgeon, No of performed operations 9300
2015–…	Tartu University Hospital, Centre of Transplantation, transplant surgeon, head of the pancreas transplant program
2018–…	University of Tartu, contractual lecturer
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2015–…	Courses of 'Advanced Trauma Life Support', co-director
2017–…	Courses of 'Definitive Surgical Trauma Care', instructor
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2005–2017	University of Tartu, Clinic of Anesthesiology and Intensive care, lecturer
1995–2005	University of Tartu, Chair of Cardiothoracic and Vascular Surgery, assistant
1991–2000	Tartu Maarjamõisa Hospital, I Department of Surgery, general surgeon

Scientific work and other professional activities

Research fields:

Surgical pancreatology, Hernia surgery, Trauma surgery, Acute abdomen, Acute mesenteric ischemia, Endocrine surgery, Quality and safety in surgery

Publications:

58 (including 14 articles in international peer-review journals)

Estonian clinical guidelines (diagnosis and treatment):
- Gallstone disease (2003), head of the guidelines working group;
- Acute pancreatitis (2004), head of the guidelines working group;
- Abdominal wall hernias (2005), head of the guidelines working group;
- Acute abdomen (2008), head of the guidelines working group;
- Trauma (2009), head of the guidelines working group;
- Registration of complications (2013), head of the working group;
- Transfusion (2022), member of the guidelines working group

Estonian national clinical audits (Quality of surgical service) in:
- Emergency surgery (2004), auditor
- Peptic ulcer perforations (2005), auditor
- Day surgery (2006), auditor
- Acute pancreatitis (2007), auditor
- Acute abdomen (2010 and 2015), auditor

Surgical trainings

30.09.1993	'Surgical service in disasters' (1 week, Riga, Latvia)
02.07.1994	'I Surgical training at Frankfurt University Hospital' (3 months, Germany)
16.11.1994	'Surgical training at Sandviken Hospital' (1 month, Sweden)
01.08.1997	'II Surgical training at Frankfurt University Hospital' (3 months, Germany)
26.09.1998	'XI Surgical week – pancreatic surgery' (1 week, Ulm, Germany)
06.06.2000	'Surgical service in Disaster medicine' (2 weeks, Reikjavik, Island)
12.11.2000	'XIII Surgical week – pancreatic surgery' (1 week, Ulm, Germany)
12.10.2001	'XIV Surgical week – pancreatic surgery' (1 week, Ulm, Germany)
2003-2006	'International Course Pancreas-2000' (6 weeks, Sweden, Norway, Denmark, Germany)
03.01.2005	'Indonesian earthquake relief' (2 weeks, Banda-Aceh, Indonesia)
10.09.2011	'Surgical training in pancreas transplant' (1 month, Innsbruck, Austria)
01.08.2012	'Surgical training in pancreas transplant' (1 month, Munich, Germany)
01.09.2014	'Surgical training in pancreas transplant' (3 weeks, Oslo, Norway)

Memberships

2021–…	'Pancreatology' (journal), reviewer
2015–…	Scandiatransplant, Nordic Pancreas and Islet Transplant Group
2015–…	Council of Centre of Transplantation of Tartu University Hospital
2015–…	'Estonian physician' (journal), reviewer
2011–…	'Gastroenterology review' (journal), member of editorial board
1989–…	Tartu Surgeons' Association (1995–2001 secretary of the Board)

2003–2015 Scandinavian-Baltic Pancreatic Club
2001–2004 Estonian Association of Surgeons, secretary of the Board
1994–2006 German Association of Surgeons

14. ELULOOKIRJELDUS

Nimi:	Marko Murruste
Sünniaeg:	28. oktoober 1965
Kodakondsus:	Eesti
Aadress:	Pihla talu, Oomiste küla, Kambja vald, Tartu maakond, 62014 Fortuuna 1-33, Tartu, 50603
Telefon:	+372 5331 8065; +372 731 8065
E-mail:	marko.murruste@kliinikum.ee

Hariduskäik

2018–2022	Tartu Ülikool, Meditsiiniteaduste valdkond, doktroiõpe
1990–1991	Tartu Ülikool, Arstiteaduskond, internatuur üldkirurgias
1984–1990	Tartu Ülikool, Arstiteaduskond, arstiteaduse põhiõpe *cum laude*
1973–1984	Türi Keskkool

