Tampere University

YRJÖ VAALAVUO

Pancreatic Cystic Neoplasms

Treatment, Surveillance and Prognosis

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ACADEMIC DISSERTATION
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ABSTRACT

Background. Incidence of pancreatic cysts is rising. The main reasons for this increase are ageing population, better imaging modalities and an increase in the use of imaging tests. Most pancreatic cysts are found incidentally while other medical issues are being addressed. The largest group of pancreatic cysts are intraductal papillary mucinous neoplasms (IPMN). IPMN tumours can be further divided into branch-duct (BD), main-duct (MD) and mixed-type IPMN. The malignant potential of IPMN:s is dependent on the grade of dysplasia. All IPMN tumours have the potential to develop into invasive carcinoma, but the risk is lowest in BD subtype. Most pancreatic cysts do not require surgical resection, but lifelong surveillance is warranted in many cases. There are several guidelines to help clinical decision-making in managing pancreatic cystic neoplasms (PCN). Current guidelines include several controversies regarding the intensity and methods of surveillance. Indications for surgery also vary between different guidelines. Although this field of medicine has been rigorously studied in recent years, not enough is known about whether to operate or to follow a cyst or even if either course of action is necessary. Pancreatic cysts cause a substantial economic burden for the health care system and also a mental burden for patients.

Aims. The aim of this study was to identify nationwide patient characteristics, prognostic factors of resected PCNs and to assess long-term survival of patients with resected IPMN tumours. A further aim was to evaluate the effectiveness and feasibility of the current IPMN surveillance guidelines in clinical practice by analysing the development of indications for surgery.

Materials and methods. In Study I data on all pancreatic resections performed in Finland in the period 2000-2008 were identified by combining data from the national operations register and patient archives records. Preoperative, operative and follow-up data were gathered. Histopathological slides were re-assessed whenever necessary. Short and long-term survival was recorded. Study II was a retrospective analysis of all IPMN tumours operated on in Finland in the period 2000-2008. Imaging studies were re-evaluated. Survival data were collected over a 10-year follow-up period. Study III was a prospective cohort study of IPMN tumours under

surveillance in Tampere University Hospital in the years 2013-2018. Surveillance was performed according to the European guidelines on PCN.

Results. In Study I, out of 2,024 patients who underwent pancreatic surgery, PCN was found in 225 cases. This study revealed that one fourth of the tumours were malignant. Histological re-assessment moreover revealed that a third of IPMNs were misdiagnosed as other PCNs. In Study II 88 resections were performed with confirmed IPMN histology (47 MD-IPMNs, 27 MT-IPMNs, 14 BD-IPMNs), and overall 44% of these patients had a malignant tumour. Malignancy was detected on 7% of BD-IPMN patients and 62% of MD-IPMN patients. Ten-year survival for patients with malignant tumours was 23% compared to 73% in benign cases. Out of 128 patients included in Study III, 23 were operated on upfront and malignant IPMN tumour was detected in four out of 23 patients. Out of 105 patients under surveillance two were operated on; both patients had low grade dysplasia (LGD) in final histological analysis. Median follow-up time in the surveillance group was 26 months. Relative indication for surgery was detected in 16% of the patients during surveillance. Nearly 15% became unfit for surgery during the surveillance period.

Conclusions. Most PCN are benign and do not require surgical management at any time. The malignant potential of IPMN tumours is dependent on the degree of dysplasia and on the subtype of the IPMN tumour. Surgery before the tumour has transferred to malignant is the most important prognostic factor. The challenge lies in detecting potentially harmful lesions necessitating treatment before they become malignant. More knowledge of these tumours is needed order to avoid unnecessary examinations and surgical operations. A shift in the landscape of treating PNCs can be detected between Studies I and II (the years 2000-2008) compared to Study III (2013-2018) due to better diagnostics and the introduction of guidelines has caused far more meticulous examination of each case of PCNs.

TIIVISTELMÄ

Taustaa. Haiman kystisten kasvainten esiintyvyys on kasvussa. Kolme merkittävintä tekijää tämän muutoksen taustalla ovat väestön ikääntyminen, tarkemmat kuvantamistutkimukset ja niiden lisääntynyt käyttö. Suurin osa haiman kystisistä kasvaimista todetaan sattumalta selvitettäessä muita sairauksia. Näiden kasvainten suurin alaryhmä on intraduktaalinen papillaarinen musinoosi kasvain (IPMN). IPMN-kasvaimet voidaan jakaa edelleen päätiehyt-, sivutiehyt- ja sekatyyppisiin kasvaimiin. IPMN-kasvainten riski muuttua pahanlaatuiseksi riippuu dysplasian asteesta. Kaikki IPMN-kasvaimet voivat muuttua pahanlaatuisiksi, mutta riski on pienin sivutiehyt-IPMN:ssä. Suurin osa haiman kystisistä kasvaimista ei vaadi leikkaushoitoa, kuitenkin loppuelämän kestoinen seuranta on usein suositeltua ja hoitoratkaisujen tukena käytetään kansainvälisiä hoitosuosituksia. Nykyisissä hoitosuosituksissa on ristiriitaisuuksia liittyen seurannan intensiteettiin ja kestoon. Lisäksi eri hoitosuositusten leikkausindikaatioissa on eroja. Vaikka haiman kystisiä kasvaimia on tutkittu runsaasti viime vuosina, ei silti ole vahvaa näyttöä, milloin haiman kystinen kasvain tulisi leikata, miten kystaa tulisi seurata vai onko seuranta lainkaan tarpeen. Haiman kystisten kasvainten hoidosta, etenkin seurannasta, kertyy merkittävä rasite sekä potilaille että terveydenhuollon resursseille.

Tavoitteet. Tämän väitöskirjakokonaisuuden tarkoituksena oli selvittää Suomessa leikattujen kystisten haimakasvainten erityispiirteitä sekä selvittää haimakysta-potilaiden ennustetta ja siihen vaikuttavia tekijöitä. Lisäksi tutkimuksessa selvitettiin nykyisten hoitosuosituksien käytettävyyttä kliinisessä työssä analysoimalla leikkausindikaatioiden kehittymistä.

Aineisto ja menetelmät. Ensimmäiseen osatyöhön poimittiin kansallisen hoitoilmoitusrekisterin (HILMO) ja potilastietojärjestelmien tietokannoista kaikki Suomessa tehdyt haimaleikkaukset vuosilta 2000–2008. Potilaista kerättiin esitiedot, leikkauslöydökset ja seurantatiedot. Tarvittaessa histologinen analyysi uusittiin. Toinen osatyö oli retrospektiivinen analyysi kaikista Suomessa vuosina 2000–2008 leikatuista IPMN-kasvaimista. Seurantatiedot kerättiin 10 vuoden ajalta leikkauksesta. Kuvantamistutkimukset analysoitiin uudestaan. Kolmannen osatyön aineistona oli prospektiivinen rekisteri vuosina 2013–2018 seurannassa olevista

haimakystistä Tampereen Yliopistollisessa sairaalassa. Seuranta suoritettiin eurooppalaisen hoitosuosituksen mukaan.

Tulokset. Ensimmäisessä osatyössä haimaleikkauksia oli tehty 2,024, joista 225 oli suoritettu haiman kystisen kasvaimen vuoksi. Tutkimuksessa todettiin, että neljännes kystisistä kasvaimista oli pahanlaatuisia. Lisäksi histologisessa uusinta-analyysissä todettiin, että kolmannes IPMN-kasvaimista oli tulkittu muiksi kystisiksi kasvaimiksi. Toisessa osatyössä potilasmateriaalina oli 88 potilasta, joilta oli leikattu histologisesti varmistettu IPMN-kasvain (47 Päätiehyt IPMN-kasvainta, 27 Sekatyyppistä IPMN-kasvainta, 14 Sivutiehyt IPMN-kasvainta). Pahanlaatuinen kasvain todettiin yhteensä 44 %:lla leikatuista. Pahanlaatuinen kasvain todettiin 7 %:lla sivutiehyt-IPMN:ssä ja 62 %:lla päätiehyt IPMN:ssä. Kymmenen vuoden eloonjäämisennuste oli 23 % potilailla, joilla todettiin pahanlaatuinen kasvain ja kasvaimen ollessa hyvänlaatuinen, ennuste oli 73 %. Kolmannen osatyön potilasrekisterissä oli mukana 128 potilasta, joista 23 leikattiin suoraan ilman seurantaa ja näistä potilaista neljällä todettiin pahanlaatuinen IPMN-kasvain. Seurantaan jääneistä 105 potilaasta kaksi potilasta leikattiin seuranta-aikana ja molemmilla todettiin histopatologisessa analyysissä matala-asteinen dysplasia. Mediaani seuranta-aika oli 26 kuukautta. Relatiivinen leikkausindikaatio todettiin 16 %:lla potilaista seurannan aikana. Lähes 15 %:lla potilaista yleiskunto huonontui seurantajakson aikana niin, ettei potilas enää ollut kirurgisen hoidon piirissä.

Johtopäätökset. Tutkimuksemme osoitti, että suurinta osaa haiman kystisistä kasvaimista ei tarvitse missään vaiheessa hoitaa kajoavilla toimenpiteillä. IPMN-kasvaimen taipumus muuttua syöväksi riippuu pahanlaatuisuuden asteesta ja IPMN-kasvaimen alatyypistä. Lisäksi todettiin, että leikkaus ennen kasvaimen muuttumista pahanlaatuiseksi on merkittävin ennusteeseen vaikuttava tekijä. Haasteena on löytää ne potilaat riittävän ajoissa (ennen kasvaimen muuttumista pahanlaatuiseksi), jotka hyötyvät leikkaushoidosta. Lisää tutkimustietoa tarvitaan, että voidaan välttyä tarpeettomilta tutkimuksilta ja kirurgisilta toimenpiteiltä. Haimakystien tutkiminen on muuttunut merkittävästi ensimmäisten kahden (vuodet 2000–2008) ja kolmannen (vuodet 2013–2018) osatyön välillä. Paremman diagnostiikan ja hoitosuositusten käyttöönoton jälkeen haimakystien diagnostiikka ja hoito on muuttunut järjestelmällisemmäksi.

ORIGINAL PUBLICATIONS

Publication I

Vaalavuo Y, Antila A, Ahola R, Siiki A, Vornanen M, Ukkonen M, Sand J, Laukkarinen J. Characteristics and long-term survival of resected pancreatic cystic neoplasms in Finland. The first nationwide retrospective cohort analysis. Pancreatology. 2019 Apr;19(3):456-461.

Publication II

Vaalavuo Y, Vornanen M, Ahola R, Antila A, Rinta-Kiikka I, Sand J, Laukkarinen J. Long-term (10-year) outcomes and prognostic factors in resected intraductal papillary mucinous neoplasm tumors in Finland: A nationwide retrospective study. Surgery. 2023 Apr 14:S0039-6060(23)00059-4. doi: 10.1016/j.surg.2023.02.006.

Publication III

Vaalavuo Y, Siiki A, Antila A, Rinta-Kiikka I, Sand J, Laukkarinen J. The European evidence-based guidelines on pancreatic cystic neoplasms (PCN) in clinical practice: The development of relative and absolute indications for surgery during prospective IPMN surveillance. Pancreatology. 2020 Oct;20(7):1393-1398.

The publications are referred to in the text by their Roman numerals.

AUTHOR'S CONTRIBUTION

Study I

The author conceived the study together with his supervisors, contributed to data collection and reviewed the patient records. He performed the data analysis and wrote the manuscript with input from the co-authors.

Study II

The study design was done by the author in consultation with the supervisors. The author collected and analysed the study data and wrote the manuscript.

Study III

The study was designed by the author with the help of the supervisors. The author gathered and analysed the data. The manuscript was composed by the author in consultation with the other authors.

The author carried out the submission process and revisions were made by the author with help from the supervisors and other contributors.

ABBREVATIONS

AGA	American Gastroenterological Association
AJCC	American Joint Committee on Cancer
BD-IPMN	Branch duct intraductal papillary mucinous neoplasm
CA 19-9	Carbonhydrate antigen 19-9
C-D	Clavien-Dindo
CP	Central pancreatectomy
CEA	Carcinoembryonic antigen
CEUS	Contrast-enhanced endoscopic ultrasound
CT	Computer tomography
DM	Diabetes mellitus
DNA	Deoxyribonucleic acid
DP	Distal pancreatectomy
DSS	Disease-specific survival
EUS	Endoscopic ultrasound
ERCP	Endoscopic retrograde cholangiopancreatography
FDG-PET	Fluorodeoxyglucose positron emission tomography
FNA	Fine needle aspiration
DGE	Delayed gastric emptying
GNAS	Guanine-nucleotide-binding protein-alpha stimulating
HGD	High-grade dysplasia
IAP	International Association of Pancreatology
INV	Invasive carcinoma
IPMN	Intraductal papillary mucinotic neoplasm
IU	International unit
KRAS	Kirsten rat sarcoma virus
LGD	Low-grade dysplasia
MCN	Mucinous cystic neoplasm
MD-	IPMN Main duct intraductal papillary mucinous neoplasm
MIS	Mini-invasive surgery
MPD	Main pancreatic duct
MRCP	Magnetic resonance cholangiopancreatography

MRI	Magnetic resonance imaging
MT-IPMN	Mixed-type intraductal papillary mucinous neoplasm
NGS	Next-generation sequencing panel
PanIN	Pancreatic intraepithelial neoplasms
PCN	Pancreatic cystic neoplasms
PD	Pancreaticoduodenectomy
PDAC	Pancreatic ductal adenocarcinoma
POPF	post-operative pancreatic fistula
PPH	post pancreatectomy haemorrhage
R-0	microscopically margin-negative resection
RNA	Ribonucleic acid
SCN	Serous cystic neoplasm
SPN	Solid pseudopapillary neoplasm
US	Ultrasonography
WHO	World Health Organization

CONTENTS

1 INTRODUCTION

Pancreatic cystic neoplasms (PCN) consist of a heterogenous group of tumours in which the malignant potential varies from zero to highly malignant. Cystic lesions can be divided into pseudocysts (usually caused by trauma or infections) and true pancreatic cystic lesions. PCNs are usually found incidentally in cross-section imaging. Numbers of incidentally found PCNs are rising, and their management causes a substantial burden on the healthcare system (McDonald et al., 2015). Some studies have reported incidental PCNs in 30-49% of patients in cross-section imaging (Kromrey et al., 2018). The high prevalence of PCNs is also confirmed in autopsies (Kimura et al., 1995).

The most common PCN is intraductal papillary mucinotic neoplasm (IPMN) (Valsangkar et al., 2012). These tumours can be further divided into branch duct IPMN (BD-IPMN), main duct IPMN (MD-IPMN) and mixed-type IPMN (MT-IPMN) depending on their anatomic location. Risk assessment of PCNs is usually made using cross-section imaging and laboratory tests. In selected cases endoscopic ultrasound (EUS) can be used.

The prognosis of PCN patients depends on the type of lesion and the degree of dysplasia. While serous cystic neoplasms (SCN) carry almost zero malignant potential and are treated conservatively, malignant, resected IPMNs have 17-65% five-year survival (Roldán et al., 2023; McMillan et al., 2016; Gavazzi et al., 2022).

Several guidelines may be used to help in the management of PCNs. In Finland, the European evidence-based guidelines on PCNs are generally used (European Study Group on Cystic Tumours of the Pancreas, 2018). Also, the International Association of Pancreatology (IAP) and the American Gastroenterological Association (AGA) have published their own guidelines (Tanaka et al., 2017; Vege et al., 2015). The European guidelines cover all the most common PCNs such as IPMN, mucinous cystic neoplasm (MCN), SCN and solid pseudopapillary neoplasm (SPN). The IAP guidelines focus solely on IPMN tumours while the AGA guidelines focus on asymptomatic PCNs. Each of these guidelines includes recommendations for diagnostics, surveillance, operative treatment and post-operative care including follow-up. In the case of IPMN tumours the guidelines mention several signs, for

example main pancreatic duct dilatation, as indications for surgery, which leads to recommending pancreatic surgery, while also taking note of the patient's general condition. If surgery is not recommended, patients fit enough for surgery are recommended to be followed-up. There are several controversies between different guidelines. The various guidelines differ in their recommendations on length, intensity and method of surveillance. Indications for surgery likewise vary.

The controversies in the guidelines reflect the lack of evidence on treating PCN patients. Lack of evidence also leads to poor accuracy in these guidelines, which can lead to unnecessary operations (Lekkerkerker et al., 2017; Nadine et al., 2023). The Interest in studying PCNs has been high in recent years and a better understanding of the disease is needed order to choose the right follow-up and treatment option for each patient **(table 3)**.

This thesis focuses on the characteristics, operative treatment and prognosis of pancreatic cystic tumours in Finland with additional focus on IPMN surveillance in Tampere University Hospital.

2 REVIEW OF THE LITERATURE

2.1 Anatomy and physiology of the pancreas

2.1.1 Location and macroscopic anatomy

The pancreas is a retroperitoneal organ with an average volume of 72.7 cm^3 (Szczepaniak et al., 2013). The hook shaped, approximately 15cm long pancreas is divided into four parts: head, neck, body and tail. The head of the pancreas is surrounded by a loop of the duodenum, the superior mesenteric artery and vein pass behind the neck of the pancreas, the stomach is in front of the body of the pancreas and the pancreatic tail extends to the hilum of the spleen (Henry et al., 2019).

2.1.2 Ductal system

The pancreatic duct (duct of Wirsungianus) passes through the whole pancreas and joins the common bile duct at the ampulla of Vater (Henry et al., 2019). The pancreatic duct drains into the duodenum at the major papilla of the duodenum (papilla of Vater). The accessory pancreatic duct (of Santorini) drains independently into the duodenum and is present in approximately 40% of the population. There are also other less common variations in pancreatic duct anatomy such as pancreas divisum (the pancreatic ducts are not fused and most pancreatic secretions drain through the minor papilla) and pancreas annulare (the pancreatic tissue wraps around the descending duodenum) (Yu et al., 2006; Kamisawa et al., 2010; Prasanna et al.,2015). The pancreatic duct is slightly narrower at the tail compared to the head and its diameter increases in older population. There is no consensus on the normal pancreatic duct diameter but usually <3mm is considered normal (Frøkjær et al., 2020).

2.1.3 Physiology

The function of the exocrine pancreas is the secretion of digestive enzymes to the gastrointestinal tract. The exocrine pancreas is primarily composed of acinar and ductal cells. Connected conical shaped acinar cells construct a central lumen, in which the cells secrete digestive enzymes such as trypsinogen, chymotrypsinogen, lipase, phospholipase, amylase, carboxypeptidase and elastase. The pancreatic ducts are classified into four types; intercalated ducts (receive secretions from acini, flattened cuboidal epithelium), intralobular ducts (receive secretions from intercalated ducts, cuboidal epithelium), interlobular ducts (receive secretions from intralobular ducts, cuboidal and columnar epithelium) and the main pancreatic duct (receives secretions from interlobular ducts, columnar epithelium). The ductal cells form the pancreatic ductal system, which drains digestive enzymes to the duodenum, where most of the enzymes are activated (Henry et al., 2019; Szlachcic et al., 2021). The ductal system secretes bicarbonate-rich fluid when at rest 0.2-0.3mL/min and up to 4.0mL/min when stimulated by food. Total exocrine secretion amounts to 2000-3000ml per day (Pandol, 2010; Ishiguro et al.,2012).

The tissue of the endocrine pancreas is constructed of islet cells and its mass is 1-2% of the mass of the pancreas. The endocrine pancreas distributes hormones such as glucagon, insulin, somatostatin, pancreatic polypeptide and ghrelin via the bloodstream to the target organs (Henry et al., 2019; Szlachcic et al., 2021).

2.2 Pancreatic neoplasms

Pancreatic tumours include a broad spectrum of different tumours from entirely benign to highly malignant tumours. Pancreatic tumours can be divided by malignant potential into benign, pre-malignant or malignant neoplasms (**Table 1**).

Table 1. WHO classification of tumors of the pancreas (5th edition) (Digestive System Tumours: WHO Classification of Tumours 5th Edition 2019)

Benign tumours and precursors	**Malignant tumours**
Serous cystadenoma	Ductal adenocarcinoma,
Glandular intraepithelial neoplasia, PanINs	Acinar cell carcinoma
Intraductal papillary mucinous neoplasm (IPMN)	Pancreatoblastoma
Intraductal oncocytic papillary neoplasm	Solid pseudopapillary neoplasm (SPN)
Intraductal tubulopapillary neoplasm	Neuroendocrine neoplasm
Mucinous cystic neoplasm (MCN)	

2.3 Pancreatic cystic neoplasms (PCN)

Cystic pancreatic lesions can be classified into epithelial and non-epithelial lesions. Pseudocysts are usually complications of trauma or infections (usually pancreatitis). They are not neoplasms and have no malignant potential. Cystic tumours can be classified histologically into epithelial and non-epithelial and by malignant potential into neoplastic and non-neoplastic (**Table 2, Figure 1**).

Table 2. Classification of cystic lesions of the pancreas according to European Study Group of Cystic Tumours of the Pancreas (European Study Group on Cystic Tumours of the Pancreas., 2018)

Epithelial neoplastic	**Epithelial non-neoplastic**
Intraductal papillary mucinous neoplasm (IPMN)	Lymphoepithelial cyst
Mucinous cystic neoplasm (MCN)	Mucinous non-neoplastic cyst
Serous cystic neoplasm (SCN)	Enterogenous cyst
Serous cystadenocarcinoma	Retention cyst/dysontogenic cyst
Cystic neuroendocrine G1-2	Peri-ampullary duodenal wall cyst
Acinar cell cystadenoma	Endometrial cyst
Cystic acinar cell carcinoma	Congenital cyst (in malformation syndromes)
Solid pseudopapillary neoplasm (SPN)	
Accessory-splenic epidermoid cyst	
Cystic hamartoma	
Cystic teratoma	
Cystic ductal adenocarcinoma	
Cystic pancreatoblastoma	
Cystic metastatic epithelial neoplasm	
Others	
Non-epithelial neoplastic	**Non-epithelial non neoplastic**
Benign non-epithelial neoplasm (e.g. lymphangioma)	Pancreatitis-associated pseudocyst
Malignant non-epithelial neoplasm (e.g. sarcomas)	Parasitic cyst

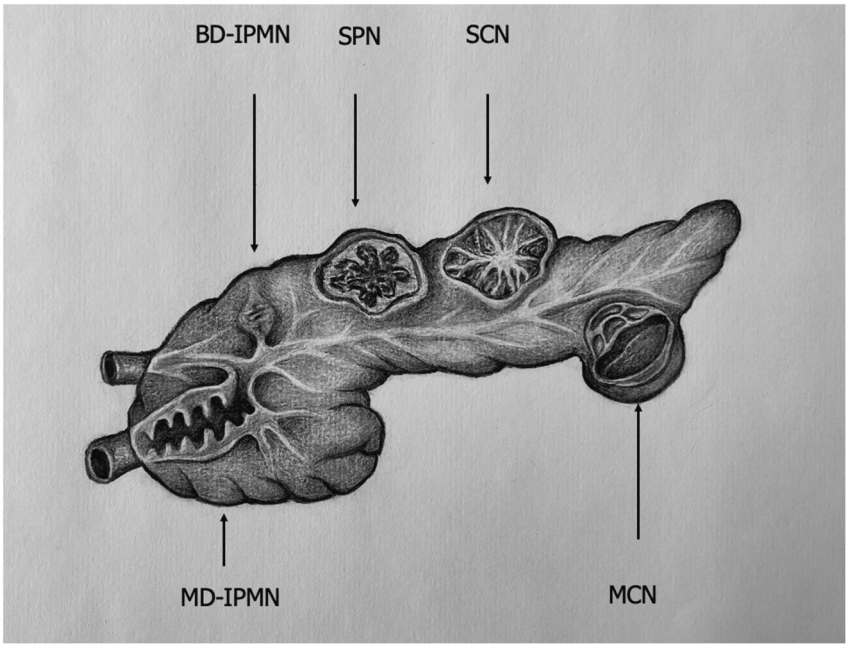

Figure 1. Cystic tumours of the pancreas (courtesy of Kaisa Vaalavuo)

2.3.1 Intraductal papillary mucinous neoplasm (IPMN)

2.3.1.1 Definition and characteristics

IPMN was described for the first time in the 1980s and was included in the WHO classification system in 1996. In the WHO classification IPMN is defined as a grossly visible, predominantly papillary or rarely flat, noninvasive mucin-producing epithelial neoplasm arising in the main pancreatic duct (MPD) or branch ducts. IPMN tumours are also classified by the involvement of the pancreatic duct system; MD-IPMN is dilatation of the main pancreatic duct (other reasons for obstruction having been excluded). MPD dilatation can be divided into segmental (dilatation in only part of the MPD) and diffuse (dilatation of the whole MPD) (Jung et al., 2022). BD-IPMN arises from branch ducts and MT involves both branch and MPD. IPMNs are distinguished from pancreatic intraepithelial neoplasms (PanINs) and incidental microcysts by size; IPMN are usually required to be > 1cm in diameter (there is no consensus on the minimal size of the IPMN and radiologists often diagnose cysts <1cm as BD-IPMN) (Adsay et al., 2016). IPMNs can moreover be divided into four

morphological subtypes; gastric, intestinal, oncocytic and pancreatobiliary. (Distler et al., 2013; Castellano-Megías et al., 2014; Kwon et al., 2019; Fuji et al., 2021). IPMNs are mostly located on the head of the pancreas but may occur in any part of the pancreas (**Figure 2 and 3**) (Kerlakian et al., 2019).

