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INTRADUCTAL PAPILLARY MUCINOUS NEOPLASM OF THE PANCREAS

A STUDY WITH MAGNETIC RESONANCE IMAGING

Katarina Johansson

ACADEMIC DISSERTATION

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To Edith, Hugo, and Ingrid

CONTENTS

LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following publications:

I **Johansson K**, Kaprio T, Nieminen H, Lehtimäki TE, Lantto E, Haglund C, Seppänen H. A retrospective study of intraductal papillary neoplasia of the pancreas (IPMN) under surveillance. Scandinavian Journal of Surgery. 2022 March 111(1):1–9

II **Johansson K**, Mustonen H, Nieminen H, Haglund C, Lehtimäki TE, Seppänen H. MRI follow-up for pancreatic intraductal papillary mucinous neoplasm: an ultrashort versus long protocol. Abdominal Radiology. 2022 47(2):727–737

III **Johansson K**, Mustonen H, Seppänen H, Lehtimäki TE. Anatomical pancreatic variants in intraductal papillary mucinous neoplasm patients: a cross-sectional study. BMC Gastroenterology. 2022 22(394):1–9

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

ABBREVIATIONS

1.5 T	1.5 Tesla
3 T	3 Tesla
3D	three-dimensional
ADC	apparent diffusion coefficient maps
AGA	American Gastroenterological Association
AI	Artificial intelligence
BD-IPMN	branch duct intraductal papillary mucinous neoplasm
CA 19-9	carbohydrate antigen 19-9
CBD	common bile duct
CEA	carcinoembryonic antigen
CT	computed tomography
DWI	diffusion-weighted imaging
ERCP	endoscopic retrograde cholangiopancreatography
EUS	endoscopic ultrasound
FLASH	fast low angle shot
FNA	fine needle aspiration
fs	fat saturation
HASTE	half-Fourier single-shot turbo spin-echo
HGD	high-grade dysplasia
HRS	high-risk stigmata
HUH	Helsinki University Hospital
IPMN	intraductal papillary mucinous neoplasm
LP	long protocol
MCN	mucinous cystic neoplasm
MD-IPMN	main duct intraductal papillary mucinous neoplasm
MDT	multidisciplinary team meeting
MIP	maximum intensity projection
MMPD	meandering main pancreatic duct
MPD	main pancreatic duct
MRCP	magnetic resonance cholangiopancreatography
MRI	magnetic resonance imaging
MX-IPMN	mixed type intraductal papillary mucinous neoplasm
PAD	pathological-anatomical diagnosis
PanIN	pancreatic intraepithelial neoplasm
PCN	pancreatic cystic neoplasm
PDAC	pancreatic ductal adenocarcinoma
SCN	serous cystic neoplasm
SD	standard deviation
S-LP	longer protocols, short or long protocol
SP	short protocol

SPACE	sampling perfection with application-optimized contrasts using different flip angle evolution
SPN	solid pseudopapillary neoplasm
T1WI	T1-weighted imaging
T2WI	T2-weighted imaging
TE	echo time
TR	repetition time
USP	ultrashort protocol
US	ultrasound
VIBE	volumetric interpolated breath-hold
WF	worrisome features

ABSTRACT

Intraductal papillary mucinous neoplasm (IPMN) of the pancreas is a cystic tumor that has the potential of malignant transformation. In this thesis, our aims were to investigate the natural course of IPMN disease and possible causes that may associate with IPMN disease or its severity. Additionally, we examined whether a shorter and thus more cost-effective imaging protocol could be used in IPMN surveillance without losing any of its diagnostic value.

First, we studied the natural course of side-branch IPMN disease by evaluating patient images and medical records from 521 patients who visited the Helsinki University Hospital pancreatic outpatient clinic between 2014 and 2016. Every patient´s first and last surveillance images were evaluated retrospectively. A total of 377 side-branch IPMN patients were identified and classified into the following groups: presence or absence of worrisome features (WF) or high-risk stigmata (HRS) at the beginning of surveillance, the appearance of WF or HRS during surveillance, elevated or normal level of carbohydrate antigen 19-9 (CA 19-9), and stable or growing cysts that are under 15 mm. At the beginning of surveillance, 50% of patients had an under 15-mm primary cyst, of which 40% did not grow during surveillance. High-grade dysplasias or carcinomas did not exist in patients with normal CA 19-9 levels during surveillance. In conclusion, patients having side-branch IPMN cysts smaller than 15 mm that do not increase in size under surveillance and have no WF or HRS can be surveilled less frequently in the future.

Second, we examined whether a shorter magnetic resonance imaging (MRI) protocol—the so-called ultrashort-protocol (USP) MRI—could be used for IPMN surveillance. Retrospectively, 183 IPMN patients that visited the Helsinki University Hospital pancreatic outpatient clinic between April 2015 and December 2016 were collected in this study. A total of 112 patients were included in the study. Two radiologists compared two imaging sets (USP versus long-protocol [S-LP]) per every patient separately, measuring the largest cyst and the main pancreatic duct (MPD) diameters and evaluating the presence or absence of MPD or cystic mural nodules and solid pancreatic tumors. Cyst or MPD nodules detection coincided in 95% and 99% of cases, WF or HRS detection in 92%, and solid pancreatic tumors in 99%. In conclusion, an ultrashort-protocol MRI provides nearly identical information compared to the longer protocols.