Teenistuskäik

2000–…	Tartu Ülikooli Kliinikum, Kirurgiakliinik, üldkirurgia ja plastikakirurgia osakonna üldkirurgia vanemarst-õppejõud, läbi viidud operatsioonide arv ca 9300
2015–…	Tartu Ülikooli Kliinikum, Transplantatsioonikeskuse transplantatsiooni kirurg, pankrease siirdamise programmi juht
2018–…	Tartu Ülikool, lepinguline lektor
2004–…	Järvamaa Haigla, kirurgilise teenistuse kuraator
2015–…	‘Advanced Trauma Life Support’ kursuse kaasdirektor
2017–…	‘Definitive Surgical Trauma Care’ kursuse instruktor
2017–…	‘Advanced Surgical Skills of Exposure for Trauma’ kursuse instruktor
2005–2017	Tartu Ülikool, Anestesioloogia ja intensiivravi kliiniku lektor
1995–2005	Tartu Ülikool, Kardiotorakaal- ja vaskulaarkirurgia õppetooli assistent
1991–2000	Tartu Maarjamõisa Haigla, I kirurgia osakonna üldkirurg

Teadus- ja muud erialased tegevused

Uurimisvaldkonnad: kirurgiline pankreatoloogia, kõhuseina songade kirurgia, raske trauma käsitlus, ‘äge kõht’, äge mesenteriaalisheemia, endokriinkirurgia, kirurgiateenistuse kvaliteet ja ohutus.

Publikatsioonid:
58 (neist 14 rahvusvahelistes eelretsenseeritavates ajakirjades)

Eesti ravijuhendid (1.–6. töögruppide juht, 7. töögrupi liige):
1. ‘Sapikivitõbi’ (2003),
2. ‘Äge pankreatiit’ (2004),
3. ‘Kõhuseina songad’ (2005),
4. ‘Äge kõht’ (2008),
5. ‘Kehatüve trauma’ (2009),
6. ‘Tüsistuste registreerimise printsiibid’ (2013),
7. ’Transfusioonravi I’ (2022).

Eesti kirurgiateenistuse kvaliteedi auditid (audiitor):
1. ‘Erakorraline kirurgia’ (2004),
2. ‘Peptilise haavandi perforatsioonid’ (2005),
3. ‘Päevakirurgia’ (2006),
4. ‘Äge pankreatiit’ (2007),
5. ‘Äge kõht’ (2010),
6. ‘Äge kõht’ (2015).

Kirurgilised enesetäiendused

30.09.1993	‘Kirurgiline abi katastroofide korral’ (1 nädal, Riia, Läti)
02.07.1994	‘I täiendus Frankfurdi Ülikooli Kirurgiakliinikus’ (3 kuud, Saksamaa)
16.11.1994.	‘Täiendus Sandvikeni Haiglas’ (1 kuu, Rootsi)
01.08.1997	‘II täiendus Frankfurdi Ülikooli Kirurgiakliinikus’ (3 kuud, Saksamaa)
26.09.1998	‘XI Pankrease kirurgia nädal’ (1 nädal, Ulmi Ülikool, Saksamaa)
06.06.2000	‘Kirurgiline abi katastroofide korral’ (2 nädalat, Reikjavik, Island)
12.11.2000	‘XIII Pankrease kirurgia nädal’ (1 nädal, Ulmi Ülikool, Saksamaa)
12.10.2001	‘XIV Pankrease kirurgia nädal’ (1 nädal, Ulmi Ülikool, Saksamaa)
2003–2006	‘Rahvusvaheline programm Pancreas-2000’ (6 nädalat, Rootsi, Norra, Taani, Saksamaa)
03.01.2005	‘Kirurgiline abi katastroofide korral’ (2 nädalat, Indoneesia)
10.09.2011	‘Täiendus pankrease siirdamise alal’ (1 kuu, Innsbruck, Austria)
01.08.2012	‘Täiendus pankrease siirdamise alal’ (1 kuu, München, Saksamaa)
01.09.2014	‘Täiendus pankrease siirdamise alal’ (3 nädalat, Oslo, Norra)

Liikmelisus

2021–…	Ajakirja ‘Pancreatology’ retsensentige kogu liige
2015–…	Tartu Ülikooli Kliiinikumi Transplantatsioonikeskuse Nõukogu liige
2015–…	Scandiatransplant, ‘Nordic Pancreas and Islet Transplant Group’ liige
2015–…	Ajakirja ‘Eesti Arst’ retsensentige kogu liige
2011–…	Ajakirja ‘Gastroenterology review’ toimetuse liige
1989–…	Tartu Kirurgide Seltsi liige (1995–2001 juhatuse sekretär)
2003–2015	Skandinaavia-Balti Pankrease Klubi liige
2001–2004	Eesti Kirurgide Assotsiatsiooni juhatuse sekretär
1994–2006	Saksa Kirurgide Seltsi liige

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