BD-IPMNs can be visualized in cross-section imaging as single or in clusters of small grape-like cysts. In most cases, communication between cyst and a normal-calibre MPD can be seen. In complicated cases septaes, nodules, enhancing or thickened wall can be visualized. Dilatation of the MPD can be a sign of complicated IPMN. MT-IPMNs have imaging features of both MD and BD-IPMN (**Table 4**) (Pedrosa et al., 2010; Lim et al., 2001). The distribution of IPMN subtypes varies in surgical series: BD 22-76%, MT 8-53%, MD 18-26%; Lafemina et al., 2013; Hipp et al.,2019).

Figure 2. MRI examination of Branch duct intraductal papillary mucinous neoplasm, Main duct intraductal papillary mucinous neoplasm and Mixt-type intraductal papillary mucinous neoplasm (Laukkarinen, 2019)

IPMN tumours are graded by the WHO to low-grade dysplasia (LGD), high-grade dysplasia (HGD) and invasive carcinoma (INV). The American Joint Committee on Cancer (AJCC) staging system 8th edition for Pancreatic ductal adenocarcinoma (PDAC) is also validated for staging invasive IPMN carcinoma (Adsay et al., 2016; Fan et al., 2019; Margonis et al., 2023).

2.3.1.2 Epidemiology

IPMN is the most common PCN in surgical series (27-38% of PCNs) and is usually detected incidentally (Gaujoux et al., 2011; Valsangkar et al., 2012). The are no population-based publications on the incidence and prevalence of IPMN tumours without selection bias. In a single population-based study, the incidence of IPMN was 2/100,000 person/year and prevalence 26/100,000. However, the incidence of

IPMN is rising; in the same study the incidence increased from 0.3/100,000 in the period 1984-1985 to 4.5 in the period 2004-2005 (Reid-Lombardo et al., 2008). Kromrey et al. detected a pancreatic cyst in 49% of the 1,077 patients in a population-based study. In five-year surveillance, the incidence was 2.6%/year (Kromrey et al., 2018). Cysts were not further analysed, but estimates can be made of a high rate of IPMN tumours given the rate of IPMN tumours among all PCNs. There are at least three reasons for the increase in the prevalence of IPMNs. First, cross-section imaging modalities are developing and are used more often, which leads to more unsuspected pancreatic cysts being found (McDonald et al., 2015). Second, the population is ageing and the incidence of IPMN is higher in elderly individuals (Ricci et al., 2019). Third, IPMN tumours were previously more misdiagnosed, for example as MCNs (Niedergethmann et al., 2008).

Apart from the age of the patient, there are other risk factors for developing IPMN: diabetes mellitus (DM), especially with use of insulin, chronic pancreatitis and family history of PDAC. IPMNs are slightly more common in males. Some of the risk factors are partially overlapping with IPMN and PDAC risk factors. (Capurso et al., 2013).

2.3.1.3 Malignant potential and risk factors

In surgical series the rates for malignant tumours vary: BD-IPMN 3-45%, MD-IPMN 36-64% and MT-IPMN 12-57% (Schnelldorfer et al., 2008; Yan et al., 2017; Watanabe et al., 2018; Hipp et al., 2019). A Swedish national register study of 251 patients reported a rate of malignancy below 10% in resected IPMN tumours (Aronsson et al., 2018). In most series, BD-IPMN had the most benign tumours while MD-IPMNs had the most malignancies.

Risk factors for malignancy have been studied rigorously since the first IPMN tumours were described. While the size of the tumour has been a risk factor for malignancy, other features have emerged. In the recent literature and the latest guidelines, the most established risk factors for malignancy of IPMN are MPD dilatation, contrast-enhancing mural nodule, presence of jaundice, solid component, cyst diameter, elevated levels of serum carbohydrate antigen 19-9 (CA 19-9) and increasing growth rate of the cyst (Han et al., 2018; Kolb et al., 2018; Hackert et al., 2015; Marchegiani et al., 2018; Hirono et al., 2012; Ateeb et al., 2019; Kang et al., 2011; Ogura et al., 2013; Suzuki, et al., 2021; Pozzi Mucelli et al., 2022; Kazami et al., 2022; Marchegiani et al., 2018).

MPD dilatation over 5mm considered to be risk factor for malignancy, but other cut-off values than 5mm are also considered (Zhang et al., 2023; Petrone et al., 2018; Sugimoto et al., 2017). Higher risk of malignancy is also associated with diffuse dilatation compared to segmental dilatation (Kim et al., 2019). The prognosis is more favorable, if involvement of the MPD is minimal in MT-IPMN, (Sahora et al., 2014). While contrast-enhancing mural nodule is well established risk factor for malignancy, clear cut-off diameter for mural nodules size has not been demonstrated (Marchegiani et al., 2018). More numerous risk factors in each patient also increases the likelihood of malignancy (Zelga et al., 2022). Other suggested risk factors for malignant IPMN are new onset DM, family history of PDAC, chronic pancreatitis, (Capruso et al., 2013; Takenaka et al., 2017). However, combining all radiological modalities and laboratory tests, the predictive value of detecting any IPMN tumour before its malignant transformation remains low and the rate of unnecessary operations is high (Peisl et al., 2023; van Huijgevoort et al., 2023; Lekkerkerker et al., 2017; Giannone et al., 2022).

While the risk factors for malignancy in IPMN tumours are well documented, the natural course of the disease is relatively unknown. In stable cysts the risk of progression is low. Kolb et al. (Kolb et al., 2018), reported a growth rate of low-risk BD-IPMN of less than 0.3mm/year in a study of 189 patients while in a study by Kayal et al., (Kayal et al., 2017) 44% of the cysts did not grow at all in a cohort of 141 patients in minimum of four-year surveillance. However, the risk of malignancy in BD-IPMN patients is cumulative. In a series of 804 patients the incidence rates for PDAC were 3.5% at 10 years and 12% at 15 years after the initial diagnosis (Oyama et al., 2020) and the probability of progression was 43% in 10 years in cohort of 540 patients (Capruso et al., 2020).

Only a few publications have been presented on conservatively treated IPMN patients with risk factors of cancer. In a contribution by Del Chiaro et al. (Del Chiaro et al., 2017), out of 503 patients, 49 had indications for surgery but were inoperable for reasons related to their general condition. In this group, the five-year IPMN-specific survival was 75%. Surci et al. (Surci et al., 2022) compared non-surveilled population (N=376) with BD-IPMN to a surveillance group (N=299) and found no significant difference in pancreatic cancer incidence in five-year surveillance. Also, Vanella et al. (Vanella et al., 2018;) and Cauley et al. (Cauley et al., 2011) stated that patients with risk factors for cancer, but unfit for surgery, were at higher risk of death due to other reasons than IPMN related causes.

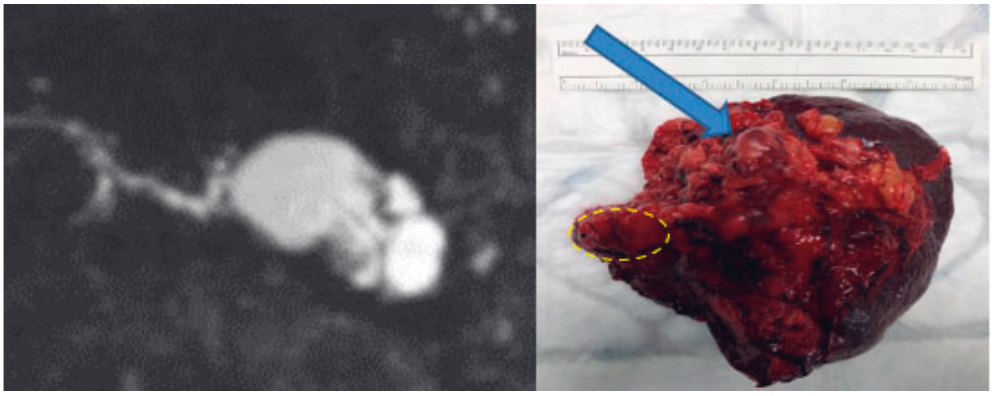

Figure 3. MRI examination on BD-IPMN and surgical specimen of the same BD-IPMN. Dotted oval; resection margin, Arrow; the cyst. Histopathological analysis showed: Branch duct-IPMN with high-grade dysplasia, clear resection margin. (Courtesy of Prof. Laukkarinen)

2.3.1.4 Recurrence and prognosis

The malignant potential of IPMNs varies widely and prognosis is mostly dependent on the degree of dysplasia (Blackham et al., 2017; Kang et al., 2014; Kaiser et al., 2022; Min et al., 2020). A Swedish national register study of 251 patients reported 90% survival in non-invasive IPMNs and 39% in invasive tumours in three-year follow-up (Aronsson et al., 2018). In malignant, operated, IPMNs 5-year survival has been reported to be 17-65% (McMillan et al., 2016; Kaiser et al., 2022; Marchegiani et al., 2015; Gavazzi et al., 2022). BD-IPMNs have reported to have better 5-year DFS compared to IPMNs with MPD involvement (82% vs. 73%) (Kang et al., 2014). Also, the prognosis of malignant MT-IPMN was superior compared to malignant MD-IPMN (OS 47 months vs. 12 months) in a study of 390 patients by Ceppa et al. (Ceppa et al., 2015). Also subtype of IPMN tumour effects on prognosis of IPMN patients. In meta-analysis of 1,617 patients Koh et al., (Koh et al., 2015) reported that the pancreatobiliary subtype has the highest likelihood of INV (68%), while the gastric subtype has the lowest likelihood of INV at 10%).

Recurrence to INV may occur not only when INV is present in the specimen. Amini et al. (Amini et al., 2022) found invasive recurrence in 6.4% and non-invasive recurrence in 26.9% of the patients in 5-year surveillance in a cohort of 449 resected IPMN patients. In MD-IPMN type, MPD involvement may play a role in the recurrence and there is evidence that recurrence is more frequent if the MPD dilatation is diffuse rather than segmental (Yogi et al., 2015; Jong et al., 2022; Kim et al., 2019). Also, family history of PDAC may increase the risk of malignant

recurrence. In a study of 126 patients with resected non-invasive IPMN, patients with family history of PDAC had 1.88 adjusted hazard ratio of recurrence in multivariate analysis (Pflüger et al., 2022). A significant number of recurrences is possible after five-year surveillance. In study of 1074 patients by Hirono et al, (Hirono et al., 2020), found recurrence in 14% of the operated patients, and the recurrence occurred after five years in 34% of the cases. In one series overall recurrence was 10.7% in INV and 5.4% in non-invasive IPMNs in a 44.4-month follow-up period (Oyama et al., 2020). Recurrence of the tumour of the pancreas remnant compared to extrapancreatic recurrence has more favorable prognosis and if the pancreas remnant is re-operated on, the prognosis is better than if not operated on (Fuji et al., 2022). IPMN derived carcinoma recurrence is mostly in the lungs, in PDAC the recurrence occurs mostly locally or in the liver (Capretti et al., 2022).

Gavazzi et al., (Gavazzi et al., 2022) reported five-year OS of 65.4% in IPMN-carcinoma patients compared to OS of 14.2% in PDAC patients. Significantly better DFS and OS have been also reported by other authors in IPMN-derived carcinoma compared to PDAC, especially in lower tumour stages (Capretti et al., 2022; Waters et al., 2011; Koh et al., 2014; Holmberg et al.,2023; Holmberg et al., 2023).

Finally, in some publications patients with IPMN were reported to have increased risk of extra-pancreatic malignancy (Panic et al., 2018; Facciorusso et al., 2022). A recent meta-analysis by Kumar et al. of 8,240 patients, showed a significantly increased risk of other gastrointestinal malignancies in IPMN patients (Kumar et al., 2021).

Table 3. Summary of pancreatic cystic neoplasm (PCN) studies with high relevance in the period 2016-2023

Study	Subject	Finding
Kromrey et al 2018	PCN incidence	Incidence of PCN was 49.1 in population-based study
Aronsson et al., 2018	Rate of malignancy on resected IPMN patients	National register study, 9.6% of resected IPMNs were malignant
van Huijgevoort et al., 2023	Predicting value of IPMN guidelines	Current IPMN guidelines have poor predicting value of malignancy
Del Chiaro et al., 2017	Conservative treatment of IPMN patients with risk factors	Fairly good prognosis when IPMN with risk factors is treated conservatively due to poor general condition
Hirono et al., 2020	IPMN-recurrence	IPMN recurrence is frequent after five years of surveillance
Capretti et al., 2022	Resected IPMN vs resected PDAC prognosis	IPMN have better prognosis than PDAC especially in lower tumour stages
Blair et al., 2022	Type of resection on case of diffuse MPD dilatation	Partial pancreatectomy is a feasible strategy for diffuse MD-IPMN compared to total pancreatectomy
Hughes et al., 2022	Adjuvant therapy on IPMN patients	Adjuvant therapy should be reserved for patients with adverse tumour pathology
Aronsson et al., 2018	Economic aspect of BD-IPMN surveillance	Surveillance by current protocol was the most cost-effective treatment strategy
Johansson et al., 2022	BD-IPMN surveillance intervals	In selected cases surveillance intervals could be expanded
Pozzi-Mucelli et al., 2016	Short protocol MRI for BD-IPMN surveillance	Short MRI protocol would decrease cost of IPMN surveillance
Marchegiani et al., 2023	BD-IPMN surveillance discontinuation	Discontinuation of BP-IPMN surveillance is safe on selected elderly patients

PCN, pancreatic cystic neoplasm; IPMN, Intraductal papillary mucinotic neoplasm; PDAC, pancreatic ductal adenocarcinoma; MD, main duct; BD, branch duct; MPD, main pancreatic duct; MRI magnetic resonance imaging

2.3.2 Mucinous cystic neoplasm (MCN)

2.3.2.1 Definition

MCNs were first described in the late 1970s, although MCNs and IPMN were distinguished as separate entities in the WHO classification of 1996 (Compagno et al., 1978; Kloppel et al., 1996). The most obvious difference between MCN and IPMN and the diagnostic criteria for MCN is the presence of the ovarian-type stroma in MCN tumours (Murakami et al., 2006). MCNs are moreover defined as mucin-producing cysts, forming an epithelial neoplasia and they do not communicate with the pancreatic duct system. In cross-section imaging MCNs are uni- or multilocular single cysts with thick fibrotic wall containing mucin (Naveed et al., 2014). MCNs are typically found in the body or tail of the pancreas (**Figure 3, Table 4).** MCN tumours are graded by WHO into LGD, HGD and INV (Adsay et al., 2016).

2.3.2.2 Epidemiology

Incidence of MCNs is unknown. However, it is known that around one quarter of resected PCNs are MCNs (Gaujoux et al., 2011; Postlewait et al., 2018). Over 95% of MCN patients are females and the mean age is 45 years (Crippa et al., 2008; Griffin et al., 2017). No risk factors for MCN are known, but pregnancy may induce a rapid growth of MCN (Dhamor et al., 2023).

2.3.2.3 Malignant potential and risk factors

The rate of malignancy in MCN tumours varies 10-25% in surgical series (Gil et al., 2013; Höhn et al., 2020; Kim et al., 2022). Risk factors for malignancy in MCN tumours are cyst size, male gender, elevated level of CA 19-9, calcifications, wall thickening, septations of the cyst and presence of tumour-related symptoms (Marchegiani et al., 2021; Keane et al., 2018; Postlewait et al., 2018 Zhen et al., 2022).

2.3.2.4 Recurrence and prognosis

Recurrence of benign MCN tumours after microscopically margin-negative resection (R-0) is almost zero. In HGD or even in stage 1-2 tumours the prognosis is also good; recurrence rates being below 5%, or even zero in some series (Hui et al., 2018; Liang et al., 2021). Five-year survival for invasive MCN varies widely between studies; 26-95.7% (li et al., 2020; Jang et al., 2015).

2.3.3 Serous cystic neoplasm (SCN)

2.3.3.1 Definition and characteristics

SCNs are composed of glycogen-rich epithelial cells that form small cysts containing serous fluid. Cysts form honeycomb-like structures with a distinguishable central scar (**Figure 4, Table 4**). SCNs are mostly detected in middle-aged/elderly women, the female/male ratio being 3/2 (Basturc et al., 2009; Chen et al., 2020).

2.3.3.2 Epidemiology, malignant potential and prognosis

Of resected PCNs 34% are SCN:s. (Gaujoux et al., 2011; Valsangkar et al., 2012; Lombardo et al., 2018). The malignant potential of SCN is close to zero although there are few reported cases of malignant transformation of SCN. In one surgical series of 678 SCN patients, four (0.6%) had serous cystadenocarcinomas in their pathology reports (Wu et al., 2019). SCNs can be difficult to differentiate from other cystic neoplasms, which explains the high rate of resections of this benign tumour (Roldán et al., 2023).

2.3.4 Solid pseudopapillary neoplasm SPN

2.3.4.1 Definition and characteristics

SPNs are PCNs with mass appearing as cysts but now known to be cavities filled with necrotic or degenerative mass (**Figure 4 and Table 4**). Calcification on the wall of the cavity may occur. SPN usually occurs in young females, the female/male ratio being 20/1. The most common localization of SPN is the tail of the pancreas. (Basturc et al., 2009; Dinarvand et Lai, 2017).

2.3.4.2 Epidemiology, malignant potential and prognosis

SPN is a rare tumour; less than 5% of PCNs are classified as SPNs. They have some malignant potential (10-15% of cases) although metastatic disease is rare. Overall, five-year survival approaches 89-98% in patients undergoing surgical resection (Lubezky et al., 2017; Tjaden et al., 2019; Wang et al., 2021).

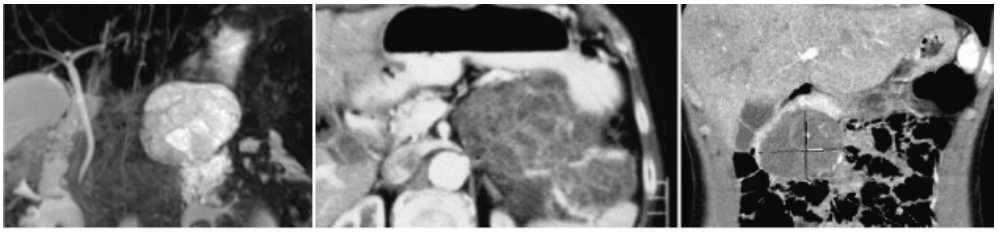

Figure 4. Magnetic resonance imaging examination of mucinous cystic neoplasm, solid pseudopapillary neoplasm and serous cystic neoplasm. (Laukkarinen, 2019)

Other true cystic lesions of the pancreas are rare; less than 5% of the cystic lesions of the pancreas. In this heterogeneous group malignancy varies between highly malignant tumours, such as cystic ductal adenocarcinoma, compared to totally benign congenital cysts. Cysts may originate from different sources such as cystic metastases from other origins, duodenal wall, acinar cells or, for example, from the lymphatic tissue of the pancreas. Other cystic tumours are listed and classified in **Table 2.** (Basturc et al., 2009).

Table 4. Typical features of pancreatic cysts (Tanaka et al., 2017; Löhr et al., 2023)

	BD-IPMN	MCN	SCN	SPN	Pseudocyst
Age	65	45	60	25	Any
Sex F=female, M=male	F<M	F>>>M	F>M	F>>>M	F<M
Location	Whole pancreas	Body+tail	Whole pancreas	Whole pancreas	Whole pancreas
Cyst fluid Mucinous	Yes	Yes	No	No	No
MPD Communication	Yes	No	No	No	Varies
Multifocal	Yes/no	No	Yes/no	extremely rare	Yes/no
Calcification	Very rare	"Eggshell"	Central sunburst	Rare	No

BD-IPMN, Branch-duct intraductal papillary mucinous neoplasm; MCN, mucinous cystic neoplasm; SCN, serous cystic neoplasm; SPN, solid pseudopapillary neoplasm; MPD, main pancreatic duct

2.4 Diagnostics of pancreatic cystic neoplasms (PCNs)

2.4.1 Incidental findings

Most pancreatic cysts are detected incidentally, and the use of cross-sectional imaging often leads to such incidental findings. The number of imaging examinations ordered has been rising by over 10% per year in recent years and even decades (Smith-Bindman et al., 2019). Technological advances in imaging software and hardware have also led to the detection of more incidental findings; in one study incidental cyst was detected in 41.6% of the patients in MRI (Moris et al., 2005). In EUS performed on patients with no known pancreatic condition cyst was detected in 21.5% (Martinez et al., 2018). A high rate of pancreatic cysts has also been confirmed in autopsys; In one autopsy series the incidence of pancreatic cysts was 24.5% (Kimura et al., 1995). The population is aging, and this increases the risk of detecting incidental findings (Chen et al., 2021). In trauma computer tomography (CT) over 20% of the studies led to incidental findings in the abdominal area (Andraves et al., 2017; Paluska et al., 2007).

Depending on the organ of the abdomen and type of lesion, most cystic lesions, for example simple liver cysts in the abdominal area, need no further investigations. However, pancreatic cystic lesions usually need to be evaluated once detected.

2.4.2 Symptoms

Symptoms such as upper abdominal pain, nausea and vomiting are usually related to large size of the cyst. Pancreatitis or jaundice can occur if the cystic tumour obstructs the flow of pancreatic juices or prevents biliary drainage. Once symptoms are detected, imaging studies are usually the next diagnostic step.

2.4.3 Imaging

2.4.3.1 Ultrasonography (US)

US is usually the initial imaging modality for evaluating hepatobiliary conditions in primary health care. Most incidental PCNs are first detected in US and there are no contraindications for US. It is also cheap, but the results can be biased by interobserver variation. Moreover, due to the location of the pancreas in the retroperitoneum, US is not the ideal modality for diagnosing pancreas-related conditions. In most cases, if a cyst or other mass in the pancreas is detected by US, the patient is referred to further investigations, usually for cross-section imaging.

2.4.3.2 Magnetic resonance imaging (MRI) and computer tomography (CT)

The incidence of pancreatic cysts detected in patients examined with MRI imaging for other purposes and without underlying pancreatic conditions has been reported to be as high as 44.7% (Girometti et al., 2011). MRI may be better than CT for characterizing small pancreatic cysts, but both modalities are similar at detecting malignancy in a pancreatic cyst. MRCP is superior to other modalities for detecting pancreatic cyst communicating with MPD (Visser et al., 2007; Sainani et al., 2009). There may be some increase in the accuracy, sensitivity and specificity when combining MRI+MRCP and CT for classifying pancreatic cysts (Jang et al., 2015). CT alone is used for detecting extrapancreatic masses, metastases, calcification of

the cyst and nodules in the abdomen and chest area (Bhosale et al., 2010). CT imaging takes less time than MRI, but unlike MRI, CT produces some ionizing radiation. For better accuracy CT and MRI are usually used with contrast media. Contrast media examinations are contraindicated if the patient is allergic to contrast media or has severe renal dysfunction. If the patient has a metallic foreign object in the body, MRI is contra-indicated in some cases. Shorter MRI -imaging protocols for PCNs have been developed in order to decrease the costs of PCN surveillance (Pozzi-Mucelli et al., 2016; Johansson et al., 2022).

2.4.3.3 Endoscopic ultrasound (EUS)

EUS is not a screening method but rather a means to acquire more information on a tumour after its detection by other means and resection of the tumour is under consideration. Fine needle aspiration (FNA) can be added to EUS for collecting cytological samples and tumour markers. EUS can also be used with contrast-enhancement (CEUS) to further increase the ability to assess worrisome features like enhancing septae or mural nodules and can be helpful in differentiating PNCs from PDAC (Sun et al., 2021; Yashika et al., 2021). In detecting malignancy in pancreatic cysts, EUS can be as useful as CT and MRI (Choi et al., 2017; Wesali et al., 2021). Overall EUS can improve the diagnostics of PCN patient and by using EUS pancreatic surgery can be avoided or delayed in some cases (Giannone et al., 2022). EUS is heavily dependent on the endoscopist and interobserver reliability may impair the usefulness (Yamamiya et al., 2020). EUS is an invasive procedure and the rate all of complications was 2.33% in prospective studies in a meta-analysis by Wang et al., (Wang et al., 2011).

2.4.3.4 Endoscopic retrograde cholangiopancreatography (ERCP)

ERCP in MD-IPMN diagnostics has been used primarily in research settings. The possible advantages of ERCP include obtaining brush samples, histology and a macroscopic view (if pancreatoscopy is used) of MPD. ERCP is an invasive procedure usually performed under sedation. Due to the risk of ERCP related complications, mainly pancreatitis, ERCP is not routinely used in the diagnostics of pancreatic cysts (Vehviläinen et al., 2022; Yoshika et al., 2016).

2.4.3.5 Positron emission tomography (PET)

Currently fluorodeoxyglucose (FDG)-PET imaging is not included in the diagnostic regimen of IPMN. There is some evidence that PET would be helpful in differentiating between malignant and benign lesions (Ohta et al., 2017; Takanami et al., 2011; Yamashita et al., 2019, Kauhanen et al., 2015). The performance of FDG-PET has been compared to conventional imaging with IAP guidelines for detecting malignant BD-IPMNs and MD-IPMNs. Roch et al., (Roch et al., 2015) reported PET to be more specific but less sensitive compared to the IAP guidelines. Combining the IAP guidelines with PET diagnostics improved both sensitivity and specificity.

2.4.4 Biomarkers

2.4.4.1 CA 19-9

The normal CA 19-9 value is below 37 IU/L depending on test kit in use and may be elevated in many gastrointestinal cancers: oesophageal, gastric, pancreatic and biliary. Benign conditions such as icterus and hepatic cysts may also elevate CA 19-9 (Scarà et al., 2015; EASL 2022). Up to ten percent of the population have Lewis-negative phenotype and do not produce CA 19-9, which can lead to false negative test results (Parra-Roberts et al., 2018). According to some publications, an elevated level of CA 19-9 is an independent risk factor for malignancy of IPMN tumours (Jones et al., 2009; Xu et al., 2011).

2.4.4.2 Cyst fluid analysis

Mucinous (MCN, IPMN) and non-mucinous cysts are differentiated most reliably using cyst fluid carcinoembryonic antigen (CEA). A cutoff level of 192ng/mL is usually used having 75% sensitivity and 84% specificity. The level of CEA does not correlate with the malignant potential of the cyst; therefore, it cannot be used to differentiate benign and malignant cysts (Brugge et al., 2004). Cyst fluid amylase can differentiate pseudocysts from other pancreatic cysts. However, cyst fluid amylase cannot be used for other purposes in pancreatic cyst diagnostics (van der Waaij et al., 2005). Kirsten rat sarcoma virus (KRAS) mutation analysis is the most widely

used mutation analysis combined with cytology obtained by EUS-FNA. In a systematic review by Gillis et al. combining KRAS with cytology, sensitivity was 71% and specificity 88% for detecting any abnormalities including atypical, suspicious or malignant (Gillis et al., 2015). Combining guanine-nucleotide-binding protein-alpha stimulating (GNAS) with KRAS and cytology analysis, the sensitivity for detecting malignancy reached 92% while limiting the specificity to 50% (Bournet et al., 2016). Next-Generation Sequencing Panels (NGS) have also been developed for studying PCNs and are showing promising results for detecting neoplasia (Singhi et al., 2018). NGS panel samples can also be obtained using through-the-needle-biopsy (TTNB) method (Rift et al., 2023).

2.5 Management of pancreatic cystic neoplasms (PCNs)

2.5.1 Rationale of management

The malignant potential of pancreatic cysts varies from benign to highly malignant. Correct management of these cysts enables adequate treatment or surveillance for lesions that might harbour malignancy. On the other hand, the aim is to minimize needless operations or follow-ups.

2.5.2 Guidelines

The European consensus statement guidelines on PCN were introduced in 2013 (European Study Group on Cystic Tumours of the Pancreas, 2013). These guidelines were replaced by the European evidence-based guidelines on pancreatic cystic neoplasms, which are the first guidelines to rely on evidence rather than expert opinion (European Study Group on Cystic Tumours of the Pancreas, 2018). These guidelines cover most known cystic pancreatic lesions and not only IPMNs. Recommendations are given for all aspects of managing pancreatic cysts; diagnostics, surveillance, treatment, follow-up and adjuvant treatment.

The International Association of Pancreatology (IAP) published the Sendai guidelines in 2006, which were revised in 2016 (Tanaka et al., 2006; Tanaka et al., 2017). The current guidelines focus solely on the treatment of IPMN tumours, while the 2012 revision also included MCN tumours.

A third set of guidelines was presented by the AGA (Vege et al. 2015). These guidelines focuses only in asymptomatic PCN:s SPN, PDAC, MD-IPMN excluded (**Table 5**).

2.5.2.1 Intraductal papillary mucinous neoplasm (IPMN)

The European evidence-based guidelines on the PCN treatment algorithm for IPMN patients suggest surveillance for patients (fit for surgery) with no indication for surgery; MRI/EUS+Clinical evaluation+serum CA9-9 after six months, then yearly. Surveillance continues as long as the patient is fit for surgery. In case of one relative indication for surgery (Cyst growth rate ≥5 mm/year, increased serum CA 19.9 level (>37 U/ mL in the absence of jaundice), MPD diameter between 5 and 9.9 mm, cyst diameter ≥40 mm, symptoms (new onset of DM or acute pancreatitis) and contrast-enhancing mural nodules) patients without significant co-morbidities are recommended to undergo surgery. With significant co-morbidities intensive surveillance is recommended. If two relative indications are present patients with significant co-morbidities are also referred to surgery. If absolute indications for surgery (presence of jaundice, cytology positive for HGD or cancer, presence of a contrast-enhancing mural nodule (≥5mm) or solid mass) are present, surgery is recommended for all patients. If histological analysis confirms the IPMN diagnosis after partial pancreatectomy lifelong surveillance is warranted (European Study Group on Cystic Tumours of the Pancreas, 2018) (**Table 5**).

Table 5. Guidelines for Management of pancreatic cystic neoplasms (European Study Group on Cystic Tumours of the Pancreas., 2018; Tanaka et al., 2017; Vege et al. 2015)

Guideline, year	European guidelines, 2018	International Association of Pancreatology, 2017	American Gastroenterological Association, 2015
Type of PCN	IPMN, MCN, SCN, SPN, rare cystic lesions	IPMN	Asymptomatic PCN, (SPN, PDAC, MD-IPMN excluded)
Absolute indication for surgery of BD-IPMN	-Jaundice (tumour related) -Positive cytology, INV/HGD -Solid mass -MPD ≥ 10 mm -Enhancing mural nodules ≥5 mm -MPD dilatation ≥10mm	-Obstructive jaundice in patients with cystic lesion of the head of the pancreas -Enhancing mural nodule ≥ 5mm -MPD ≥ 10mm	Solid component and a dilated pancreatic duct and/or concerning features on EUS
Relative indication for surgery of BD-IPMN	-Growth rate ≥5 mm/year -Increased serum CA 19.9 level (>37 U/mL in the absence of jaundice) -MPD 5-9.9 mm -Cyst diameter ≥40 mm -Symptoms (new-onset of diabetes mellitus or acute pancreatitis) -Contrast- enhancing mural nodules <5 mm	-Cyst size >3 cm -Pancreatitis -Enhancing mural nodule < 5mm -Thickened/enhancing cyst walls -MPD size 5-9mm -Abrupt change in caliber of pancreatic duct with distal pancreatic atrophy -Lymphadenopathy -Increased CA 19-9 -Cyst growth rate ≥ 5mm/2 years)	size >3 cm, a dilated main pancreatic duct, or the presence of an associated solid component,
Follow-up on stable cyst in patients fit for surgery	-MRI/EUS+Clinical evaluation+serum CA9-9 after 6 months, then yearly	-Cyst <1 cm: CT/MRI after 6 month -> every 2 years -Cyst 1-2cm: CT/MRI after 6 month -> 1 year x2 -> lengthen interval up to 2 years -Cyst 2-3 cm: EUS in 3-6months -> lengthen interval up to 1 year alternating MRI with EUS. Consider surgery in young, fit patients -Cyst >3cm: Alternating MRI with EUS every 3-6 months. Strongly consider surgery in young, fit patients	-Cysts <3cm: MRI 1 year -> 2 years for a total of 5 years -Discontinuation of follow-ups after 5 years
Follow-up after surgery	-Until unfit for surgery -Dependent of histopathology finding	-Until unfit for surgery -Dependent of histopathology finding	-LGD: No surveillance -HGD or INV: MRI 2 year interval
Indication for EUS	- If the PCN has either clinical or radiological features of concern and surgery is considered	-Always if worrisome features are present. If mural nodules ≥5 mm, suspected MPD involvement or suspicious cytology for malignancy -> Concider surgery	-≥2 high-risk features - Significant changes in the characteristics of the cyst

PCN, pancreatic cystic neoplasm; IPMN, Intraductal papillary mucinotic neoplasm; MCN, mucinous cystic neoplasm; SCN, serous cystic neoplasm; SPN, solid pseudopapillary neoplasm; PDAC, pancreatic ductal adenocarcinoma; MD, main duct; BD, branch duct; INV, invasive carcinoma, HGD, high-grade dysplasia, MPD, main pancreatic duct; EUS, endoscopic ultrasound; CA 19.9, carbonhydrate antigen 19-9; MRI magnetic resonance imaging; CT, computer tomography; LGD, low-grade dysplasia

The treatment algorithm of IAP follows the same principles as the European guidelines with high-risk stigmata (obstructive jaundice in patients with cystic lesion of the head of the pancreas, enhancing mural nodule ≥ 5mm and MPD ≥ 10mm) (absolute indication for surgery) and worrisome features (pancreatitis, enhancing mural nodule < 5mm, thickened/enhancing cyst walls, MPD size 5-9mm, abrupt change in calibre of the pancreatic duct with distal pancreatic atrophy, lymphadenopathy, increased CA 19-9, cyst growth rate ≥ 5mm/2 years) (relative indication for surgery). However, the IAP guidelines focus more on the size of the cyst as indications for surgery compared to European guidelines. Intensity of surveillance also relies on the size of the cyst. International guidelines suggest performing EUS always if worrisome features are present. In the European guidelines the use of EUS is optional and dependent on the case (Tanaka et al., 2017).

In the AGA guidelines the indication for surgery is more restricted; Solid component and a dilated pancreatic duct and/or concerning features on EUS. EUS is recommended if at least two high-risk features are present or if significant changes in the characteristics of the cyst are present. The most important difference in the AGA guidelines compared to other guidelines is the recommendation to discontinue surveillance after five years if there has been no significant change in the characteristics of the cyst. Also, surveillance after resection is recommended only if HGD or INV is present (Vege et al., 2015).

2.5.2.2 Mucinous cystic neoplasm (MCN)

The current European guidelines state that MCN ≥ 40mm, symptomatic or with other risk factors such as mural nodule should be resected. Also, if the size of an MCN is increasing, the rate of growth is factor when surgery is considered. If the MCN measures 30-40mm, patient's age, co-morbidities, surgical risks should be assessed when surgery is considered. The surveillance protocol of conservatively treated patients is the same for MCN as for IPMN. The recurrence rate after surgery of benign MCN is close to zero, however the guidelines make no recommendation on this matter (European Study Group on Cystic Tumours of the Pancreas, 2018; Liang et al., 2021). In the international guidelines of 2012, resection of MCN is recommended regardless of the size of the tumour and surveillance after surgery is not required in benign tumours (Tanaka et al., 2012).

2.5.2.3 Other cystic tumours

SCN is considered a benign tumour and resection for asymptomatic patients is not recommended. Asymptomatic patients are recommended to be followed-up for one year. Resection of SPN is recommended in the European guidelines. There are no recommendations for the treatment of other rare pancreatic cystic tumours. Management should be decided in a multidisciplinary setting (European Study Group on Cystic Tumours of the Pancreas, 2018).

2.5.3 Operative treatment

The extent of the pancreatic resection is based on the location of the tumour and the presumed diagnosis of the tumour. Standard pancreatic resection includes distal pancreatic resection (DP) (tail or tail and middle part of the pancreas is resected), pancreaticoduodenectomy (PD) (Whipple procedure) (head of the pancreas, duodenum, gallbladder, part of the bile duct and usually part of the stomach is resected) and total pancreatectomy (pancreaticoduodenectomy+tail resection). In tumour enucleation only the part of the pancreas in contact with the tumour is resected. Central pancreatectomy (CP) is performed to preserve the endocrine and exocrine function of the pancreas; the middle part of the pancreas is resected while the head and the tail of the pancreas is preserved (Lv et al., 2018). In DPs mini-invasive surgery (MIS) (laparoscopic or robotic) is the mainstay (Henn et al., 2023). An open approach is mostly used in PDs, but MIS has become an option in the last decade. While the safety of MIS has been demonstrated in experienced centres, the oncological safety needs to be confirmed (van Hilst et al., 2021).

Perioperative mortality after pancreatic surgery has decreased in recent decades due to development improvements in surgical technique and postoperative care. Also, centralization of pancreatic surgery has reduced mortality after surgery (Ahola et al., 2019). Nevertheless, the rate of complications remains high. The most common specific complications after pancreatic surgery are delayed gastric emptying (DGE), postoperative pancreatic fistula (POPF) and post pancreatectomy haemorrhage (PPH). In a meta-analysis of over 60,000 PD patients the rate of 30-day mortality was 1.7%, overall complications 54.7%, and serious, Clavien-Dindo (CD) >2 complications 25.5% (Kokkinakis et al., 2022).

Both the European and the international guidelines recommend standard oncological resection with lymphadenectomy for IPMN tumours. Limited, parenchymal sparing resections may be an option for patients with very low

probability of malignancy (Tanaka et al., 2017). The European guidelines also promote the same kind of operation for MCN (European Study Group on Cystic Tumours of the Pancreas, 2018). CP has been used in some centres for low-risk tumours. CP is associated with higher morbidity than conventional resections. Lee et al. (Lee et al., 2020) reported significantly higher rates of morbidity in CP (33%) compared to DP (14%) in cohort of 165 patients. In terms of preserving pancreatic function, CP did have an advantage compared to PD in exocrine function. When CP was compared to DP, there were no advantages in endocrine or exocrine function.

According to the European guidelines in case of multifocal disease every cyst should be assessed individually to determine the extent of the resection. In case of diffuse dilatation of MPD there is no consensus on whether to perform total pancreatectomy or only partial pancreatectomy followed by close surveillance of the remnant pancreas (Ecker et al., 2022). There is, however, growing evidence that partial pancreatectomy is an appropriate strategy for diffuse MD-IPMN rather than the standard total pancreatectomy (Blair et al., 2022; Crippa 2016). Frozen section examination of the planned resection line is recommended and, if HGD or INV is present, total pancreatectomy is warranted to achieve negative margins. Perioperative pancreatoscopy can be used for further examinations of the planned remnant pancreas (Pucci et al., 2014; Navez et al., 2015, De Jong et al., 2023). Also, the European guidelines suggest that the use of perioperative pancreatoscopy can be helpful in detecting lesions in planned remnant MPD.

Use of EUS-guided ablative techniques is not recommended outside clinical trials (European Study Group on Cystic Tumours of the Pancreas, 2018; Tanaka et al., 2017).

2.5.4 Oncologic treatment

There is no evidence, only case reports, for the use of neoadjuvant therapy in locally advanced IPMN and MCN, therefore current guidelines include no recommendations on this matter (Westermark et al 2016). There is some conflicting evidence of adjuvant therapy in malignant IPMN patients. Some authors found no benefit from adjuvant therapy (Choi et al., 2021). Some recommend adjuvant therapy in aggressive IPMN; survival benefit was demonstrated by McMillan et al. in a cohort of 1,220 patients: at tumour stage 2-4, positive margins, positive lymph nodes or when poorly differentiated tumours occurred (McMillan et al., 2016; Mungo et al., 2021). Hughes et al., (Hughes et al., 2022) conclude in their meta-analysis of 3,252

patients that adjuvant therapy should be reserved for patients with adverse tumour pathology. The European guidelines recommend adjuvant therapy for patients with INV regardless of lymph node status (European Study Group on Cystic Tumours of the Pancreas, 2018).

2.5.5 Surveillance after surgery

After resection, the European and International guidelines (with the exception of total pancreatectomy) recommend surveillance until the patient is unfit for surgery. Risk factors for recurrence that warrant more intense surveillance are HGD or carcinoma in the specimen, family history of PDAC, positive resection margins (HGD or carcinoma), MPD dilatation of remnant pancreas (Simpson et al 2019; Pflüger et al., 2022; Kim et al., 2022, Takigava et al., 2020). LGD in the resection margin is not associated with increased risk of recurrence (Leonhardt et al., 2023). According to the guidelines, the intensity of the surveillance depends on the grade of dysplasia in the final pathology report (European Study Group on Cystic Tumours of the Pancreas, 2018; Tanaka et al., 2017). The AGA guidelines recommend surveillance every two years for patients who are good candidates for surgery if malignancy or HGD has been detected in the primary operation. For patients without HGD or malignancy surveillance is not recommended (Vege et al., 2015). In the event of a recurrence, re-resection for the remnant pancreas should be considered (Hirono et al., 2020; Fuji et al., 2022).

2.6 Effects of pancreatic cystic neoplasm (PCN) management

As stated previously, the number of patients in IPMN surveillance is constantly increasing. All guidelines recommend discontinuation of surveillance when patients are not fit for surgery. When the burden of co-morbidities increases the benefits of IPMN surveillance decrease (Sahora et al., 2015; Marchegiani et al., 2022). In the literature there are no publications stating whether this discontinuation of survival actually happens properly or if there are significant numbers of patients in surveillance protocols who will not benefit from the surveillance.

Aronsson et al., (Aronsson et al., 2018) compared the economic aspects of BD-IPMN management in a Markov decision model. At baseline of this model was a 65-year-old asymptomatic patient with incidentally found low-risk BD-IPMN. A

comparison was made between four strategies; upfront total pancreatectomy, partial pancreatectomy, initial surveillance by using European guidelines and watchful waiting (watchful waiting=investigations only if symptoms appeared). Surveillance by current protocol was the most cost-effective. However, if the risk of BD-IPMN progression was lower than expected, the watchful waiting strategy would become the most cost-effective.

Surveillance is currently the method of choice for managing low-risk IPMN tumours and the greatest cost in surveillance comes from imaging studies. One method of cutting costs would be to increase the intervals between control imaging. There is some evidence that increasing control intervals does not impair the prognoses of patients with stable BD-IPMN (Pergolini et al., 2018; Khaled et al., 2018). Also, Johansson et al. (Johansson et al., 2022) had a cohort of 377 Finnish patients on median of 5.4-year surveillance. Almost 20% of the patients in this study had <15mm cyst with no worrisome features and which did not grow at all during the study. The authors conclude that intervals of surveillance could be expanded in this group of patients based on the low risk of tumour progression.

Derived by the burden of BD-IPMN surveillance, there is growing interest in discontinuation of surveillance in patients with low-risk IPMN tumours. Marchegiani et al., (Marchegiani et al., 2019) suggested that discontinuation of surveillance of "trivial" BD-IPMNs in patients over 65 years of age might not increase the risk of developing PDAC.

There have also been attempts to save costs by modifying imaging protocols: shorter MRI protocols have been developed and proven to be an adequate method of surveillance (Delaney et al., 2021; Johansson et al., 2022; Pozzi-Mucelli et al., 2016). Most short protocols require no contrast media, which theoretically has a negative effect on the quality of the examination. However, Johansson et al. (Johansson et al., 2022) reported almost identical information gathered in short versus long protocols. Pozzi-Mucelli et al. (Pozzi-Mucelli et al., 2016) estimated that the cost of one MRI examination in short protocol would be one quarter of the cost of a normal protocol examination. According to the 2015 invoicing policy at the Karolinska University Hospital in Sweden, the price difference was 1,043 vs. 260 EUR. For patients diagnosed with BD-IPMN at the age of 45 the cost saving would be around 50,000 EUR if surveillance were abandoned at the age of 80. Also, the examination time would be decreased, allowing more examinations per day.

The last question concerning long-lasting surveillance concerns the possible effects on the mental health of the patient. In their publications Overbeek et al. (Overbeek et al., 2019) and Nieminen et al. (Nieminen et al., 2023) concluded that

the psychological burden of the surveillance is low and further that the negative impact on quality of life is minimal. On the other hand, in a case-control study by Marinelli et al. (Marinelli et al., 2020) it was found that patients under surveillance had more anxiety and stress than patients undergoing surgery. It is impossible to draw conclusions from these results, but patients' mental status is one factor to be bear in mind while the treatment plan is being discussed.

PCNs and especially IPMN tumours have been a subject of rigorous study in recent years, and most of the publications are surgical series focusing on the risk factors of malignancy. The number of publications reporting on patients treated conservatively is surprisingly low. There is a need for high-volume, international long-term data on surveillance. A good example of this kind of collaboration is the ongoing Pacyfic study by Erasmus University with a progressive, multicentre on-line register of over 2,000 IPMN patients under surveillance (Pacyfic study group,). Series with long-term surveillance are likewise not so common. Long-term data is important for at least two reasons: 1. it is known that recurrence may occur after a long period of time. 2. the prognosis of surgically and conservatively treated patients (if no INV is present) is favorable, so differences between these two groups may only occur after decades.

The natural course of PCN behavior is still relatively unknown. We have only estimates of the prevalence on these tumours, and it is not known how often surgery is actually performed on the real-life PCN population. Guidelines have been developed to help clinicians in decision-making, but the risk of undertreatment and overtreatment is present when current guidelines are used (Tamburrino et al., 2023). The actual benefit of adopting these guidelines is yet to be demonstrated.

3 AIMS OF THE STUDY

The aim of this study was to investigate the surgical treatment of PCNs in Finland. In the retrospective part of this study the emphasis was to ascertain the types of resected PCNs in Finland, assess whether the operations were justified, determine which patients are good candidates for surgery and what the outcomes are after surgery. The prospective part was designed to test the effectiveness of the IPMN guidelines in the management of patients in Tampere University Hospital.

The specific aims of the study were:

I To Investigate characteristics of resected PCNs in a nationwide register

II To assess the prognostic factors and 10-year survival for resected IPMN tumours in Finland

III To demonstrate the feasibility of IPMN surveillance according to the new European guidelines by analysing the development of relative and absolute indications for surgery in a clinical setting

4 PATIENTS AND METHODS

4.1 For Studies I and II

All pancreatic resections performed in Finland in the period 2000–2008 were identified by combining data from the patient records and the national operations register (HILMO). The patient records were assessed to identify patients with possible PCN. Patients with other conditions, such as pseudocysts and PDAC, were excluded. Patients with resected PCN were included in the study population (**Figure 5**).

From the patient records of this final study population the following data were collected; demographics, comorbidities, symptoms, radiological findings, surgical procedures, complications, final histopathological diagnoses and survival. Postoperative complications were registered and graded according to the CD Classification of Surgical Complications. Histological findings were classified according to the WHO classification of pancreatic tumours. All pathological reports were reviewed, and, if necessary, the histopathological slides re-reviewed by an experienced pancreatic pathologist. For **Study II**, an experienced radiologist re-assessed all available imaging studies. Some of the datasets were incomplete due to inability to obtain all histological samples or radiological examinations. Mortality data were gathered for **Study I** on 31 March 2016 and for **Study II** on 26 November 2020 from the Finnish Registry Office.

Statistical analyses were performed using SPSS 22.0 for Windows (IBM Inc., Somers, USA) (**Study I** and **study II**) and SPSS 26.0 for Windows (**Study III**). Unless otherwise specified, descriptive statistics are reported using count, percentage, median and range. Chi-square test was used in univariate analyses and logistic regression analyses for multivariate analyses. $P<0.05$ was considered statistically significant. Kaplan-Mayer analysis was used to analyse long-term survival.

Permission to access the patient files and histological slides was obtained from the National Institute for Health and Welfare (THL) (permission 1854/5.05.00/2012) and the National Supervisory Authority for Welfare and Health (Valvira) (permission 10263/06.01.03.01/2012).

4.2 Study III

A prospective register for IPMN patients in Tampere University Hospital was established on 1 October 2015. Patient files starting from 1 January 2013 were added to the database. For this study, data from the register were gathered until 31 December 2018. All IPMN cases, including patients operated upfront, assessed in Tampere University Hospital were included in the study. Patients were managed according to the European experts' consensus statement on cystic tumours of the pancreas published in 2013. The primary imaging modality was MRI. CT or EUS was used if necessary. Serum CA 19-9 levels were measured. At the first contact the patient was invited to attend the outpatient clinic. Cases were assessed at the MDT meeting if necessary. Follow-ups were carried out according to the recommendations of the guidelines; For the first year, follow-up was conducted at six-month intervals and thereafter yearly until the patient was not fit for surgery.

At baseline the following data were gathered: Demographics, comorbidities, symptoms and radiological findings. At each follow-up point radiological findings, surgical procedures, final histopathological diagnoses and survival were added to the database.

5 RESULTS

5.1 Studies I and II

In S**tudy I**, out of 2,024 pancreatic resections performed in Finland in the study period 2000-2008, 225 were due to PCN **(Figure 5)**. Median age of the patients was 61.0 (14-87) years and 143 (63.3%) were females. Most of the patients (69.5%) had pancreas related symptoms such as pain, jaundice, pancreatitis or weight loss. Preoperatively CT was performed on 96.5% of the patients, MRI on 28.2% and EUS on 6.6% of the patients. In imaging the median tumour diameter was 40.0 (range 4-220) mm, 87.4% of the cysts were solitary lesions **(Table 6)**.

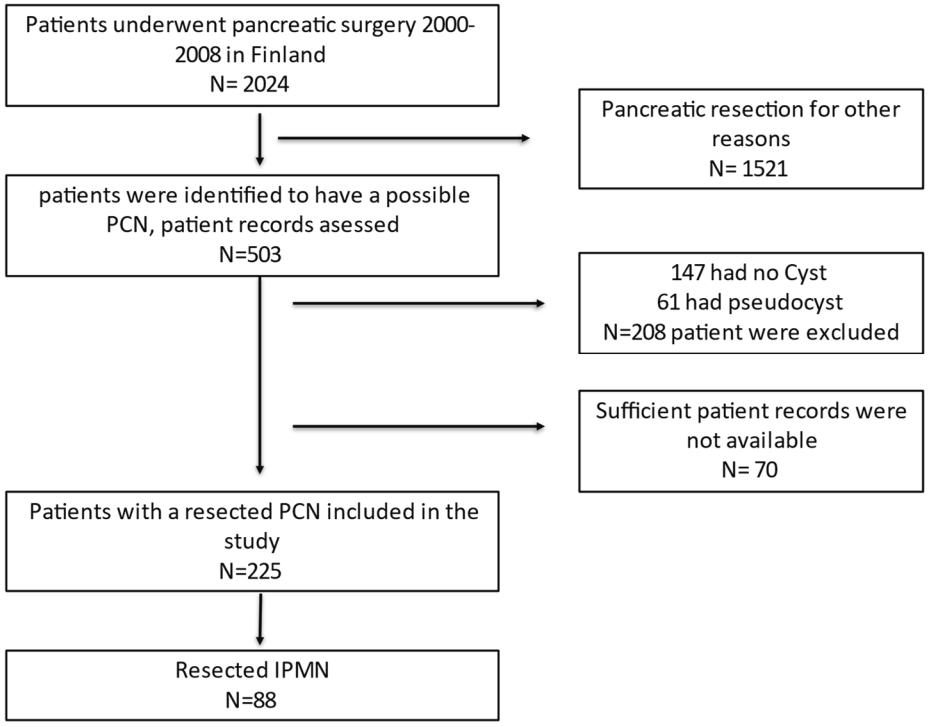

Figure 5. Flowchart of patients in **Studies I and II**

DP was performed on 59.6%, PD 32.4%, total pancreatectomy 5.3% and enucleation on 2.7% of patients. Morbidity according to CD classification was CD 1-2 30.2%, CD 3-4 17.8%, and CD 5 1.3% (**Table 6)**.

IPMN (41.7%) was the most common histopathological diagnosis (22.1% MD-IPMN, 13.3% MX-IPMN, 6.2% BD-IPMN). Other tumour characteristics are presented in **Table 6**. Malignancy was present in 23.6% of the tumours and 6.7% were HGD. Over half of the malignant tumours were MD-IPMNs and 58% of the MD-IPMNs and 30% of the MCNs were malignant. Risk factors for malignancy in uni- and multivariate analysis were age over 60 years ($p<0.003$, odds ratio 3.486), symptoms ($p<0.016$, odds ratio 3.259), and tumour location in the pancreatic head or uncinatus area ($p< 0.016$, odds ratio 2.624).

Pathology reports were re-evaluated in 25 cases by an experienced pathologist and histopathological slides re-reviewed in 42 cases. In 44 cases MCN diagnosis was changed, mostly to IPMN. Five-year survival for all patients with resected PCN was 76.7%; 86.9% for patients without malignancy, 76.6% for patients with HGD and 27.3% for patients with malignant resected PCN.

Table 6. Characteristics of 225 resected pancreatic cystic neoplasms (PCN:s) in Finland 2000-2008 in **Study I**

	MD-IPMN	MT-IPMN	BD-IPMN	MCN	SCN	SPN	EPIT	Other	All
N, %	50 (22,1)	30 (13,3)	14 (6,2)	40 (17,7)	41 (18,1)	8 (3,5)	22 (9,7)	20 (8,8)	225
Age years,	70.5	67.0	63.5	51.0	64.0	21.0	56	47.0	61.0
median (range)	(44-87)	(40-81)	(53-72)	(27-82)	(33-79)	(14-47)	(24-75)	(24-75)	(14-87)
Sex Female %	50	56,6	42,9	100	82,9	87,5	27,3	40	63,6
Tumour size, median (range) mm	33	40	30	50	40	65	25	25	35
	(3-120)	(10-95)	(10-50)	(2-180)	(8-120)	(13-130)	(6-80)	(12-100)	(2-180)
Location, n (%)									
1Head	19 (48,7)	10 (41,7)	7 (50)	4 (11,4)	9 (25,7)	2 (25,0)	4 (28,6)	3 (15.0)	58 (30.9)
2 Uncinatus	1 (2,6)	0 (0,0)	1 (7,1)	1 (2,9)	1 (2,95)	0 (0,0)	0 (0,0)	1 (5.0)	5 (2.7)
3 Body	6 (15,4)	7 (29,2)	3 (21,4)	10 (28,6)	7 (20,0)	3 (37,5)	4 (28,6)	3 (15)	43 (22.9)
4 Tail	13 (33.3)	7 (29,2)	3 (21,4)	20 (57,1)	18 (51,4)	3 (37,5)	6 (42,9)	13 (65)	82(43.6)
Operation, n (%)									
1 PD	25 (50)	14 (46,7)	8 (57,1)	6 (15)	10(24,4)	2 (25,0)	6 (27,3)	2 (10.0)	73(32.3)
2 DP	19 (38)	13(43,3)	3 (21,4)	33(82,5)	29(70,7)	68 (75,0)	16 (72,7)	15 (75.0)	134 (59.3)
3 Enucleation	0 (0,0)	1 (3,3)	0 (0,0)	1 (2,5)	1 (2,4)	0 (0,0)	0 (0,0)	3 (15.0)	6 (5.3)
4 total	6 (12)	2 (6,7)	3 (21,4)	0 (0)	1 (2,4)	0 (0,0)	0 (0,0)	0 (0.0)	12 (5.3)
Symptomatic, n (%)	38	21	6	27	23	6	13	12	146
	(84,4)	(75.0)	(42,9)	(77,1)	(59)	(75)	(59,1)	(63,2)	(69,5)

MD-IPMN, Main duct-Intraductal papillary mucinotic neoplasm; MT-IPMN, Mixed-type Intraductal papillary mucinotic neoplasm; MCN, mucinous cystic neoplasm; SCN, serous cystic neoplasm; SPN, solid pseudopapillary neoplasm; EPIT, epithelial non- neoplastic tumours (EPIT); PD, Pancreaticoduodenectomy; DP, Distal pancreatectomy,

In **Study II**, in the period 2000-2008, 88 pancreatic resections were performed for IPMN tumours **(Figure 5)**. Median age of the patients was 65 (40-87) years and 58% were females. Almost three quarters of the patients (72.7%) were symptomatic. The largest cyst had a median diameter of 37.7mm (range 7-100). Several radiological

factors were analysed to detect malignancy pre-operatively, but the only statically significant factor was when an experienced radiologist suspected malignancy.

PD was performed on 43/88 (48.9%) of the patients and overall morbidity of all patients (CD 1–5) was 50%. Rate of complications among PD patients was 67.4% and among 32.5% of the patients the complications were considered severe (CD 3–5).

Distributions by subtype were MD-IPMN 47/88 (53.4%), MT-IPMN 27/88 (30.7%), and BD-IPMN 14/88 (15.9%). Analyses of the histological subtypes were performed for 23 patients; 8/23 (34.8%) had oncocytic (ONC), 11/23 (47.8%) had intestinal (INT) and 4/23 (17.4%) pancreatobiliary (PB) subtype of IPMN. LGD was present in 40/88 (45.5%), HGD in 9/88 (10.2%) and INV in 39/88 (44.3%) of the cases.

Median survival of the patients was 121 (0-252) months and overall five-year survival was 63.6%. Non-invasive tumours (LGD+HGD) had better five-year ($p<0.01$) survival than invasive tumours. Disease-specific five-year survival (DSS) was 97.1% in the LGD group compared to 40.0% in the INV group. Respective ten-year survival was 72.5/66.7/23.1% in the LGD/HGD/INV groups and only 7% of the patients in the LGD group died of pancreatic cancer (**Table 7, Figure 6**).

Table 7. Survival of 88 IPMN patients in **Study II**

	median (range)	IQR	1-year survival %	5-year survival %	10-year survival %	5-year disease-specific survival %	Pancreatic cancer mortality n (%)
BD	155 (3-252)	74.75-232.25	92.9	85.7	64.3	100	1/14 (7.1)
MD	87 (1-240)	21-141	85.1	59.6	44.7	65.1	20/47(42.6)
MT	124 (6-240)	17-171	92.6	59.3	51.9	66.7	10/27 (37.0)
LGD	142 (3-252)	101-185.75	97.5	87.5	72.5	97.1	2/40 (5)
HGD	118 (15-229)	58.5-168.5	100	77.8	66.7	87.3	1/9 (11.1)
INV	25 (1-226)	12-109	76.9	35.9	23.1	40.0	28/39 (71.8)
ONK	60.5 (3-242)	5.25-133.5	50	50	50	57.1	3/8 (37.5)
INT	124 (12-240)	15-178	100	72.7	72.7	80.0	2/11 (18.2)
PB	19 (12-34)	13.25-30.75	100	0.0	0.0	0.0	4/4 (100)
ALL	121 (0-252)	24.25-161.5	88.6	63.6	50.0	70.9	31/88 (35.2)

IQR, interquartile range; BD, branch-duct IPMN; MD, main-duct IPMN; MT mixed-type IPMN; LGD, low-grade dysplasia; HGD, high-grade dysplasia INV, invasive carcinoma; ONK, Oncocytic subtype; INT, Intestinal subtype; PB, Pancreatobiliary subtype

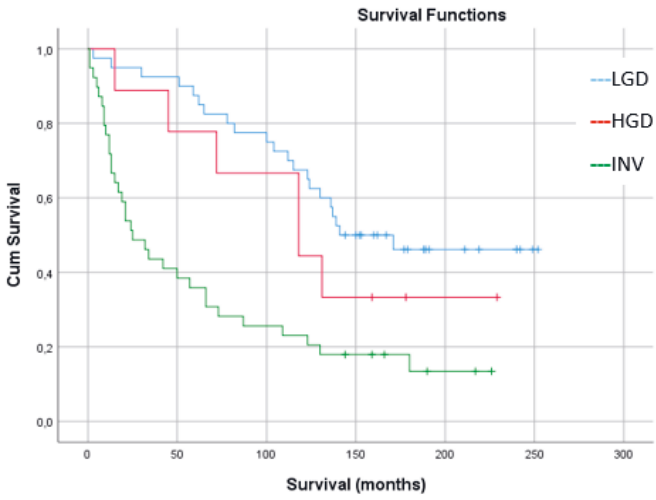

Figure 6. Kaplan–Maijer analysis of survival for low-grade dysplasia; (LGD), high-grade dysplasia (HGD) and invasive carcinoma (INV) in resected IPMN patients in **Study II**.

5.2 Study III

In Tampere University Hospital IPMN register, out of 128 patients (all with suspected BD-IPMN) included in the study, 23 were decided to operate upfront. Patients with upfront surgery were more symptomatic (60% vs 1%) and had larger cysts (40mm vs 15mm).

Five patients had an absolute indication for surgery in the upfront surgery group (malignant histology, two patients; MPD over 10mm, two patients; Jaundice, one patient). Seven patients had two relative indications and eleven patients had one relative indication. In final histology four patients had a malignant IPMN tumour and two had HGD (**Figure 7**).

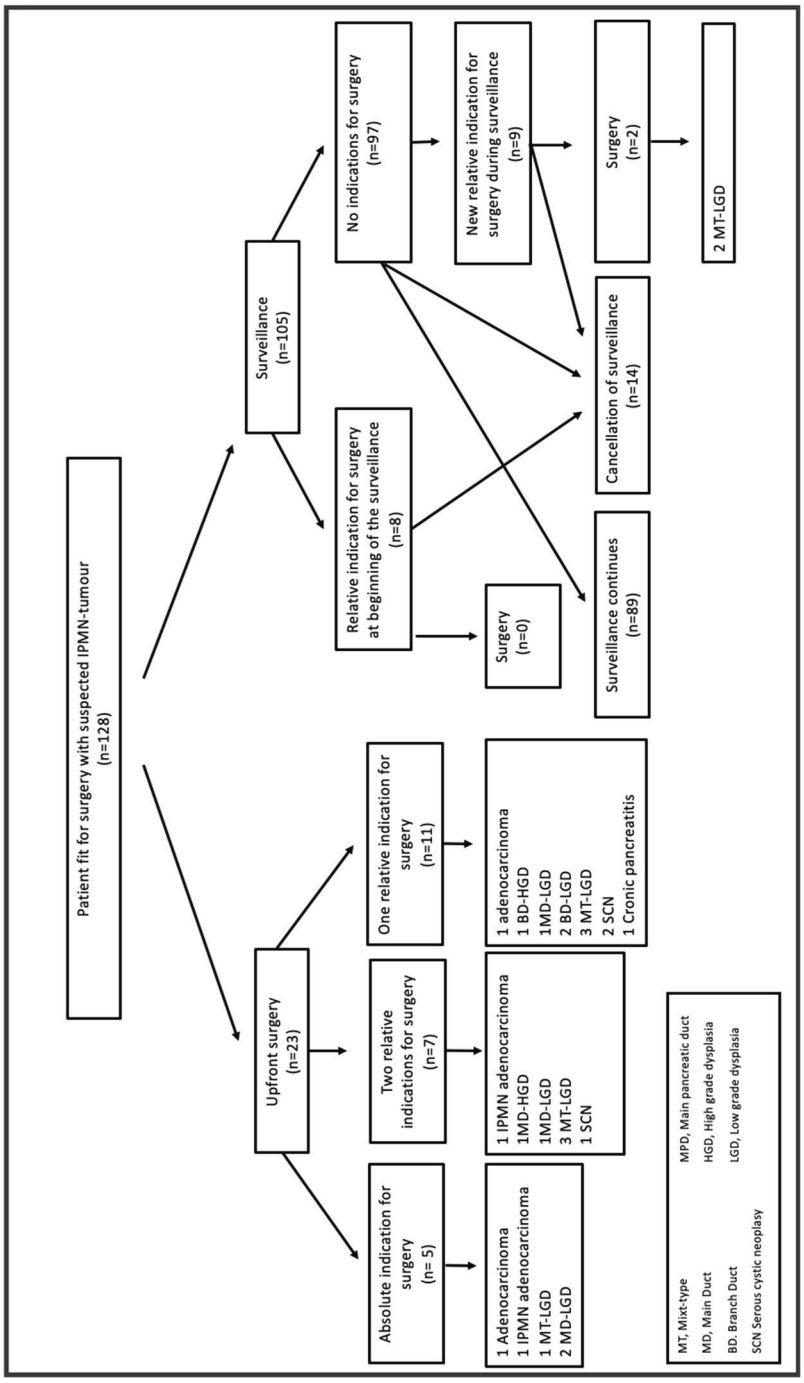

Figure 7. Flowchart of patients in IPMN surveillance in **Study III**

Median surveillance time in the surveillance group was 26 months. From the surveillance cohort 2/105 patients were operated on and the final histology of both patients was MT-IPMN with LGD. Relative indication for surgery was present in 8/105 (7.6%) patients at the beginning surveillance and 9/105 (8.6%) patients developed at least one relative indication for surgery during surveillance (**Table 8**). None of the patients in the follow-up cohort were diagnosed with or died of pancreatic cancer. Due to their poor general condition, surveillance was discontinued in 14.1% of the patients in non-operated group.

Table 8. Absolute and relative indications for surgery among 105 IPMN patients in surveillance in **Study III**

Absolute indication	**Beginning of surveillance**	**During surveillance**	**All**	**Operated on during surveillance**
Solid mass	0	0	0	0
Jaundice	0	0	0	0
Enhancing mural nodule ≥5 mm	0	0	0	0
MPD (Main pancreatic duct) diameter ≥10 mm	0	0	0	0
Relative indication[a]				
Cyst growth rate ≥5mm/year	0	3	3	0
Cyst diameter ≥40 mm	1	1	1	0
Increased levels of serum CA 19.9 (>37U/mL)	6	2	8	0
Enhancing mural nodule <5 mm	0	1	1	1[b]
Main pancreatic duct (MPD) diameter 5-9.9 mm	0	3	3	1[b]
Acute pancreatitis (caused by IPMN)	1	0	1	0
ALL (one patient had two relative indications)	8	10	17	2

[a] One patient had two relative indications

[b] Histology of both patients was Mixed type-IPMN with Low-grade dysplasia

6 DISCUSSION

6.1 1 Studies I-III

PCNs, and especially IPMN tumours, have been a subject of mounting interest in recent years. Despite increasing evidence, controversies about management of these lesions persist. In this thesis the demographics and long-term prognoses of patients with PCN were investigated. In addition, the feasibility of the new IPMN guidelines was demonstrated.

Preoperative findings

In **Study I** the resected tumours were large (median size 35mm) and most of the patients (69.5%) had pancreas-related symptoms. The small number of incidentally found tumours resected can be explained by less use of cross-section imaging during study period, meaning that only symptomatic tumours are found and resected. In preoperative imaging MRI was seldom used, in 28% of the cases, which reflects the poor availability of MRI in the study period. Over half of the tumours primarily diagnosed as MCNs were misdiagnosed, the diagnosis was corrected to IPMN in most cases. Similar changes in diagnoses have also been described by other authors (Niedergethmann et al., 2008). These findings reflect the development in the treatment of PCNs. Two paradigm changing developments occurred immediately before and during the study period; IPMN was included in the WHO classification in 1996 and the first guidelines for treating IPMN and MCN were launched in 2006. Since these developments were fairly new, they, especially the first guidelines, had little impact on the treatment of the patients in **Studies I** and **II**. After that, the shift has been rapid; in **Study III** all patients were treated according to the European guidelines, which is now common practice in managing IPMN patients in Finland.

Preoperative risk factors for malignancy

The identification of PCN patients at risk of developing malignancy before the transfer to malignant is the goal in treating PCN patients. In **Study I** independent

risk factors for malignancy were age over 60 years, symptoms and tumour location in the pancreatic head or uncinatus area. Tumour related symptoms are well documented risk factor for malignancy in IPMN patients, also some authors have also found increased risk for malignancy if tumour is located on head or uncinatus area of the pancreas (Del Chiaro et al 2017). Kerlakian et al., (Kerlakian et al., 2019) reported HGD or INV on 49% of tumours located on head or uncinatus area, compared to 27% on tumours located in body or tail area of the pancreas, in study of 275 resected IPMN tumours. In the case of IPMN tumours, there are several known risk factors for malignancy which, according to the current guidelines, require surgery. In **Study II** most of these factors, including tumour size, mural nodules and MPD dilatation, were tested, but none reached statistically significant difference. This negative finding may be explained partially by the low quality of radiological studies in the study cohort (less use of MRI studies). The quality of radiological workup can be compared to that in **Study III**, in which patients operated on upfront had mostly undergone MRI imaging and risk factors like MPD dilatation were well documented. In the early 2000s (timeframe of **Studies I and II**) pancreatic surgery was not centralized in Finland, and operations were carried out in many low-volume centres, which may have negatively affected the diagnostics of the PCN.

Out of the 23 patients operated on upfront in **Study III**, 18 patients had relative indications and five patients had absolute indications for surgery. MPD dilatation was the most common (12 patients) indication for surgery. MPD dilatation is a well-documented risk factor for malignancy (Hamada et al., 2023) and therefore upfront surgery on these patients was justified.

Surveillance

Once an IPMN tumour has been detected and has been designated for surveillance rather than surgery, the surveillance lasts until the patient is not fit for surgery. In **Study III**, 23 patients were operated upfront and the remaining 105 patients formed the surveillance cohort. None of the patients in surveillance cohort had absolute indication for surgery at the beginning of the surveillance. During surveillance of median 26 months, 68% of the patients had no increase in the size of the cyst nor increase in CA 19-9 level. Similar studies reporting slow progression have been published (Han et al., 2017). Relative indication for surgery was present in eight patients, and in six out of eight of these the indication was elevated CA 19-9. None of these patients underwent surgery. During surveillance eight patients developed at least one (one patient developed 2) relative indication for surgery and it was decided

that two of these patients would undergo surgery. Out of six conservatively treated patients the decision not to operate was based on minimal progression of the tumour. It was decided not to operate on the patient with two relative indications due to poor general condition. In clinical decision-making, the value of different indications for surgery varies. Evidence for risk of malignancy, for example, in MPD dilatation or solid tumour component is well established (Attiyeh et al., 2018; Ateeb et al., 2019). On the other hand, making the decision to operate based solely on an elevated level of CA 19-9 would be unjustified in spite of some studies promoting raised level of CA 19-9 as an independent risk factor for malignancy (Roch et al., 2014; Jang et al., 2017). Furthermore, multiple indications for surgery present an increased risk of malignancy and therefore surgery should be considered even if the risks in surgery are elevated. Also, conservative treatment is a feasible option for patients with significant co-morbidities. A systematic review states that mortality for other reasons than IPMN (with relative indications for surgery) can be much higher in patients with significant co-morbidities (Vanella et al., 2018).

Due to patients' poor general condition surveillance was discontinued in 14% of the cases. However, the number of patients admitted to surveillance protocols exceeded the number of discontinued surveillances, which causes by time an intolerable burden on the healthcare system. In elderly patients with co-morbidities, the continuation of the surveillance should be assessed critically at every control interval.

All elderly patients, even without significant co-morbidities might not benefit from IPMN-surveillance. The risk for developing pancreatic cancer in Finland according to the Finnish Cancer Registry (Suomen syöpärekisteri), is roughly 2%, and if the risk of developing IPMN-derived carcinoma is below that, the IPMN surveillance would be unjustified. In a retrospective study of 3,844 patients, Marchegiani et al., (Marchegiani et al., 2023) concluded that patients with presumed BD-IPMN without risk factors for malignancy after five years of surveillance have comparable risk of developing pancreatic malignancy with general population. The recommendation was to end the surveillance after five years of stability in patients > 75 years with cyst < 30 mm, and in patients >65 years if the cyst was ≤ 15mm. By adopting these recommendations, a significant amount of healthcare resources would be released to other, more meaningful purposes. None of the patients in S**tudy III** were diagnosed with pancreatic cancer during surveillance. Although the surveillance period was short (median 26 months), surveillance according to the European guidelines seems feasible for detecting malignancies.

Histological findings

In **Study I** IPMN was the most common histological diagnosis (42%), followed by SCN and MCN (18% each). The proportion of MCN tumours was slightly smaller than in many other surgical series (Gaujoux et al., 2011; Valsangkar et al., 2012). One possible explanation for the lower rate on MCN tumours in this study was that after pathological re-evaluation part of the MCN:s were classified as IPMNs. Overall, 41 SCN (18% of all tumours resected) tumours were resected in this study. The number of SCN tumours was high given that SCN tumours should be resected only in special cases due to the benign nature of the tumour. Differential diagnosis of SCN and MCN can be difficult (Roldán et al., 2023). The SCN cases in this study were probably diagnosed as cysts requiring surgery rather than as cysts classified as SCN requiring surgery. The challenge of making the right preoperative diagnosis for SCN persists, as pointed out in the recent literature (Slobodkin et al., 2020). In **Study II**, 53.4% of the tumours were classified as MD-IPMNs, 30.6% as MT-IPMNs and 16.3 as BD-IPMNs 16.3%. The rate of resected BD-IPMNs compared to MD-IPMNs and MT-IPMNs was lower than in recent publications, which reflects the increased number of BD-IPMNs in surveillance programmes (Marchegiani et al., 2015). In **Study III**, only four patients (4/23) had BD-IPMN in the upfront surgery group and none (0/2) in the operated after surveillance group. Likely the rate of resection of BD-IPMN in the surveillance group would have increased over time, since the majority, if not all, patients under surveillance were classified as BD-IPMN.

Malignancy was detected in 23.6% and HGD in 6.7% of the patients in **Study I**. All malignant tumours were in groups carrying elevated risk of malignancy; IPMN and MCN (2 malignant cases in the group 'others'). In **Study II**, three quarters of the MD-IPMNs were malignant or HGD. Besides IPMN and MCN, HGD was detected in 25% of the SPN patients. In the BD-IPMN group 12/14 (86%) of tumours were benign. All SCN tumours were benign, as expected. In **Study III** only 2/23 (8.7%) patients had IPMN-derived carcinomas in the upfront surgery group, and both patients operated on in surveillance group had LGD.

Low rates of malignancy in IPMN have also been reported by other authors. Aronsson et al., (Aronsson et al., 2018) had a malignancy rate below 10% in a Swedish nationwide register study. Johansson et al. (Johansson et al 2022.,) reported a cohort of 334 BD-IPMN patients in surveillance. During surveillance ten patients were operated on and only one had INV. Finally, Marchegiani et al., (Marchegiani et al., 2023) had a cohort of 3,844 presumed BD-IPMN patients in surveillance. A total

of 164 (4.3%) were operated on for IPMN and INV was found in 26 patients (15.9%).

Long-term results

In **Study I** the overall five-year survival rate was 76.7% and 88.9-100% in all other diagnostic groups besides IPMN and MCN. Five-year survival for IPMN was 68% and 79% for MCN. As expected, the prognosis relied heavily on the degree of dysplasia; five-year survival with malignant tumours was only 27% compared to 77% among HGD and 87% among benign cases. Also, in slowly developing conditions like IPMN, survival data even beyond five years are necessary. To the best of our knowledge no data on ten-year survival have been published in a nationwide setting. In **Study II**, five and ten-year survival with malignant IPMN tumours were 36% and 23% compared to 78% and 73% in the HGD group. Some authors, but not all, have reported statistically significant differences in survival among HGD and INV patients (Blackham et al., 2018; Aronsson et al., 2018). In **Study II** we could make no statically significant distinction between these groups in terms of five and ten-year survival.

Five-year survival In **Study II** for INV IPMN was 35.9%. McMillan et al. (McMillan et al., 2016) reported a five-year survival of low as 17%. However, the patients in this study were operated on during the period 1998-2010 and in the more recent literature higher survival rates have been reported. Gavazzi et al. (Gavazzi et al., 2022) reported 64.5% five-year survival of resected INV IPMN patients. Many factors could affect the decidedly low survival among the patients in **Study II**. Tumours were large and symptomatic when diagnosed, which could refer to advanced tumour. Also, centralization of pancreatic surgery increases short- and long-term survival of the patients (Ahola et al., 2019). At the time of Study II pancreatic surgery was not centralized in Finland which also may explain part of the poor survival. Finally, survival of resected INV IPMN is superior compared to resected PDACs. In a nationwide register study of resected PDACs in Finland between years 2000-2008 four-year survival rate in high volume centres was 13.0% and 6.7% in low volume centers which both are inferior rates compared to IPMN survival rate (Ahola et al., 2017).

In **Study II,** mortality from pancreatic cancer was 2/40 in the LGD group. Histology from the primary operations of these two patients was MT-IPMN and BD-IPMN. Favorable prognosis for benign IPMNs has also been reported by other authors: Aronsson et al., (Aronsson et al.,) reported 90% 3-year survival for non-

invasive IPMNs and Kurahara et al., (Kurahara et al., 2014) had 100% disease specific 5-year survival for benign resected IPMNs in cohort of 61 patients. The remnant pancreas (if total pancreatectomy had not been performed) harbours a risk for a malignant tumour which necessitates surveillance until the patient is not fit for surgery, as recommended in the guidelines. Mortality from pancreatic cancer was higher in the MD-IPMN and MT-IPMN groups than in the BD-IPMN (the MD and MT groups had more INV tumours than the BD group) but this difference did not reach statistical significance.

6.2 Strengths and limitations

The strength of this study is the nationwide cohort in **Studies I** and **II**. Also, the fairly long follow-up period is also a strength, especially in a disease like this, with slow evolution. There are nationwide cohorts in some other countries, but they lack a surveillance period of ten years. There are surgical series with much larger cohorts in high-volume centres, but these series may have been affected by selection bias, which is not an issue in a nationwide cohort. All available radiological and histological data were analysed by an expert pathologist and radiologist. A limitation of this study was incomplete datasets. We were able to collect full datasets with imaging studies and histological slides for only part of the patients. The poor quality of the datasets prevented us from conducting a meaningful quantitative analysis, for example, of preoperative risk factors for malignancy. Finally, because of fairy old patient cohort (Years 2000-2008) in studies I and II, some result cannot be meaningfully reflected to more recent studies. Since years 2000-2008 there has been many improvements in treatment of PNC patients in Finland including centralization of the pancreatic surgery and implementation of the guidelines.

In **Study III** we gathered all the IPMN patients in what at the time was the Pirkanmaa Hospital District. A strength of this study was that we were able to describe the whole pathway of patients diagnosed with IPMN. A limitation of this study was the short observation period (median 26 months) regarding the slow growth of risk factors in IPMN tumours.

6.3 Future perspectives

New techniques are emerging in the field of artificial analysis and molecular analysis of IPMN tumours. Extracellular vesicle analysis, also known as liquid biopsy, is a non-invasive method for identifying malignancy in IPMN patients (Yang et al., 2021; Qi et al., 2018). These methods could also be used in the surveillance of IPMN. Deep learning models can be used to analyse EUS-FNA samples aiming at better diagnostic accuracy (Schulz et al., 2023). Also, it can be used to enhance the quality of MRI imaging in the investigation of IPMN tumours (Matsuyama et al., 2022). Furthermore, artificial intelligence models may improve the diagnosing of malignancies in PCN patients (Kuwahara et al., 2019). In the field of clinical research, the treatment of IPMN patients can be improved by performing two types of studies. First, diagnostic accuracy can be increased by developing (and testing the model in an RCT setting) nomograms with large numbers of patients with resected IPMNs. While the number of patients in IPMN surveillance increases, the development of such models in international collaboration is essential. An example of such collaboration is the RCT of 3,708 patients by Kim et al. (Kim et al., 2023). Second, and probably more important, would be large-scale studies of patients in IPMN surveillance in an RCT setting.

7 CONCLUSIONS

Based on the studies included in this thesis we conclude that:

I In the nationwide register study one fourth of the resected PCNs were malignant, with a five-year survival of 27%, compared to 87% among benign cases. A large number of IPMN tumours were misdiagnosed as MCNs.

II Three quarters of the MD-IPMNs were malignant or HGD and 86% of BD-IPMNs were benign. In case of invasive IPMN-carcinoma, ten-year survival was less than 25% but if the tumour was resected in the pre-malignant stage (LGD and HGD) the survival was over 70%.

III Surveillance of the BD-IPMN tumours according to the European guidelines seems to be feasible. Overall, 16% of the patients had a risk factor for malignancy, but none of the patients were diagnosed with PDAC during 26 months of surveillance. Out of 105 patients under surveillance, two were operated on and neither of them had malignancy or high-grade dysplasia in histopathological analyses. Almost 15% of the patients under surveillance had their surveillance discontinued due to poor general condition.

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Characteristics and long-term survival of resected pancreatic cystic neoplasms in Finland. The first nationwide retrospective cohort analysis.

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Characteristics and long-term survival of resected pancreatic cystic neoplasms in Finland. The first nationwide retrospective cohort analysis

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ABSTRACT

Background: Pancreatic cystic neoplasms (PCN) are being found increasingly in imaging studies. Even though the characteristics of PCN lesions have been studied extensively in single and multicentre settings, nationwide data is lacking. The aim of this study was to determine the nationwide epidemiologic characteristics and long-term survival of all resected PCNs.

Methods: For this retrospective cohort analysis, all PCNs operated on in Finland during the period 2000–2008 were identified. Data was collected from all patients: on demographics, comorbidities, symptoms, radiological findings, surgical procedures, complications, histopathological diagnoses and survival. Incomplete pathology reports and any uncertain diagnoses were re-assessed. Survival data was collected after a five-year follow-up period.

Results: The final database included 225 patients with operated PCN. After reviewing the incomplete pathology reports, in 44 cases the original diagnosis was changed, mostly from MCN to IPMN. The most common histopathological diagnoses were IPMN (94/225; 50/225 MD-IPMN, 30/225 MX-IPMN and 14/225 BD-IPMN), SCN (41/225) and MCN (40/225). Overall, 53/225 (23.6%) of the tumours were malignant. Malignancy was detected in MD-IPMN 29/50 (58%), MX-IPMN 10/30 (33.3%), MCN 12/40 (30%), BD-IPMN 2/14 (14.3%) patients. Median 5-year survival for all patients was 77%: 87% in patients without malignancy, 77% with HGD and 27% in patients with a malignant resected PCN.

Conclusion: One fourth of the PCNs operated on nationwide were malignant, with a five-year survival of 27%, compared to overall survival of 87% in patients with non-malignant disease and 77% in those with HGD. Detecting – and operating on - a PCN before the malignant transfer remains a great challenge.

Introduction

Pancreatic cystic lesions (PCN) are being found increasingly in imaging studies, mainly due to ageing, increased imaging and improved radiological techniques [1,2]. The prevalence of resected intraductal papillary mucinous neoplasms (IPMN) has been reported to be on the increase, while the prevalence of mucinous cystadenoma (MCN) seems stable or is decreasing [1–3]. The reasons for this change remain unknown, but it has been suggested that some IPMNs have earlier been misdiagnosed as MCNs [4]. The malignant potential of PCNs varies from completely benign tumours, such as serous cystadenoma (SCN) and epithelial non-neoplastic tumours (EPIT), to tumours with a low malignant potential, such as branch duct (BD) IPMN, and to tumours with high malignant potential, such as main duct (MD) and mixed type (MX) IPMNs and solid pseudopapillary neoplasms (SPN) [5,6]. In earlier reports the majority of resected PCNs have been benign. To avoid unnecessary operations, good-quality preoperative assignment is crucial [7].

Even though the characteristics of resected PCNs have been

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studied extensively in single and multicentre settings, nationwide epidemiologic data is lacking.

The aim of this study was to determine the nationwide epidemiologic characteristics and long-term survival of all resected PCNs.

Methods

All pancreatic lesions operated on in Finland during the period 2000–2008 were identified by combining data from the national operations register and patient archives. After this, patients' medical records, including pre and postoperative data, were reviewed to identify patients likely to have undergone resection of a PCN. Conditions other than PCNs (mostly pseudocysts and pancreatic ductal adenocarcinomas) were excluded. The patients with resected PCN formed the final study population of this retrospective cohort analysis.

For the final study population, data was collected on demographics, comorbidities, symptoms, radiological findings, surgical procedures, complications, final histopathological diagnoses and survival. Due to incomplete patient records, preoperative data, including radiological findings, were partially missing for some patients. Variables with incomplete data sets were displayed with available data. A patient was deemed "symptomatic" if pancreas-related symptoms such as upper abdominal pain, jaundice, pancreatitis or weight loss were recorded at the time of PCN resection.

Radiological pancreatic findings such as size, location and number of cysts were gathered from the radiology reports. Postoperative complications were registered from the each hospital's medical records and graded according to the Clavien-Dindo Classification of Surgical Complications [8].

Pathology reports were reviewed. Incomplete reports and any uncertain diagnoses were re-assessed and, whenever necessary, the histopathological slides re-reviewed by an experienced pancreatic pathologist. These typically included any cases where a PCN had been classified as an MCN without mentioning the content of an ovarian type stroma.

Short and long-term mortality data was gathered from the Finnish registry office 31/3/2016. Follow-up time for all patients was five years.

Statistical analyses were performed using SPSS 22.0 for Windows (IBM Inc., Somers, USA). Unless otherwise specified descriptive statistics are reported using count, percentage, median and range. Chi-square test was used in univariate analyses and logistic regression analysis for multivariate analyses. $P < 0.05$ was considered statistically significant. Kaplan-Mayer analysis was used to analyze long-term survival.

Permission to review patient files and histological slides was obtained from the National Supervisory Authority for Welfare and Health (Valvira) (permission 10263/06.01.03.01/2012) and from National institute for health and welfare (THL) (permission 1854/5.05.00/2012).

Results

During the study period 2000–2008 a total of 2,024 patients underwent pancreatic surgery in Finland. Of these, 503 were identified as having presumably undergone resection of PCN. After carefully reviewing the patient records including preoperative radiological reports and postoperative histological reports, 147 patients without a real PCN and 61 patients with a pseudocyst were excluded. A further 70 cases for whom the patient records were not available were excluded. Thus 225 patients were included in the final study cohort (Fig. 1). These 225 patients were operated on in 22 different hospitals. 51% of the patients (115/225) were operated in the two high-volume centres; either in Helsinki University Hospital (67 patients) or in Tampere University Hospital (48 patients).

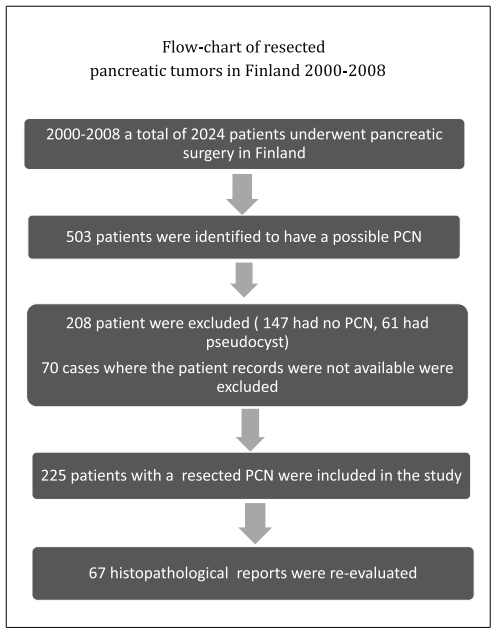

Fig. 1. Flow-chart of resected pancreatic tumours in Finland 2000–2008.

Frequency of pancreatic resections for PCN per year doubled during the study period 2000–2008. The population of Finland was 5.18 million in 2000 and 5.31 million in 2008. During the period 2000–2002 a resection for PCN was performed on 0.3/100 000, and during 2006–2008 on 0.6/100 000 people.

Preoperative findings

Median age was 61.0 (14–87) years, and 143 (63.3%) patients were female. At the time of operation, 25/154 (16.2%) patients had type 2 and 4/154 (2.6%) type 1 diabetes. Smokers amounted to 11/121 (9.1%) and 146/210 (69.5%) patients had symptoms related to PCN, the most common being pain 98/201 (46.7%), jaundice 21/201 (10.0%), pancreatitis 20/210 (9.5%) and weight loss 19/210 (9.0%), (Table 1).

In the preoperative imaging, computed tomography (CT) was performed in 191/198 (96.5%), magnetic resonance imagining (MRI) in 56/198 (28.2%) and endoscopic ultrasound (EUS) in 13/198 (6.6%) of the patients. In imaging the median tumour diameter was 40.0 (range 4–220) mm, 104/119 (87.4%) of the cysts were solitary lesions, and 125/188 (66.5%) of tumours were located left of the portal vein; the location was in the tail in 82/188 (43.6%), in the body in 43/188 (22.9%), in the head 58/188 (30.9%) and in the uncinatus area in 5/188 (2.7%) of the patients. Main pancreatic duct dilatation over 6 mm, calcifications of cysts or mural nodules were observed in 19/188 (21.5%) of the patients (Tables 1 and 2).

Surgery and complications

Distal pancreatic resection (DR) (tail resection or body and tail

Table 1
Baseline characteristics and preoperative findings of patients with resected PCN:n 2000–2008 in Finland.

Baseline characteristics	
Median age years, range	61.0 (14–87)
Gender, female/male, n (%)	143/82 (63.3/37.7)
Smoking, n (%)	11/121 (9.1)
Diabetes, n (%)	29/154 (18.8)
Symptoms	
Symptomatic, n (%)	146/210 (69.5)
Pain, n (%)	98 (46.7)
Jaundice, n (%)	21 (10.0)
Pancreatitis, n (%)	20 (9.5)
Weight loss, n (%)	19 (9.0)
Examinations	
CT, n (%)	191/198 (96.5)
MRI, n (%)	56/193 (29.0)
EUS, n (%)	13/192 (6.8)

Table 2
Radiological findings of patients with resected PCN:n 2000–2008 in Finland.

Size of tumour	
Median diameter of cyst, (range)mm	40.0 (4–220)
Location of cysts	
Head	58 (30.9)
Uncinatus	5 (2.7)
Body	43 (22.9)
Tail	82 (43.6)
Number of cysts	
1	87.4
2	4.2
3	0.9
>3	3.5
Worrisome features	
Any features, n (%)	19/88 (21.5)
MPD over 6 mm, n (%)	9/88 (10.2)
Calcification of cysts, n (%)	8/88 (9.1)
Mural nodules, n (%)	8/88 (9.1)

resection) was performed on 134/225 (59.6%), pancreaticoduodendectomy (PD) on 73/225 (32.4%), total pancreatectomy 12/225 (5.3%) and enucleation on 6/225 (2.7%) patients (Table 3a).

Overall morbidity according to the Clavien-Dindo Classification was 111/225 (49.3%). Of the complications 68/225 (30.2%) were classified as minor (Clavien-Dindo 1–2) and 40/225 (17.8%) as major (Clavien-Dindo 3–4). In-hospital mortality (Clavien-Dingo 5) was 3/225 (1.3%). Overall 30-day mortality was 5/225 (2.2%). Out of these five patients, four underwent PD and one patient DP. Four out of five patients had a malignant tumour. Ninety-day mortality was 7/225 (3.1%). After PD overall major complications (Clavien-Dindo 3–5) were more than after DP (21 (28.7%) vs. 15 (11.2%), $p < 0.001$) (Tables 3a and b).

Histopathological results

In the histopathological analyses median tumour size was 35 mm (range 2–180). Malignant tumours were seen in 53/225 (23.5%) of the patients and high-grade dysplasia (HGD) was present in 15/225 (6.6%) of the specimens (Table 4 and Table 6).

The most common histopathological diagnosis was IPMN, 94/225 (41.7%); 50/225 (22.1%) MD-IPMN, 30/225 13.3% MX-IPMN and 14/225 (6.2%) BD-IPMN. Other common diagnoses were SCN in 41/225 (18.1%), MCN in 40/225 (17.7%), EPIT in 22/225 (9.7%), and SPN in 8/225 (3.5%). Other, more rare tumours, such as cystic neuroendocrine tumours, myofibroclastic tumours, lymphangioma and acinar cell neoplasms accounted for a total of 20/225 (8.8%) of the

Table 3a
Type of surgery, rate of complications by Clavien-Dindo score, 30-day and 90-day mortality of resected PCN:s.

Type of surgery	
DP, n (%)[a]	134, (59.6)
PD, n (%)[b]	73, (32.4)
Total pancreatectomy, n (%)	12 (5.3)
Enucleation, n (%)	6 (2.7)
Complications	
Operation related morbidity and mortality	111 (48.4)
Clavien-Dindo 1–2, n (%)	68 (30.2)
Clavien-Dindo 3–4, n (%)	40 (17.8)
Clavien Dindo 5, n (%)	3 (1,3)
30-day mortality, n (%)	5[c] (2.2)
90-day mortality, n (%)	7 (3,1)

[a] DP = Distal pancreatic resection.
[b] PD = Pancreaticodudenectomy
[c] 2 patients died after discharging from hospital.

Table 3b
Clavien-Dindo score for each type of surgery.

	Clavien-Dindo 0	Clavien-Dindo 1-2	Clavien-Dindo 3-4	Clavien-Dindo 5
PD, n (%)[a]	27 (37,0)	24 (32,8)	21 (28,7)	3 (1,3)
DP, n (%)[b]	78 (58,2)	41 (30,6)	15 (11,2)	0 (0)
Enucleation, n (%)	5 (83,3)	1 (16,7)	0 (0)	0 (0)
Total Pancreatectomy, n (%)	6 (50,0)	2 (16,7)	4 (33,3)	0 (0)

[a] DP = Distal pancreatic resection.
[b] PD = Pancreaticodudenectomy

cases (Table 4).

IPMNs were evenly distributed for gender, whereas 7/8 of SPNs and 40/40 of MCNs were seen in females. IPMNs were located equally in the right and left side of portal vein, 30/40 (75%) of MCNs were located in the body or tail (Table 4).

Overall, 53/225 (23.6%) of the tumours were malignant and 15/225 (6.7%) had HDG. Malignancy was detected in MD-IPMN 29/50 (58%), MX-IPMN 10/30 (33.3%), MCN 12/40 (30%), BD-IPMN 2/14 (14.3%), SPN 0/8 (0%), SCN 0/41 (0%) and others 0/20 (0%). Quantities of HGD tumours were: MD-IPMN 6/50 (12%), MX-IPMN 3/30 (10%), MCN 2/40 (5%), BD-IPMN 0/14 (0%), SPN 2/8 (25%), SCN 0/40 (0%) and others 2/20 10%). Of the PDs 33/73 (45.2%) and of the DPs 16/134 (11.9%) were performed for malignant tumours (Table 6.).

Risk factors for malignancy in univariate analyses were age over 60 years ($p < 0.01$), symptoms ($p = 0.03$) and tumour location in the pancreatic head or uncinatus area ($p < 0.01$). The same risk factors for malignancy lasted in multivariate analyses: age over 60 years ($p < 0.003$, odds ratio 3.486), symptoms ($p < 0.016$, odds ratio 3.259), and tumour location in the pancreatic head or uncinatus area ($p < 0.016$, odds ratio 2.624). Equal numbers of malignant tumours were seen in patients with and without potential risk factors, including smoking, diabetes or cyst size >3 cm. PCNs with and without worrisome features in preoperative imaging (main pancreatic duct dilatation over 6 mm, calcification of cysts, mural nodules) also had similar frequency of malignancy [7,11] (Tables 5a and b).

In 67/225 (29.8%) of the patients the original pathological reports were inconclusive. In 25 cases re-evaluation was made by experienced pancreatic pathologist based on original pathological reports and 42 cases histopathological slides needed to be re-reviewed. In most of these cases, the tumours were classified as MCNs in the original pathologic report but did not fulfill the criteria regarding the presence of ovarian type-stroma [6]. Original MCN diagnoses were confirmed in 23 cases, and in 44 cases the

Table 4
Characteristics of resected PCN:s.

Variable	MD-IPMN	MX-IPMN	BD-IPMN	MCN	SCN	SPN	EPIT	Other	All
N	50	30	14	40	41	8	22	20	225
Age years, median (range)	70.5 (44–87)	67.0 (40–81)	63.5 (53–72)	51.0 (27–82)	64.0 (33–79)	21.0 (14–47)	56 (24–75)	47.0 (24–75)	61.0 (14–87)
Sex Female %	50	56,6	42,9	100,0	82,9	87,5	27,3	40,0	63,6
N, %	50 (22,1)	30 (13,3)	14 (6,2)	40 (17,7)	41 (18,1)	8 (3,5)	22 (9,7)	20 (8,8)	225
Tumour size, median (range) mm	33 (3–120)	40 (10–95)	30 (10–50)	50 (2–180)	40 (8–120)	65 (13–130)	25 (6–80)	25 (12–100)	35 (2–180)
Location, n (%)									
1 Head	19 (48,7)	10 (41,7)	7 (50)	4 (11,4)	9 (25,7)	2 (25,0)	4 (28,6)	3 (15.0)	58 (30.9)
2 Uncinatus	1 (2,6)	0 (0,0)	1 (7,1)	1 (2,9)	1 (2,95)	0 (0,0)	0 (0,0)	1 (5.0)	5 (2.7)
3 Body	6 (15,4)	7 (29,2)	3 (21,4)	10 (28,6)	7 (20,0)	3 (37,5)	4 (28,6)	3 (15)	43 (22.9)
4 Tail	13 (33.3)	7 (29,2)	3 (21,4)	20 (57,1)	18 (51,4)	3 (37,5)	6 (42,9)	13 (65)	82 (43.6)
Operation, n (%)									
1 PD	25 (50)	14 (46,7)	8 (57,1)	6 (15)	10 (24,4)	2 (25,0)	6 (27,3)	2 (10.0)	73 (32.3)
2 DP	19 (38)	13 (43,3)	3 (21,4)	33 (82,5)	29 (70,7)	68 (75,0)	16 (72,7)	15 (75.0)	134 (59.3)
3 Enucleation	0 (0,0)	1 (3,3)	0 (0,0)	1 (2,5)	1 (2,4)	0 (0,0)	0 (0,0)	3 (15.0)	6 (5.3)
4 total	6 (12)	2 (6,7)	3 (21,4)	0 (0)	1 (2,4)	0 (0,0)	0 (0,0)	0 (0.0)	12 (5.3)
Symptomatic, n (%)	38 (84,4)	21 (75,0)	6 (42,9)	27 (77,1)	23 (59)	6 (75)	13 (59,1)	12 (63,2)	146 (69,5)

Table 5a
Risk factors for malignancy in resected PCN:s.

Variable	No carcinoma n = 172	Carcinoma n = 53	p-value
Age 60 years or more/age less than 60 years	65.6%/89.3%	34.4%/10.7%	<0.001
Tumour location[a]	65.1%/86.4%	34.9%/13.6%	<0.001
Symptomatic/ asymptomatic	72.2%/89.4%	27.8%/10.6%	0.0030
Gender female/male	77.6%/74.4%	22.4%/25.6%	0.737
Diabetes	75.9%/76.0%	24.1%/24.0%	0.988
Cyst size 3 cm or more	76.3%/88.9%	23.7%/11.1%	0.055

[a] 1: caput or uncinatus; 2: body or tail.

Table 5b
Multivariate logistic regression analyze for risk of malignancy.

Variable	p-value	Odds ratio	95% Confidence interval
Age over 60 years	0.003	3.486	1.523–7.984
Tumour location	0.016	2.624	1.193–5.772
Symptomatic	0.028	3.259	1.136–9.344

diagnoses changed. Changed diagnoses included 27 MD-IPMN, 9 MX-IPMN, 2 BD-IPMN, 3 SCN, 2 acinar cell neoplasms and 1 ductal adenocarcinoma.

Long-term survival

Of the patients 220/225 (97.8%) survived over 30 days after the operation. Median 5-year survival for all patients with resected PCN was 76.7%: 86.9% for patients without malignancy, 76.6% for patients with HGD and 27.3% for patients with malignant resected PCN. In 46/53 (86.8%) of the patients with a malignant tumour death was related to pancreatic cancer (Table 6, Fig. 2).

Out of the total 94 IPMNs, 53 were benign. Three (5.7%) of these patients (BD-IPMN with LGD, MX-IPMN with LGD and MD-IPMN with HGD) died of pancreatic cancer during the follow-up period, 49–79 months after the operation.

Discussion

PCNs are a heterogeneous group of tumours with a varying malignancy potential. The nationwide epidemiologic characteristics of resected PCNs are largely unknown. Our aim was to study the nationwide characteristics and long-term prognosis of resected PCNs in Finland.

Table 6
% of malignant tumours and 5-year survival of patient's with resected PCN.

	Benign	Benign %	Hgd	Hgd %	Malignant	Malignant %	5-year survival %
MD-IPMN	15	30.0	6	12.0	29	58.0	62.5
MX-IPMN	17	56.7	3	10.0	10	33.3	63.3
BD-IPMN	12	85.7	0	0	2	14.3	83.3
MCN	26	65.0	2	5	12	30	78.8
SCN	41	100.0	0	0	0	0	88.9
SPN	6	75	2	25	0	0	100
EPIT	22	100	0	0	0	0	92.9
Other	18	90.0	2	10	0	0	90.0
All	157	69.8	15	6.7	53	23.6	76.7
Benign							86.9
HGD							76.6
Malignant							27.3

This paper described the preoperative characteristics, surgical details, distribution of diagnoses and long-term survival of all resected PCNs in Finland between 2000 and 2008. By having an experienced pancreatic pathologist re-review the histopathological analyses whenever necessary we were able to set the correct diagnoses of the tumours. To the best of our knowledge this is the first nationwide study on resected PCNs. There are larger published series of resected PCNs from high-volume academic centres and of multicentre origin, which may contain selection bias, which should not be present in this nationwide study [4,7].

According to the literature, the number of incidentally found, resected PCNs is rising [5]. PCNs are detected more often mostly due to improvements in and increased usage of imaging techniques. Moreover incidental PCNs have been monitored more closely since European [9] and international [10] guidelines were published in 2013 and 2012. The size of resected PCNs has decreased in recent decades [7]. In this study the resected PCNs were mostly symptomatic 146/210 (69.5) and the median size of the tumour was also larger than reported in the recent literature. Tumour size and high proportion of symptomatic patients can be explained by changes in the criteria concerning operating on PCNs and by better imaging techniques. In the early 2000s the availability of MRI and EUS was inferior compared to today, which explains the fairly frequent use of CT and low use of MRI and EUS [11].

The rate of morbidity - and even mortality - after pancreatic surgery was high, but around the same level as described in the literature (Table 3). A patient who is fit for surgery and with a strong indication renders it advisable to proceed to operation. If, on the other hand, the patient is borderline operable and/or the indication is relative, the decision whether to operate becomes less

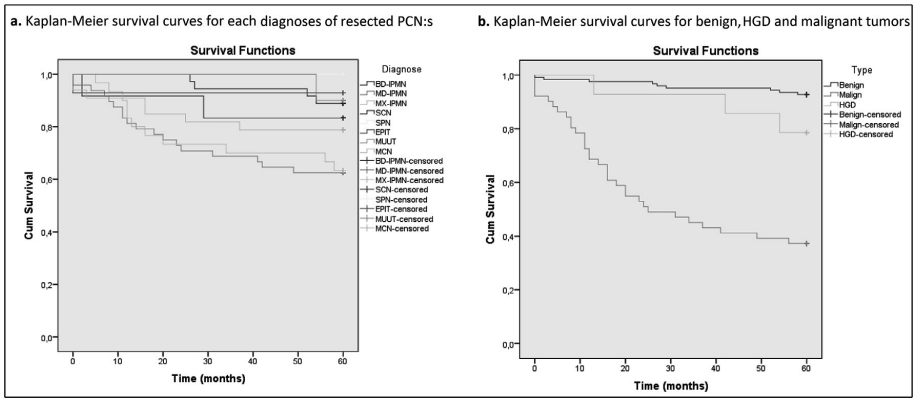

Fig. 2. **a.** Kaplan-Meier survival curves for each diagnoses of resected PCN:s. **b.** Kaplan-Meier survival curves for benign, HGD and malignant tumours.

clear-cut. As described by Del Chiaro, patients unfit for surgery had relatively high IPMN-specific survival [12]. In any case, optimal results for patients with PCN demand high quality preoperative workup, correct patient selection as well as proper follow-up.

Since IPMN tumours were first described by Ohashi in 1982 [12], the incidence of IPMN has been increasing in large retrospective series [3,5]. During the same period of time, the proportional incidence of resected MCNs has decreased significantly. There is an ongoing discussion - as Valsangkar et al. [4] point out - whether the actual incidence is increasing, or whether the reported increase is more related to the change in the histopathological classification of tumours. Niedergethmann et al. [14] reviewed histological specimens of 207 cystic or small solid tumours out of 1,424 pancreatic specimens. Fifty-four of these specimens revealed an IPMN tumour. Our results were similar: a significant proportion of the original diagnoses changed to IPMN after reviewing. Most of these had previously been diagnosed as MCN or unclassified cystic tumour of the pancreas. These findings support the hypothesis that the real incidence of IPMN-tumours may not be increasing, at least not as dramatically in the as suggested. Thus the reason for the increase in the incidence of IPMN may be related to changes in pathological criteria, improvement in the quality of pathology, improved imaging techniques and an increase in the frequency of cross-sectional imaging.

The relevance of making an accurate distinction between IPMN and MCN tumours is related to the different recurrence pattern of IPMN and MCN. Even after resection IPMN tumours require lifelong surveillance (total pancreatectomy patients excluded) since there is a substantial risk of recurrence even if the resection margins were negative [4,9,15]. Benign MCNs, on the contrary, have a recurrence level close to zero so follow-up is not recommended [4,16].

In our material the proportion of IPMN tumours was 94/225 (42%), SCN 41/225 (18%) and MCN 40/225(18%). Distribution of diagnoses is similar to that reported for large series of resected PCNs [4,5,7,13]. The number of IPMN tumours is slightly higher, which can be partially explained by the revised diagnoses after re-reviewing the histopathology. SCN tumours should only be resected when symptomatic, in case of rapid growth, if the diagnosis is uncertain or if there is concern about malignancy [17–19]. However, imaging diagnostics of SCN is not always easy. Making a radiologic distinction between SCNs and MCNs can be especially difficult [20]. Availability of MRI and EUS was moreover limited during the study period, which impaired the quality of the preoperative assessment and likely resulted in unnecessary operations. In our material, 24/41 (59%) of the patients with resected SCNs had pancreas related symptoms as expected, even though none of the patients had any signs of malignancy or HGD in histopathological analyses (Tables 1 and 4 and Table 6).

The European and international guidelines for IPMN and MCN have gathered risk factors related to the risk of tumours transforming from benign to malign [9,10]. From radiology reports we were able to obtain data on main pancreatic duct dilatation over 6 mm, calcification of cysts and mural nodules. In our analyses none of these factors were significant risk factors for malignant tumours. Main pancreatic duct dilatation is diagnosed reliably by MRI examination. In this population only 56/198 (28.2%) of patients were examined by MRI. A lack of MRI studies can partially explain why main pancreatic duct dilatation is not a risk factor for malignancy, or even for HGD, in this study. In this material the risk factors for malignant tumours were age over 60 years ($p < 0.01$), symptomatic patient ($p = 0.03$) and tumour location in the caput or uncinatus of the pancreas ($p < 0.01$). These factors were also independent risk factors in the multivariate logistic regression analyses. It is known that symptomatic tumours carry more risk of malignancy and that age increases the cumulative risk of having a malignant tumour. Patient age and/or poor general condition may lead to more pressing indications for surgery, which causes fewer tumours to be operated on before they become malignant. It has been reported that IPMN tumours to the right of the porta carry an increased risk of progression compared to those on the left side of the porta [12]. Also, the majority of zero or low malignancy potential tumours such as SCN and EPIT were located on the left side of the vena portae (Tables 4.and6).

Most patients with resected PCNs were females (143/225). The literature reports no gender difference in the prevalence of PCNs [1,21]. In our material, however, a large proportion of tumours were diagnosed as MCNs or SCNs, which are predominantly diagnosed in women, explaining the difference in gender distribution (Table 4.).

Out of the 94 IPMNs 44 showed no signs of malignancy or HGD in the histopathological analyses. During long-term follow-up three of these 44 patients (6.8%) still died of pancreatic cancer. This strongly supports the guidelines recommending follow-up of resected IPMNs.

Patients with benign tumours had 87% 5-year survival. Even with HGD tumours the 5-year survival was 76.6%, whereas in

malignant tumours it was only 27%. These numbers serve to confirm that detecting – and operating on - a PCN before malignant transfer is essential for long-term survival. In spite of the significant morbidity involved in pancreatic resections, in benign cases it does not affect patients' 5-year survival compared to that of general population [22].

We conclude that in this first nationwide study of resected PCNs, one fourth of the tumours were malignant, with a five-year survival of 27%, compared to overall 87% in patients with non-malignant disease and 77% with HGD. A surprisingly large number of diagnoses were revised after re-review of the specimens by an experienced pancreatic pathologist. A correct histopathological diagnosis affects the optimal follow up plan for each patient. As the number of detected PCNs is increasing, all efforts should be invested in optimal pre- and postoperative workup of these patients. Operating a PCN before the malignant transfer as well as prompt recognition of entirely benign lesions, to spare patients from the morbidity inevitably related to pancreatic surgery, remain a great challenge.

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PUBLICATION II

Long-term (10-year) outcomes and prognostic factors in resected intraductal papillary mucinous neoplasm tumors in Finland: A nationwide retrospective study.

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Long-term (10-year) outcomes and prognostic factors in resected intraductal papillary mucinous neoplasm tumors in Finland: A nationwide retrospective study

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ABSTRACT

Background: The degree of dysplasia is the most important prognostic factor for patients with resected intraductal papillary mucinous neoplasms. Intraductal papillary mucinous neoplasms are predominantly premalignant conditions; in most cases, surveillance is an adequate treatment. If worrisome features are present, surgery should be considered. However, there is limited data on the long-term prognosis of resected intraductal papillary mucinous neoplasms. We aimed to ascertain the nationwide survival of patients with resected intraductal papillary mucinous neoplasms and identify factors associated with survival.

Methods: This is a retrospective nationwide cohort study. All intraductal papillary mucinous neoplasms operated on in Finland between 2000 and 2008 were identified. Patient records were evaluated, and original radiologic data and histologic samples were re-evaluated. Survival data were collected after a 10-year follow-up period.

Results: Out of 2,024 pancreatic resections, 88 were performed for intraductal papillary mucinous neoplasm. The median age of the patients was 65 years. Histologic diagnoses were main duct intraductal papillary mucinous neoplasm 47/88 (53,4%), mixed-type intraductal papillary mucinous neoplasm 27/88 (30.7%), and branchduct intraductal papillary mucinous neoplasm 14/88 (15.9%). Of the tumors, 40/88 (45.5%) were low-grade dysplasia, 9/88 (10.2%) high-grade, and 39/88 (44.3%) were invasive cancer. The median survival was 121 (range 0–252) months. Ten-year survival was 72.5%, 66.7%, and 23.1% in the low-grade dysplasia, high-grade dysplasia, invasive cancer groups, respectively. Ten-year mortality for pancreatic cancer was 5%, 9.1%, and 71.8% in the low-grade dysplasia, high-grade dysplasia, invasive cancer groups, respectively.

Conclusion: Overall, 44.3% of the patients had a malignant tumor, and three-quarters (74.5%) of the main duct intraductal papillary mucinous neoplasms were malignant or high-grade dysplasia at the time of surgery. Ten-year survival was significantly better in patients operated on at the stage of a premalignant tumor (low-grade dysplasia + high-grade dysplasia) than in patients operated on at the stage of a malignant tumor.

Introduction

The prognosis of patients with resected intraductal papillary mucinous neoplasms (IPMN) mostly depends on the degree of dysplasia.[1] Patients with low malignant potential tumors, such as low-grade (LG) branch duct (BD)–IPMN, have excellent prognoses compared to patients with invasive main duct (MD)– or mixed-

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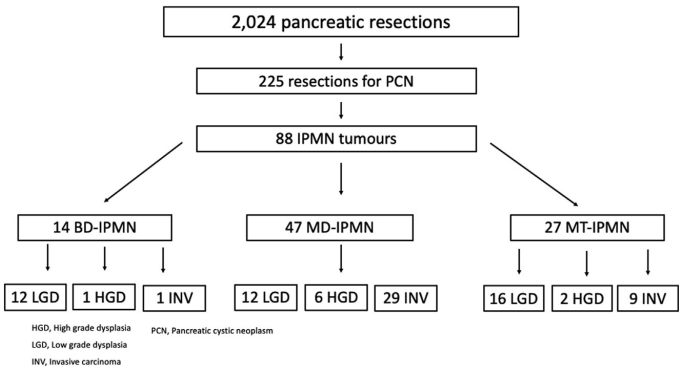

Figure 1. A flowchart of resected intraductal papillary mucinous neoplasm tumors in Finland between 2000 and 2008.

type (MT)–IPMN.[2] Beyond main pancreatic duct (MPD) involvement and the degree of dysplasia, other known factors influence long-term prognosis. Tumor size, positive lymph nodes, and positive resection margins worsen long-term outcomes.[1,2] Also, histologic subtypes are factors for patients' long-term prognosis; gastric and intestinal-type IPMNs are usually associated with superior outcomes compared to pancreatobiliary type IPMNs, which represent the more aggressive type, usually associated with high-grade dysplasia (HGD) and invasive adenocarcinoma.[3–5]

Since IPMN was included in the WHO classification system in 1996, it has been subjected to rigorous scrutiny. Several guidelines on managing IPMN tumors have been issued, such as the European Evidence-Based Guidelines on Pancreatic Cystic Neoplasms,[6] in 2017, the revised international consensus Fukuoka guidelines on the management of IPMN of the pancreas,[7] and the American Gastroenterological Association guidelines.[8] The most widely accepted risk factors for malignancy in these guidelines are main duct dilation, cyst diameter, and elevated levels of serum carbohydrate antigen 19-9.[9–16]

The IPMNs are a fairly new entity; only limited long-term data is available, especially in a nationwide setting.[17–19] Because IPMN tumors are optimally operated on during the premalignant phase, it is probable that the median survival of these patients is excellent. Thus, data on long-term outcomes, even beyond 5 years, are needed to evaluate the actual benefit for the patients undergoing surgery instead of surveillance. This study aimed to identify nationwide patient characteristics and prognostic factors in a 10-year follow-up period.

Methods

This nationwide retrospective study of resected IPMNs with a 10-year follow-up includes all pancreatic lesions operated on in Finland from 2000 to 2008. The patients were identified by combining data from the national operations register and hospital patient archives. Patients with resected IPMNs formed the final study population (Figure 1).

Patient demographics, comorbidities, symptoms, radiological findings, operation details, and histologic findings were obtained from the patient records. Postoperative complications were registered and graded according to the Clavien-Dindo (CD) classification of surgical complications.[20]

The preoperative imaging studies were reanalyzed for the study by an experienced pancreatic radiologist. Histologic evaluation with immunohistochemistry was repeated from the original histologic glasses by an experienced pancreatic pathologist. The findings were classified according to the World Health Organization classification of pancreatic tumors using hematoxylin and eosin–stained sections.[21] The presence of dysplasia was recorded, and grading was based on a 2-step grading system (low and high-grade dysplasia). The variables with incomplete data were displayed with data available; some radiological studies and pathological slides were not available for this study.

The minimum follow-up time for all patients was 10 years (range 10–21 years). Survival data, including time of death, total mortality, and mortality for pancreatic cancer, was gathered from the Finnish Registry Office on November 26, 2020.

Statistical analysis

Statistical analyses were performed using SPSS 26.0 for Windows (IBM SPSS, Inc, Armonk, NY). Descriptive statistics are reported using count, percentage, median, and range unless otherwise specified. The χ^2 analysis was used in univariate analyses. Kaplan-Meier analysis was used to analyze long-term survival.

Ethical aspects

Permission to review patient files and histologic slides was obtained from the National Supervisory Authority for Welfare and Health (Valvira) (permission 10263/06.01.03.01/2012) and from the National Institute for Health and Welfare (permission 1854/5.05.00/2012).

Results

Epidemiology

Between 2000 and 2008, 2,024 pancreatic resections were performed in Finland. Of those 2,024 resections, 225 operations were performed for pancreatic cystic neoplasms. Finally, re-evaluated histology was IPMN in 88/225 (34.5%) cases (Figure 1), and these patients were included in the study database. Resections for IPMN were performed at 12 centers; 49/88 (55.6%) of the resections were performed in the 2 largest centers, Tampere and Helsinki University Hospitals. The population of Finland was roughly 5.25 million during the study period from 2000 to 2008, and thus a resection for an IPMN was performed yearly on 0.19/100,000 patients. For reference, between 2013 and 2018, the rate of

Table I
Preoperative findings, radiologic imagining, and operating centers of patients with resected IPMNs (2000–2008) in Finland

Finding	Total, *n*	% of the patients
Sex F	51/88	58%
Sex M	37/88	42%
Type 1 diabetes	2/74	2.7%
Type 2 diabetes	17/74	22.9%
Smoking	4/44	9.7%
Previous cancer	9/65	13.8%
Symptomatic	64/88	72.7%
Duration of symptoms before operation (mo)	Mean 6.88	1–37
CT	84/88	95.5%
MRI	25/88	28.4%
CT + MRI	21/88	23.8%
EUS	5/88	5.7%
Median age at surgery	65.4	(40–87)
Number of centers	12	
Number of cases on 2 high-volume centers	49	
Number of cases in other 10 centers	39	

IPMN, intraductal papillary mucinous neoplasm; *MPD*, main pancreatic duct.*BD*, branch duct; *HGD*, high-grade dysplasia; *INV*, invasive carcinoma; *IPMN*, intraductal papillary mucinous neoplasm; *LGD*, low-grade dysplasia; *MD*, main duct; *MPD*, main pancreatic duct; *MT*, mixed-type.*CT*, computed tomography; *EUS*, endoscopic ultrasound; *IPMNs*, intraductal papillary mucinous neoplasms; *MRI*, magnetic resonance imaging.

resections for IPMN in the Pirkanmaa Hospital District was 0.76/y/100,000 patients (Table I).

Patient characteristics and preoperative findings

In 88 patients, the final histology was IPMN. The median age was 65.4 (40–87) years, and 51/88 (58%) were females. Most patients, 64/88 (72.7%), were symptomatic at the time of surgery. Patients with symptoms had symptoms for a median of 6.9 (1–37) months before surgery (Table I).

The most used (95.5%) preoperative radiologic modality was computed tomography. All preoperative used examinations (and re-examined later in this study) are presented in Table I. The median diameter of the largest cyst was 37.7 mm (7–100); in 68/88 patients (77.3%), there was a single cyst. The median main pancreatic duct (MPD) diameter was 5.1 mm (1–17). Distributions for MPD calibers were MPD <4.9 mm 40/68 (58.8%), MPD 5 to 9.9 mm 18/68 (26.5%), and MPD >10 mm 10/68 (14.7%). Cysts were detected to communicate with MPD in 35/68 (51.5%) cases. The location of the largest cyst was in the pancreatic head in 42/80 (52.4%), in the body in 19/80 (23.8%), and in the tail in 19/80 (23.8%). Parenchymal atrophy in any location of the pancreas was detected in 33/56 (58.9%) of the cases. Thickening of the cyst wall >2 mm was present in 27/54 (50%), septa of the cyst were seen in 39/68 (57.4%), mural nodules of the cyst in 17/64 (26.6%), and calcification of the cyst in 7/73 (6.8%) of the cases. An experienced radiologist suspected malignancy in re-evaluating 12/55 (21.8%) cases (Tables II and III).

Surgery and complications

Pancreaticoduodenectomy was performed on 43/88 (48.9%), distal pancreatic resection (tail resection or body and tail resection) on 33/88 (37.6%), total pancreatectomy on 11/88 (12.5%), and enucleation on 1/88 (1.15%) of the patients. Overall morbidity (CD 1–5) was 43/88 (49.9%), 22/88 (25%) of the patients had serious postoperative complications (CD 3–5), and 30-day mortality was 2/88 (2.3%) (Table IV).

Histopathologic analysis

Histologic diagnoses were MD-IPMN 47/88 (53.4%), MT-IPMN 27/88 (30.7%), and BD-IPMN 14/88 (15.9%). Overall, 40/88 (45.5%) of the tumors were LGD, 9 (10.2%) HGD, and 39/88 (44.3%) INV. Distributions of dysplasia were for MD-IPMN; LGD 12/47 (25.5%), HGD 6/47 (12.8%), INV 29/47 (61.7%), MT-IPMN; LGD 16/27 (59.3%), HGD 2/27 (7.4%), INV 9/27 (33.3%), and BD-IPMN; LGD 12/14 (85.7%), HGD 1/14 (7.1%), and INV 1/14 (7.1%). The histological subtypes were analyzed for 23 patients, of whom 11/23 (47.8%) had intestinal (INT), 8/23 (34.8%) oncocytic, and 4/23 (17.4%) pancreatobiliary (PB) subtype of IPMN tumor. For INT, oncocytic, and PB, the respective distributions of dysplasia were LGD 4/11 (36.4%), HGD 4/11 (36.4%), INV 3/11 (27.3%), LGD 5/8 (62.5%), HGD 0/8 (0.0%), INV 3/8 (37.5%), LGD 0/4 (0.0%), HGD 0/4 (0.0%), and INV 4/4 (100%) (Table V). Histologic subtype expressions are presented in Supplementary Table S1.

Long-term outcomes

The minimum follow-up time was 10 years (range 10–21). The median survival was 121 (range 0–252) months. One-year, 5-year, and 10-year survival was 88.6%, 63.6%, and 50.0%, respectively. In the subgroups formed according to the degree of dysplasia, 1-, 5,- and 10-year survival was 97.5%, 87.5%, 72.5% for LGD, 100%, 77.8%, and 72.5% for HGD, and 76.9%, 35.9%, and 23.1% for INV. There was a

Table II
Radiologic findings, type of tumor, and degree of dysplasia of resected IPMN tumors

Radiological findings	Total *n* (%)	BD-IPMN *n* (%)	MD-IPMN *n* (%)	MT-IPMN *n* (%)	LGD *n* (%)	HGD *n* (%)	INV *n* (%)
Diameter of largest cyst, mm, median (range)	37.7 (7–100)	32.4 (12–50)	38.9 (9–86)	38.5 (7–100)	37.9 (7–100)	42.4 (20–64)	36.0 (9–86)
Single cyst	68/88 (77.3)	6/14 (42.9)	41/47 (87.2)	21/27 (77.8)	28/40 (70.0)	8/9 (88.9)	32/39 (82.1)
MPD <4.9 mm	40/68 (58.8)	13/13 (100)	13/32 (40.6.)	14/23 (60.9)	25/34 (73.5)	2/6 (33.3)	13/28 (46.4)
MPD 5–9.9 mm	18/68 (26.5)	0/14 (0.0)	12/32 (37.5)	6/23 (26.1)	7/34 (20.6)	1/6 (16.7)	10/28 (35.7)
MPD >10 mm	10/68 (14.7)	0/14 (0.0)	7/32 (21.9)	3/23 (13.0)	2/34 (5.9)	2/6 (50)	5728 (17.9)
MPD diameter mm, median (range)	5.1 (1–17)	2.58 (2–6)	6.32 (2–15)	4.84 (1–17)	4.1 (1–17)	7.3 (2–11)	5.9 (2–14)
Cyst communicating with MPD	35/68 (51.5)	8/13 (61.5)	17/32 (53.1)	10/23 (43.5)	19/33 (57.6)	4/7 (57.1)	12/28 (42.9)
Location caput - Head	42/80 (52.4)	6/14 (42.9)	22/41 (53.7)	14/25 (56.0)	17/37 (45,9)	5/8 (62.5)	20/35 (57)
Location korpus - Boby	19/80 (23.8)	5/14 (35.7)	8/41 (19.5)	6/25 (24.0)	9/37 (24.3)	2/8 (25)	8/35 (22.9)
Location cauda - Tail	19/80 (23.8)	3/14 (21.4)	11/41 (26.8)	5/25 (20.0)	11/37 (29.7)	1/8 (12.5)	7/35 (20.0)
Parenchymal atrophy	33/56 (58.9)	5/10 (50)	18/29 (62.1)	10/17 (58.8)	15/24 (62.5)	4/7 (57.1)	11/25 (44.0)
Cyst wall >2 mm	27/54 (50)	3/10 (30.0)	16/27 (59.3)	8/17 (47.1)	5/22 (22.7)	6/7 (85.7)	16/25 (64.0)
Septation of cyst	39/68 (57.4)	7/13 (53.8)	20/31 (64.5)	12/24 (50.0)	20/34 (58.8)	4/7 (57.1)	15/27 (55.6)
Mural nodules of the cyst	17/64 (26.6)	1/13 (7.7)	11/32 (34.4)	5/19 (26.3)	3/31 (9.7)	4/7 (57.1)	10/26 (38.5)
Calcification of the cyst	7/73 (6.8)	0/13 80.0)	3/36 (8.8)	2/24 (8.3)	1/35 (2.9)	2/8 (25)	2/30 (6.7)
Suspected malignancy	12/55 (21.8)	1/10 (10.0)	7/28 (25)	4/17 (23.5)	0/23 (0.0)	3/7 (42.9)	9/25 (36)

BD, branch duct; *HGD*, high-grade dysplasia; *INV*, invasive carcinoma; *IPMN*, intraductal papillary mucinous neoplasm; *LGD*, low-grade dysplasia; *MD*, main duct; *MPD*, main pancreatic duct; *MT*, mixed-type.

Table III
Risk factors for malignancy in resected IPMN tumors

Risk factors for malignancy	Benign	Malignant	*P* value
Age	65 (40–87)	65 (43–79)	.798
Age >60 years	16/22 (73%)	6/22 (27%)	.063
Age <60 years	33/66 (50)	33/66 (50)	
Symptomatic	31/63 (49)	32/63 (51)	.052
Incidental	18/25 (72)	7/25 (28)	
MPD diameter	3 (1–17)	6 (2–14)	.129
Single cyst	36/68 (53)	32/68 (47)	.340
Multifocal	13/20 (65)	7/20 (35)	
MPD <4.9 mm	27/40 (68)	13/40 (32)	.212
MPD 5–9.9 mm	8/18 (44)	10/18 (56)	
MPD >10 mm	5/10 (50)	5/10 (50)	
Diameter of largest cyst	40 (7–100)	31 (9–86)	.409
Cyst not communicating with MPD	17/33 (52)	16/33 (48)	.234
Cyst communicating with MPD	23/35 (66)	12/35 (34)	
Location head	22/42 (52)	20/42 (48)	.724
Location body	11/19 (58)	8/19 (42)	
Location tail	12/19 (63)	7/19 (37)	
No parenchymal atrophy	12/23 (52)	11 (23 (48)	.689
Parenchymal atrophy	19/33 (58)	14/33 (42)	
Cyst wall >2 mm	11/27 (41)	16/27 (59)	.056
Cyst wall <2 mm	18/27 (67)	9/27 (33)	
No septa	17/29 (59)	12/29 (41)	.808
Septation of cyst	24/39 (62)	15/39 (38)	
No mural nodules of the cyst	31/47 (66)	16/47) 34	.75
Mural nodules of the cyst	7/17 (41)	10/17 (59)	
No calcification of the cyst	40/68 (59)	28/68 (41)	.959
Calcification of the cyst	3/5 (60	2/5 (40)	
No suspected malignancy	27/43 (63)	16/43 (37)	
Suspected malignancy	3/12 (25)	9/12 (75)	.02

IPMN, intraductal papillary mucinous neoplasm; *MPD*, main pancreatic duct.

statistically significant difference ($P < .01$) in survival between invasive cancers and noninvasive tumors (LGD + HGD). Survival percentages for other subgroups are presented in Table VI. Disease-specific 5-year survival was 97.1% in the LGD group compared to 40.0 in the INV group. In the LGD group, 2/40 (5%) patients died of pancreatic cancer during the 10-year follow-up. Ten-year mortality from pancreatic cancer was 1/9 (11.1%) in the HGD group and 28/39 (71.8%) in the INV group (Table VI, Figure 2).

Discussion

The degree of dysplasia is considered the most important factor in determining the patient's survival after pancreatic resection for IPMN, but only limited long-term follow-up data are available. We aimed to investigate the nationwide 10-year survival of all resected IPMN patients and to identify factors associated with survival. We found that survival was significantly better when the resection was performed before the malignant transformation. However, 5% to 11% of the patients operated on at the stage of LGD and HGD died of pancreatic cancer during the 10-year follow-up.

The IPMN treatment guidelines aim to define tumors with elevated malignant potential and time the resection before the malignant transformation.[1,22] It is well-established that only a few IPMN tumors will present features necessitating surgical resection. Some studies even suggested that small BD-IPMN tumors should not be followed up at all.[23] Once worrisome features are present, resection is recommended, although the predictive value of these known features is not optimal. The prognosis of resected IPMNs depends mainly on the degree of dysplasia.[1] A BD-IPMN with only LGD has an excellent prognosis, although the remnant pancreas needs lifelong surveillance. Also, in tumors with HGD, the prognosis is better than in invasive IPMN carcinoma.[1] In the early 2000s in Finland, the treatment of pancreatic tumors was not centralized, and operations were carried out in many low-volume centers. The quality of diagnostics was not always at the level expected today.

Table IV
Complications classified by Clavien-Dindo score and 30-day mortality of resected IPMNs

Clavien-Dindo score	*N*	0 *n*, (%)	1 *n*, (%)	2 *n*, (%)	3 *n*, (%)	4 *n*, (%)	5 *n*, (%)	30-day *n*, (5)
Pancreaticoduodenectomy	43	14 (32.6)	4 (9.3)	11 (25.6)	10 (23.3)	4 (9.3)	0 (0.0)	1
Distal pancreatectomy	33	24 (72.7)	1(3.0)	4 (12.1)	3 (9.1)	0 (0.0)	1 (3.0)	1
Total pancreatectomy	11	6 (53.5)	0 (0.0)	1 (9.1)	3 (27.3)	1 (9.1)	0 (0.0)	0
Enucleation	1	1 (100)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0
Total	88	45 (51.1)	5 (5.7)	16 (18.2)	16 (18.2)	5 (5.7)	1 (1.1)	2 (2.3)

IPMNs, intraductal papillary mucinous neoplasms.

Table V
Degree of dysplasia and rate of malignancy in IPMN subtypes and histological subtypes

		BD-IPMN	MD-IPMN	MT-IPMN
All		14 (15.9)	47 (53.4)	27 (30.6)
LGD		12/14 (85.8)	12/47 (25.5)	16/27 (59.3)
HGD		1/14 (7.1)	6/47 (12.8)	2/27 (7.4)
INV		1/14 (7.1)	29/47 (61.7)	9/27 (33.3)
	Non-INV	13/14 (93)	18/47 (38)	18/27 (67)
	P value			0.001
Oncocytic subtype*		3/8 (37.5)	3/8 (37.5)	2/8 (25)
	Invasive	0/3 (0.0)	1/3 (33)	2/2 (100)
	Non-INV	3/3 (100)	2/3 (66)	0/2 (0.0)
Intestinal subtype*		1/11 (9.1)	5/11 (45.5)	5/11 (45.5)
	Invasive	0/1 (0.0)	1/5 (20)	2/5 (40)
	Non-INV	1/1 (100)	4/5 (80)	3/5 (60)
Pancreatobiliary subtype†		0/4 (0.09	1/4 (25)	3/4 (75)
	Invasive	0/0 (0.0)	1/1 (100)	3/3 (100)
	Non-INV	0/0 (0.0)	0/1 (0.0)	0/3 (0.0)

BD, branch duct; *HGD*, high-grade dysplasia; *INV*, invasive carcinoma; *IPMN*, intraductal papillary mucinous neoplasm; *LGD*, low-grade dysplasia; *MD*, main duct; *MT*, mixed-type.

* No statistically significant difference ($P > .05$) in share of patients with malignant disease.

† All patients with pancreatobiliary cysts had malignant disease.

Table VI
One-year, 5-year, and 10-year survival for IPMN patients

	Median (range)	IQR	1-year survival%	5-year survival%	10-year survival%	5-year disease-specific survival %	Pancreatic cancer mortality *n* (%)
BD	155 (3–252)	74.75-232.25	92.9	85.7	64.3	100	1/14 (7.1)
MD	87 (1–240)	21-141	85.1	59.6	44.7	65.1	20/47(42.6)
MT	124 (6–240)	17-171	92.6	59.3	51.9	66.7	10/27 (37.0)
LGD	142 (3–252)	101-185.75	97.5	87.5	72.5	97.1	2/40 (5)
HGD	118 (15–229)	58.5-168.5	100	77.8	66.7	87.3	1/9 (11.1)
INV	25 (1–226)	12-109	76.9	35.9	23.1	40.0	28/39 (71.8)
ONC	60.5 (3–242)	5.25-133.5	50	50	50	57.1	3/8 (37.5)
INT	124 (12–240)	15-178	100	72.7	72.7	80.0	2/11 (18.2)
PB	19 (12–34)	13.25-30.75	100	0.0	0.0	0.0	4/4 (100)
All	121 (0–252)	24.25-161.5	88.6	63.6	50.0	70.9	31/88 (35.2)

BD, branch duct; *HGD*, high-grade dysplasia; *INT*, intestinal; *INV*, invasive carcinoma; *IPMN*, intraductal papillary mucinous neoplasm; *LGD*, low-grade dysplasia; *MD*, main duct; *MPD*, main pancreatic duct; *MT*, mixed-type; *ONC*, oncocytic; *PB*, pancreatobiliary.

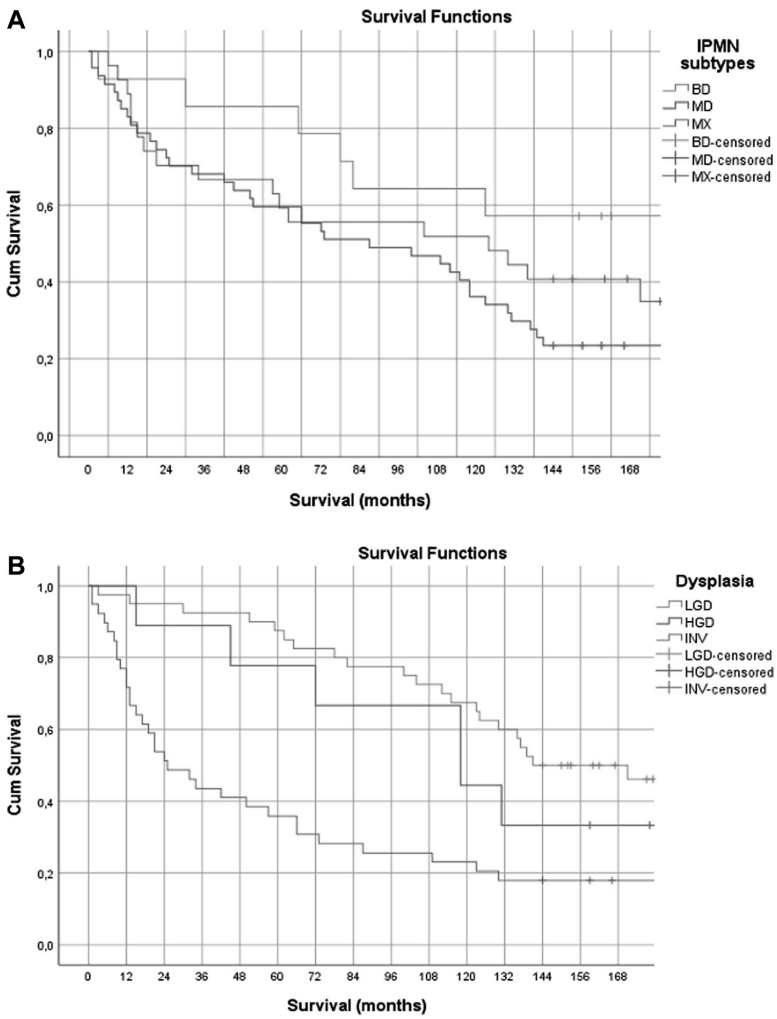

Figure 2. *(A)* Kaplan-Meier survival curves by intraductal papillary mucinous neoplasm subtypes. *(B)* Kaplan-Meier survival curves by the degree of dysplasia. *(C)* Kaplan-Meier survival curves by immunohistochemical intraductal papillary mucinous neoplasm subtypes.

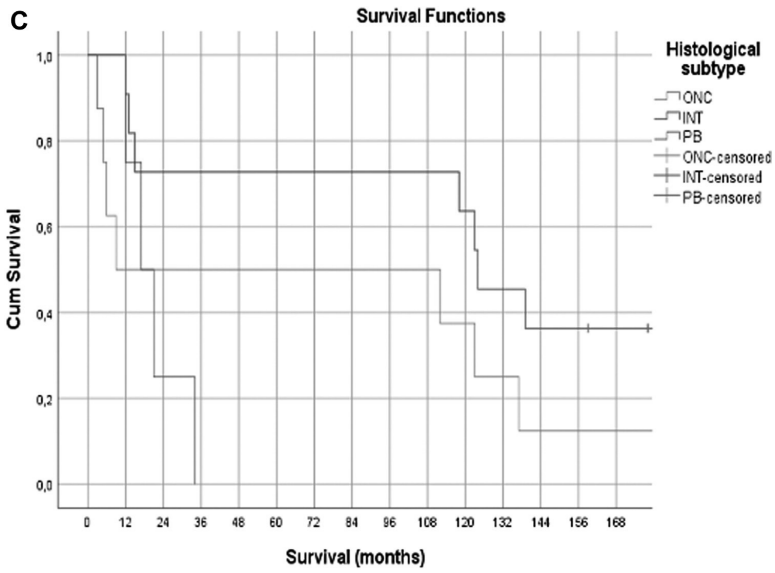

Figure 2. (*continued*).

For example, magnetic resonance imaging was performed on only 25/88 (28.4%) patients, which obviously affects the ability to evaluate features such as a cyst communicating with the MPD. Suboptimal diagnostics may have led to numerous misdiagnoses both preoperatively and postoperatively. Also, some tumors may have been diagnosed as PDAC rather than IPMN, which may partially explain the low number of resections performed in the earlier years of the study period.

The first IPMN guidelines were issued in 2006; the effect of these guidelines on managing patients in this cohort was negligible. Decisions to operate likely were based on the clinical judgment of the individual surgeon, with cyst size being the most important factor in this decision-making. Currently, surgeons in Finland rely primarily on the European guidelines. Since applying new guidelines for treating IPMN, the number of patients undergoing surgery and under surveillance has increased significantly. Although the indications for surgery have been tightened, the overall increase in the number of patients on surveillance programs has led to more resections. Population aging and increased volumes of cross-section imaging have likewise increased the likelihood of asymptomatic pancreatic cysts being detected.[24]

In our nationwide cohort, the patients were predominantly female, and the median age was slightly above 60. The number of incidentally found, asymptomatic cysts was low (27.3%) and can be explained by the less frequent use of cross-section imaging for other reasons in the early 2000s.

The rate of complications was high but similar to those found in other studies; after pancreaticoduodenectomy, 29/43 (67.4%) patients had any complication, and for 14/43 (32.5%) of the patients, the complications were considered severe (CD 3–5). In comparison, in a nationwide register study from Finland from 2012 to 2014, the rate of severe complications after pancreaticoduodenectomy was 23.3%.[25]

Most tumors (53.4%) were classified as MD-IPMN (MT-IPMN 30.6% and BD-IPMN 16.3%). The proportion of resected BD-IPMN is low compared to the resection rates in more recent publications.[26,27] Although the indications for surgery in BD-IPMN patients have been tightened, the increased volume of BD-IPMN patients under surveillance has also increased the proportion of resected BD-IPMNs compared to other subtypes.

Overall, 44.3% of the patients had a malignant operated tumor, and three-quarters (74.5%) of the MD-IPMNs were malignant or HGD. In comparison, 12/14 (85.8%) patients had an LGD tumor in the BD-IPMN group. The instance of HGD was present more equally in all groups (BD-IPMN 7.1%, MT-IPMN 7.1%, and MD-IPMN 12.8%). The rate of malignancy was high compared to other surgical series. The tumors were large (median 40.4, range 3.4–120.0 mm), symptomatic (72.7%), and detected late (length of symptoms before operation 6.88 months). Also analyzed retrospectively, several features (ie, MPD diameter, thickened cyst wall, and size of the cyst) were present that relate to malignancy. In the current guidelines, MPD dilation, among others, is a well-established radiologic feature predicting malignancy. There was a tendency for an elevated risk of malignancy in factors such as patients with symptoms, an MPD diameter of $\geq$5 mm, and a cyst wall >2 mm. However, the numbers did not reach statistical significance. The only preoperative factor of statistical significance in detecting malignancy was if a radiologist suspected malignancy. Based on this finding, the "gut feeling" of the experienced radiologist should be considered when IPMN cases are discussed in a multidisciplinary setting. Poor quality of preoperative imaging studies also may have negatively affected the ability to detect any signs of malignant transformation. The number of patients in the histologic subtype analyses was low; thus, there was no significant difference among IPMN subtypes (BD, MD, MT) or malignancy, although 75% of the PB group was MT, and all were malignant.

Survival percentages beyond 5 years in nationwide settings were not published in large quantities before this study. In our

material, the median survival overall was 121 (0–252) months, and 5- and 10-year survival was 63.6% and 50.0%. The most important prognostic factor for patients with resected IPMN is the degree of dysplasia. It is evident that when IPMN is deemed invasive carcinoma, the prognosis is dismal; for INV compared to LGD, 5- and 10-year survival was 35.9 vs 87.5 and 72.5 vs 23.1. The distinction between LGD and HGD is not so clearcut from the perspective of survival. Some, although not all, authors have reported differences in survival in these 2 groups.[1,18] In this cohort, there were no statistically significant differences in survival for LGD and HGD in 5 and 10-year surveillance. In the general population (in this age group) at the time of this study, 10-year survival was roughly 80% compared to 72.5% in the LGD group. One factor explaining this difference is the risk of a malignant tumor in the remnant pancreas if total pancreatectomy has not been performed, even if the histology of the specimen was benign.

In this study, mortality from pancreatic cancer was 2/40 (5%) in the LGD group. Mortalities from pancreatic cancer in the LGD group included deaths 59 months after the primary operation (MT-IPMN) and deaths 79 months after primary operation (BD-IPMN). The risk of a malignant tumor in the remnant advocates the surveillance of the remnant pancreas after resection as long as the patient is fit enough for surgery.[6] There are probably more factors than described above that could explain the decrease in survival in benign cases compared to the general population. As expected, mortality from pancreatic cancer was higher in HGD, especially in the INV group. Among MD, MT, and BD, survival was higher in the BD group (which can be explained by the smaller number of malignant tumors in the BD group). Still, there was no statistical significance among the groups. Also, there were no significant differences in survival between histologic subtypes (oncocytic, PB, INT), although the small number of patients may have affected this analysis.

Strengths and limitations of the study

The strength of this study is the nationwide setting. All resected patients were included; thus, there was no selection bias. Another strength of this study is the long follow-up time for all patients. This is longer than in any other published series of nationwide data. However, even though nationwide, the sample size can be considered small, and we could not complete radiologic and histologic data sets for all patients. This hurt our ability to conduct meaningful qualitative analyses and can be considered a limitation of the study. Also, the poor quality of preoperative radiologic studies (the small number of magnetic resonance imaging studies) may have impaired the detection of significant risk factors for malignancy in our analysis.

In conclusion, based on this nationwide cohort with a 10-year survival analysis, we conclude that patients with an IPMN tumor resected before malignant transformation have a good prognosis. In comparison, in the case of invasive carcinoma, 10-year survival is <25%. Also, the IPMN subtype is an important prognostic factor; in this cohort, mortality due to pancreatic cancer was 7.1% in the BD-IPMN group compared to around 40% in the MD-IPMN and MT-IPMN groups. The timing of the surgery before malignant transformation and, at the same time, avoiding unnecessary operations remains a challenge for all surgeons working with IPMN tumors.

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Conflict of interest/Disclosure

The authors have no conflicts of interests or disclosures to report.

Supplementary materials

Supplementary materials associated with this article can be found in the online version, at https://doi.org/10.1016/j.surg.2023.02.006.

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PUBLICATION III

The European evidence-based guidelines on pancreatic cystic neoplasms (PCN) in clinical practice: The development of relative and absolute indications for surgery during prospective IPMN surveillance.

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Original Article

The European evidence-based guidelines on pancreatic cystic neoplasms (PCN) in clinical practice: The development of relative and absolute indications for surgery during prospective IPMN surveillance

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ABSTRACT

Introduction: The European evidence-based guidelines on PCN recommend surveillance for IPMN patients who are fit for surgery but who have no indication for immediate surgery. Our aim was to demonstrate the feasibility of the new guidelines in clinical practice.
Methods: This is a prospective cohort study of patients included in the IPMN register in Tampere University Hospital, Finland. IPMN was diagnosed from January 1, 2013 to December 31, 2018. Patients were analyzed for surveillance and indications for surgery according to the European guidelines on PCN.
Results: Out of 128 patients in register 23 was decided to operate upfront and 105 patients were included in the surveillance programme. Invasive carcinoma was found in 4/23 of operated patients. Median follow-up time was 26 months (6–69). Median size of the cyst at the beginning and end of the surveillance was 16 mm (4–58 mm). During surveillance 0/105 (0.0%) patients had or developed an absolute indication for surgery. Relative indication for surgery was present in 8/105 (7.6%) patients in the beginning surveillance and 9/105 (8.6%) patients developed at least one relative indication for surgery during surveillance. From the surveillance cohort 2/105 patients were operated. Surveillance was abandoned in 15/105 (14.1%) patients all due to poor general condition or other medical conditions.
Conclusions: In clinical practice, surveillance of IPMN according to the European guidelines on PCN is feasible. Among our patients 16% were detected to have relative indications for surgery during the median 26 (range 3–135) months of surveillance. Nearly 15% became surgically unfit during surveillance period.

1. Introduction

The rate of malignant transformation of branch duct intraductal papillary mucinous neoplasms (BD-IPMN) without risk factors is low [1,2]. Risk factors for malignant transformation have been established in various guidelines, such as the European evidence-based guidelines on pancreatic cystic neoplasms [3], in 2017, the revised international consensus Fukuoka guidelines for the management of IPMN of the pancreas [4] and American Gastroenterological Association guidelines [5]. Patterns of surveillance and indication for surgery vary between these guidelines.

The new European evidence-based guidelines on pancreatic cystic neoplasms recommend surveillance for patients who are fit for surgery but who have no indication for immediate surgery. Absolute indications for surgery include positive cytology for malignant/high grade dysplasia, solid mass, jaundice (tumour related), enhancing mural nodules (≥5 mm), main pancreatic duct dilatation ≥10 mm. Relative indications for surgery include cyst growth rate ≥5 mm/year, cyst diameter ≥40 mm, elevated levels of serum carbohydrate antigen 19–9 (CA 19.9) (>37U/mL), enhancing mural nodule <5 mm, main pancreatic duct (MPD) diameter 5–9.9 mm, acute pancreatitis (caused by IPMN) and new-onset diabetes mellitus. For patients with significant co-morbidities but regarded fit for surgery, the guideline suggests intensive surveillance in a presence of only one relative indication for surgery. If a patient with significant co-morbidities has two or more relative indications, surgery is recommended [3].

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Our aim was to demonstrate the feasibility of the new guidelines in clinical practice by describing our IPMN surveillance programme and by analysing the development of relative and absolute indications for surgery during prospective IPMN surveillance.

2. Methods

This is a retrospective analysis of a prospective cohort. On October 1, 2015 a register for all IPMN patients under surveillance in Tampere University Hospital was established. Starting on January 1, 2013 the data was augmented by patient files retrospectively until 2015, since that the follow-up it has been prospective. For this study, the data was gathered until December 31, 2018. Patients were analyzed for surveillance and indications for surgery according to the European experts consensus statement on cystic tumours of the pancreas published 2013 [6].

MRI was used as the primary method of cross-section imaging if not contra-indicated. Computed Tomography (CT) was used if necessary. Use of EUS is not routinely considered necessary as a method of surveillance in our center. In selected cases, use of EUS can be useful diagnostic tool and number of EUS studies has been increasing in our hospital. Serum level of Ca19-9 was measured. For first year follow-up was performed at 6-month intervals and yearly after that. If necessary, patients were assessed in multidisciplinary meetings (MDT). For the first follow-up, the patients were asked to attend our outpatient clinic. Whenever a patient was no longer fit for surgery, the surveillance was terminated.

The following data was gathered at baseline: Demographics, comorbidities, symptoms and radiological findings. The database was augmented at each follow-up point to include possible surgical procedures, final histopathological diagnoses and survival. Radiological findings as follows were gathered from radiological reports: radiological diagnosis, size and number of cysts, possible worrisome features (main pancreatic duct dilatation, mural nodules/solid component, calcification and septation), speed of progression in the growth rate the size of cyst and main pancreatic cyst dilatation. A second opinion was elicited from an experienced radiologist for cases with suspected MPD dilatation.

Statistical analyses were performed using SPSS 22.0 for Windows (IBM Inc., Somers, USA). Unless otherwise specified descriptive statistics are reported using count, percentage, median and range.

Permission to review patient files was obtained from the Chief Medical Director of Tampere University Hospital.

3. Results

3.1. Baseline findings

During the study period (1 January 2013–31 December 2018) 128 patients with suspected IPMN and fit for surgery were evaluated in our hospital. Twenty-three patients were assigned to be operated upfront and 105 patients were included in the surveillance programme if the radiological diagnosis was suspected IPMN. At the beginning of the surveillance all patients had BD-IPMN. Median age of the patients was 69 years (range 28–84) and 82/129 (63.6%) were female. Baseline characteristics of the patients and tumours are described in Table 1. The group designated for upfront resection and the surveillance programme group had significant differences in incidence of symptoms 14/23 patients (60.9%) vs. 1/105 patients (0.9%) ($p < 0.05$), and maximum diameter of the cyst 40 mm vs. 15 mm ($p < 0.05$). There were no other statistically significant differences between the groups (Table 1, Fig. 1).

3.2. Patients assigned to upfront surgery

Five patients had an absolute indication; two patients had suspicion of malignancy in histology, two patients had MPD diameter ≥10 mm and one patient had Jaundice. Seven patients had two relative indications for surgery; cyst diameter ≥40 mm and MPD diameter 5–9.9 mm (4 patients), cyst diameter ≥40 mm and elevated levels of CA 19.9 (>37U/mL) (one patient), MPD diameter 5–9.9 mm and elevated levels of CA 19.9 (>37U/mL) (one patient), cyst diameter ≥40 mm and cyst growth rate ≥5 mm/year (one patient). Relative indications for surgery in patients with singe indication were; cyst diameter ≥40 mm (6 patients) and main pancreatic duct (MPD) diameter 5–9.9 mm (5 patients) (Table 2a).

In the final histopathological analysis two patients had adenocarcinoma, 2 IPMN-carcinoma, 1 BD-IPMN and 1 main duct (MD)-IPMN high grade dysplasia. In addition, 3 BD-IPMN, 3 MD-IPMN and 7 mixt type (MT)-IPMN with low grade dysplasia were detected. Three patients had serous cystic neoplasm (SCN) and 1 chronic pancreatitis was discovered. Pancreaticoduodenectomy was performed on nine, distal resection on seven, total pancreatectomy on six and surgical exploration on one patients (Table 2). Rate of 90-day mortality was 2/23 (8.7%) (Table 2b, Fig. 1).

3.3. Follow-up data

Follow up imaging was performed by MRI if not contra-indicated (contra-indications being, for example, having a pacemaker or allergy to contrast media). MRI was performed on 100/105 (95.2%), CT on 65/105 (61.9%) and both modalities on 60/105 (57.1%) of the patients. Of the cases 78/105 (74.3%) visited in the outpatient clinic, rest of the patient were contacted by phone or letter. MDT meeting was used in 37/105 (35.2%) cases. Median follow-up time in this study was 26 months (6–69). Median number of follow-up visits was three [2–7], with median frequency being one visit per every 8.6 months. Surveillance was cancelled in 15/105 (14.1%) patients due to poor general condition or other medical conditions. Mean age for patients whom surveillance was cancelled was 78.8 (range 61–84) years. Mortality was 4/105 (3.8%); 2/105 (1.9%) patients died during surveillance and 2/105 (1.9%) patients died after cancellation of surveillance. None of the patients in the follow-up cohort were diagnosed with or died of pancreatic cancer. From the surveillance cohort 2/105 patients were operated on. The final histopathological analysis was MT-IPMN with low grade dysplasia in both cases (Table 3).

3.4. Indications for surgery

Median size of the cyst at the beginning and end of the surveillance was 16 mm (4–58 mm). Median value of ca19-9 at the beginning and end of the surveillance was 9 U/mL (1–417). Mean value of ca19-9 increased from 16.22 to 20.11 U/ml. Among the patients 84/105 (80%) experienced no increase in size. Mean rate of size increase was 1.39 mm/year in 21/105 (20%) patients which experienced any increase in size. Ca19-9 values didn't increase in 85/105 (81%) patients and 71/105 (68%) of the patients didn't have increase either Ca19-9 value or cyst size (Table 3).

In the surveillance programme 0/105 (0.0%) patients had absolute indications at the beginning or developed them during the surveillance period and 8/105 (7.6%) of the patients had relative indications for surgery at the beginning of the surveillance.

In the European guidelines, a relative indication for surgery is cyst diameter ≥40 mm. At the beginning of the surveillance cyst diameter was over this threshold in 1/105 (0.95%) patients, cyst diameter being 58 mm. Because of the poor general condition of the patient surveillance was opted for over surgery. Size of the cyst remained stable

Table 1
Baseline characteristics of IPMN patients and tumours: Upfront operated and follow-up groups.

Baseline characteristics and tumour specifics			
Features	Operated upfront	Follow up	p
Number of patients	23	105	
Age median (range)	66 (37–79)	69 (28–84)	0.559
Gender female	12 (52.2%)	71 (67%)	0.85
Diabetes	11 (47.8%)	21 (19.8%)	0.07
Previous cancer	4 (17.4%)	29 (27.4)	0.23
Symptomatic	14 (60.9%)	1 (0.9%)	<0.05
Smoking	7 (30.4%)	18 (17.0%)	0.152
Ca 19–9 (kU/L)	9 (1–177)	9 (1–140)	0.832
Diameter of cyst (mm)	40 (4–58)	15 (4–54)	<0.05
MPD diameter (mm)	6 (2–20)	na	
MT[a]	13	0	
MD[a]	5	0	
BD[a]	5	105	

[a] MT, Mixt-type MD, Main duct BD. Branch duct. Preoperative diagnose.

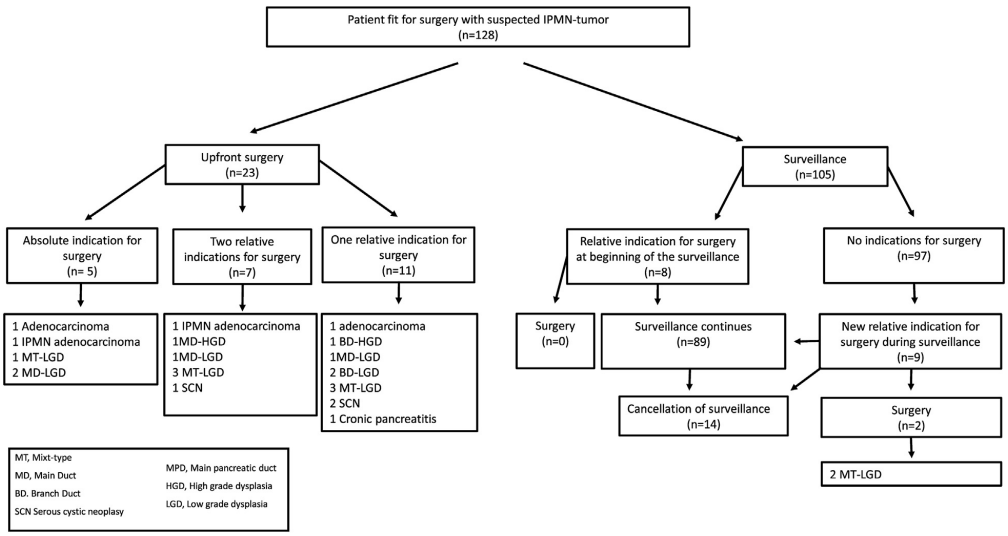

Fig. 1. Flowchart of IPMN surveillance in Tampere University Hospital 1.1.2013–31.12.2018.

Table 2a
Indication for surgery, upfront operated patients.

Indication for surgery	n
Absolute indication	
Malignant histology	2
MPD diameter ≥10 mm	2
Jaundice	1
Two relative indications	
Cyst diameter ≥40 mm and MPD diameter 5–9.9 mm	4
cyst diameter ≥40 mm and elevated levels of CA 19.9 (>37U/mL)	1
MPD diameter 5–9.9 mm and elevated levels of CA 19.9 (>37U/mL)	1
cyst diameter ≥40 mm and cyst growth rate ≥5 mm/year	1
One relative indication	
cyst diameter ≥40 mm	6
MPD diameter 5–9.9 mm	5

MPD, Main pancreatic duct.
HGD, High grade dysplasia.
LGD, Low grade dysplasia.
SCN, Serous cystic neoplasy

Table 2b
Histology and type of surgery, upfront operated patients.

Histology	N
Adenocarcinoma	2
IPMN-carcinoma	2
MD-IMPN HGD	1
BD-IMPN HGD	1
MX-IPMN LGD	7
MD-IPMN LGD	3
BD-IPMN LGD	3
SCN	3
Chronic pancreatitis	1
Type of surgery	
Pancreaticoduodenectomy	9
Distal pancreatic resection	7
Total pancreatectomy	6
Surgical exploration	1

Table 3
Follow-up data of BD-IPMN surveillance patients.

Follow-up modality	
MRI	100 (95.2%)
CT	65 (61.9%)
MRI + CT	60 (57.1%)
Follow up characteristics	
Outpatient visit	78 (74.3%)
MDT-meeting	37 (35.2%)
Follow-up period months, median (range)	26 (3–69)
Number of follow-ups median (range)	3 (2–7)
Follow up termination	15 (14.1%)
Mortality of study up population	4/105 (3.8%)
Operated patients	2/105 (1.9%)
Follow-up values	
Cyst size mm median (range)	16 (4–58)
Ca 19-9 U/ml median (range)	9 (1–392)
Patients with no progression during surveillance	
Cyst size mm	84/105 (80%)
Ca 19-9 U/ml	85/105 (81%)
Cyst size and Ca 19-9 U/ml	71/105 (68%)

during follow-up. At the beginning of the surveillance 6/105 (5.7%) patients had elevated ca19-9 levels (>37U/mL). In the absence of other worrisome features none of the patients were operated on. Acute pancreatitis (caused by IPMN) was diagnosed in 1/105 (0.95%) patients. It was decided not to operate on this patient.

During surveillance, 9/105 (8.6%) patients developed at least one relative indication for surgery. Rapid growth of the cyst (cyst growth rate $\geq$5 mm/year) was seen in 3/105 (2.9%) patients. Two of them patients had a growth of 9 mm and 5 mm/year without any other relative indications for surgery. Control MRI was advanced to six months and after that there was no growth in the cyst. These patients were not operated on. A third patient had cyst growth of 6 mm but as this patient was no longer fit for surgery surveillance was terminated.

Elevation of ca 19–9 above 37U/mL (from 29 to 81 U/mL) during surveillance was detected in 2/105 (1.9%) of patients, being a relative indication for surgery. One patient had no other relative indications for surgery and ca 19–9 value fell to 29 U/mL in nine months. The patient was not operated on and surveillance was continued. Other patient with elevated ca 19-9 had two relative indications (discussed below).

During surveillance, 1/105 (0.95%) of patients developed an enhancing mural nodule <5 mm and underwent distal pancreatic resection. In the final histological analysis, MT-IPMN with low grade dysplasia was detected.

MPD dilatation 5–9.9 mm was detected in 3/105 (2.9%) of patients. One of them with progressive MPD dilatation from 4 mm to 8 mm underwent total pancreatectomy. In the final histological analysis, MT-IPMN with low grade dysplasia was detected. Two other patients had 5 mm and 6 mm pancreatic duct dilatations with only minimal (1 mm and 2 mm) growth. The patient had no other relative indications for surgery and surveillance was continued.

One patient developed two relative indications for surgery: Ca 19–9 increased from 25 to 417 U/ml and cyst size increased from 37 mm to 41 mm However, the patient was not considered to be fit for surgery, and it was decided not to operate him. Surveillance was terminated.

The median time for developing new relative indications for surgery during follow-up was 18 (7–49) months from the beginning of the surveillance. Overall, it was decided to operate on 2/17 (11.8%) of patients with one relative indication for surgery; one patient with MPD dilatation from 4 mm to 8 mm and one with an enhancing septa. No surgery was performed on 15/17 (88.2%) of patients with relative indications. (Fig. 1, Table 4).

4. Discussion

Because of increasing incidence and prevalence of PCN patients under surveillance and consequent intolerable burden to health care system, lifelong intensive surveillance protocols need to be critically evaluated [7–12]. On the other hand, surveillance provides a method to proceed to pancreatic surgery in pre-malignant phase instead of poor prognosis when managed in cancer stage [13]. Our aim was to demonstrate the feasibility of the European evidence-based guidelines in clinical practice in our hospital. Series of resected tumours for validating the new European guidelines have been published before [14], but only few of these studies focus on surveillance. In this study we describe our surveillance programme using the European evidence-based guidelines.

It was decided to operate upfront on 23 out of 128 (17.9%) patients. Our rate of primary resection is comparable to those reported in other studies although rates of primary resections vary greatly [1]. Malignant tumour was detected in 4/23 (17.4%) of patients, which is also in line with the most recent literature [15,16]. All patients had indications for surgery according European evidence-based guideline; 18 patients had relative indications and 5 patients had absolute indications for surgery. Type of surgery was decided based on preoperative imaging or frozen section biopsies perioperatively. Biopsies were taken from resection margin of the pancreas and if needed on other locations. Based on these findings, total pancreatectomy was performed if there were suspicion of tumour involvement in the whole length of the pancreas. In this group of patients perioperative pancreatoscopy was not yet available, but since that it has been added to our diagnostic tools. One hundred and five patients were included in our surveillance programme. None of these patients had absolute indications for surgery at the beginning of the surveillance.

Surveillance was performed primarily by using MRI. EUS was not used routinely but, for selected cases EUS was available as a diagnostic tool. The quality of results obtained seems not to be influenced by the non-application of EUS.

Most of the patients (68%) did not have any increase in cyst size or in ca 19-9 level. Median size of the cysts (16 mm) did not increase during the study period although there was minimal growth in the mean size of the cysts. Slow growth (less than 1 mm/year) rates of cyst size has been reported in larger series [15,17]. Our surveillance period was relatively short, over a longer period of time slow growth in median size would be expected.

A total of eight patients had one relative indication of surgery at the beginning of the surveillance and 6/8 of these patients had elevated levels of ca 19–9 as relative indication for surgery. In the absence of other relative indications for surgery it was decided not to operate on two patients otherwise fit for surgery. A further six patients also had relative indications for surgery, but also had significant co-morbidities. It was also decided not to operate on these six patients. Risk for malignancy or high-grade dysplasia (HGD) varies between relative indications for surgery. Evidence for risk of malignancy is well established with features like MPD dilatation, enhancing nodules, growth rate of the cyst and size of the cyst [16–23]. In our cohort no patients were operated on for relative indication of raised Ca 19-9 level in spite of a growing number of papers showing raised level of ca 19–9 as an independent risk factor for cancer in IPMN patients [15,24–26].

During the surveillance, 8/105 (7.6%) patients developed one relative indication for surgery and 6/8 of these patients were treated conservatively. Three patients had a rapid growth of the cyst, two patients had new dilatation on MPD and one had elevated level of ca 19–9. All patients had been under surveillance for several years and the decision not to operate on them was based on the minimal progression of the cyst and absence of other relative

Table 4
Absolute and relative and indications for surgery in BD-IPMN surveillance.

Indications for surgery				
Absolute indication[a]	Beginning of the surveillance	During surveillance	All	Operated during surveillance
Solid mass	0	0	0	0
Jaundice	0	0	0	0
Enhancing mural nodule ≥5 mm	0	0	0	0
MPD diameter ≥10 mm	0	0	0	0
Relative indication[a]				
Cyst growth rate ≥5 mm/year	0	3	3	0
Cyst diameter ≥40 mm	1	1	1	0
Increased levels of serum CA 19.9 (>37U/mL)	6	2	8	0
Enhancing mural nodule <5 mm	0	1	1	1
Main pancreatic duct (MPD) diameter 5–9.9 mm	0	3	3	1
Acute pancreatitis (caused by IPMN)	1	0	1	0
ALL	8	10	17	2

[a] One patient had two relative indications.

indications. One patient developed two relative risk factors for surgery. Multiple relative indications for surgery present a higher risk for malignancy and therefore surgery should be considered also for patients with elevated risk for complications [27,28]. In the case of our patient with two relative indications for surgery, the operative risks were too high because of other medical conditions and therefore the patient was not operated on.

During surveillance no invasive cancer or even HGD were detected. Overall, 2/105 (1.9%) patients in this surveillance cohort underwent surgery. A male aged 74 years and a female aged 68 years. Both of these patients had an MT-IPMN with low grade dysplasia in final histopathological analysis. The indication for and timing of the operation can be questioned. The patients did not have significant co-morbidities, but each of them had only one relative indication for surgery. Pancreatic surgery is associated with significant mortality and this disease carries a fairly good prognosis when treated conservatively even in the presence of relative indications for surgery [2,29–31]. A systematic review conducted by G. Vanella et al. (2018) concludes that mortality due to causes other than pancreatic cancer is much higher in patients with worrisome features but not fit for surgery [32]. On the other hand, the patients resected for IPMN have significantly better prognosis when operated on before malignant transformation or even before transformation to HGD [33,34]. None of the patients died of pancreatic cancer during the surveillance period. In selected cases opting to continue surveillance rather than operate is a feasible option. Positive predictive value of detecting malignancy is low when using European or any other current guideline for managing IPMN patients. It is essential to further study this disease to minimize the number of unnecessary surgical interventions.

Surveillance was cancelled in a relatively high number of patients, 15/105, which relates to the patients' relatively high age (median 69 years) at the beginning of the surveillance. A surveillance programme causes significant costs to the healthcare system and also creates a burden on patients [10,35]. It is essential to select only those patients likely to benefit from the surveillance offered on the programme.

Median time for developing new relative indications for surgery was 18 (7–49) months. In this cohort surveillance was organized according to the European guidelines. However, time to developing a new relative indication is long. Some recent studies suggest that longer intervals for the control of stable disease would be safe [36,37]. Also study by Marchegiani et al. suggest that discontinuation of surveillance for selected patients over 65 years might not increase risk of developing pancreatic cancer [28].

The limitations of this study include the relatively short follow-up time and small patient cohort. In this database we are not able to make suggestions as to whether the indications for surgery are valid or whether we are monitoring the right patients. Most of the studies in this field are series of resected PCNs. The strength of this study is that it aims to describe the whole pathway of the patient with diagnosed IPMN.

5. Conclusion

We conclude that in clinical practice, surveillance of BD-IPMN according to the European guidelines on PCN is feasible. Upfront surgery was performed on 18% of the patients in this cohort. Among our patients 16% were detected to have relative indications for surgery during the median 26 (range 3–135) months of surveillance. Out of 105 patients in the total study population, two were operated on during the surveillance period. In 5 year surveillance time, nearly 15% became surgically unfit: It is thus crucial to evaluate not only cyst progression but also changes in patient's condition as surgical candidate, to promptly terminate surveillance in unfit patients.

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