Last, we studied if anatomical ductal variations have any association with IPMN disease. We retrospectively collected 108 IPMN patients and 106 subjects with healthy pancreas for the control population. Patients with meandering main pancreatic duct (MMPD) were more likely to belong to the IPMN group (odds ratio [OR] 6.4). The N-shape, which is one form of MMPD, associated with cystic mural nodules (OR 5.9), which are one of the worrisome

features. The presence of ansa pancreatica associated with more extent cysts in the pancreas (OR 12.8). In conclusion, IPMN patients exhibit more often MMPD than control patients.

ABSTRAKTI

Haiman intraduktaalinen papillaarinen musinoosi kasvain (IPMN) on kystinen tuumori, jolla on potentiaalia malignisoitua. Tämän malignisoitumisriskin vuoksi potilaat ovat seurannassa, mikä puolestaan aiheuttaa potilaille ja terveydenhuollolle merkittävää taakkaa. Tässä väitöskirjassa tavoitteenamme oli tutkia IPMN-taudin luonnollista kulkua ja mahdollisia syitä taudin syntyyn ja kehitykseen. Lisäksi tutkimme voisiko lyhyempää ja näin ollen kustannustehokkaampaa kuvantamisprotokollaa käyttää IPMN-seurannassa ilman, että diagnostiikan laatu kärsii.

Ensimmäisessä osatyössä tutkimme sivutiehyt IPMN-taudin luonnollista kulkua arvioimalla 521 potilasta, jotka olivat vuosien 2014–2016 välillä käyneet Helsingin yliopistollisen sairaalan haimakirurgian poliklinikalla ensimmäistä kertaa. Jokaisen potilaan ensimmäinen ja viimeinen seurantakuvaus arvioitiin jälkikäteen tutkimukseen. Yhteensä 377 sivutiehyt IPMN-potilasta havaittiin ja luokiteltiin seuraaviin ryhmiin: huolestuttavien tai korkean riskin piirteiden olemassaolo seurannan alussa, huolestuttavien tai korkean riskin piirteiden kehittyminen seuranta-aikana, normaali tai kohonnut CA 19-9 antigeenipitoisuus veressä, sekä stabiili tai kasvava alle 15 mm kokoinen kysta. Seurannan alussa 50%:lla potilaista oli alle 15 mm kokoinen kookkain kysta, joista 40%:ia ei kasvanut seurannan aikana. Potilailla, joilla oli normaali CA 19-9 pitoisuus seurannan ajan ei havaittu vahva-asteista dysplasiaa eikä karsinoomia. Tutkimuksemme perusteella niitä sivutiehyt IPMN-potilaita, joilla on alle 15 mm kokoisia kystiä, jotka eivät kasva seurannan aikana eivätkä omaa huolestuttavia eikä korkean riskin piirteitä, voitaisiin seurata jatkossa harvemmin.

Toisessa osatyössä tutkimme voisiko lyhyempää magneettikuvantamis (MRI) protokollaa, niin kutsuttua ultralyhytprotokollaa, käyttää IPMN-seurannassa. Retrospektiivisesti otimme tutkimukseen mukaan 183 IPMN-potilasta, jotka kävivät Helsingin yliopistollisen sairaalan haimakirurgian poliklinikalla huhtikuun 2015 ja joulukuun 2016 välillä. Yhteensä 112 potilasta sisällytettiin tutkimukseen. Kaksi radiologia analysoi potilaan kuvat kahteen kertaan: ensin alkuperäisillä kuvasarjoilla ja uudelleen vain tietyillä kahdella kuvasarjalla. Kuvista kerättiin mm. seuraavat tiedot: kookkaimman kystan koko, haimatiehyeen leveys, ja arvioitiin seinämänoduluksen tai haimatuumorin mahdollista esiintymistä. Kystan tai haimatiehyeen sisäisen seinämänoduluksen havaitseminen vastaavuus ultralyhyen ja alkuperäisten kuvien välillä oli 95%:ia ja 99%:ia, huolestuttavien tai korkean riskin piirteiden havaitsemisen 92%:ia, ja haimatuumorin 99%:ia. Tutkimuksemme perusteella ultralyhytprotokolla on verrannollinen pidemmän protokollan kanssa.

Kolmannessa osatyössä tutkimme onko anatomisilla haimatiehyeen variaatioilla yhteyttä IPMN-tautiin. Retrospektiivisesti keräsimme 108 IPMN-

potilasta sekä näille 106 vertailupotilasta, joilla oli terve haima. Potilaat, joilla oli niin kutsuttu kiemurteleva haiman päätiehyt (MMPD) olivat todennäköisemmin IPMN-potilaita (odds ratio [OR] 6.4). MMPD tiehyeen tietynlainen N-muoto puolestaan oli yhteydessä kystan seinämänodulusten esiintymisen kanssa (OR 5.9), mikä on yksi ns. huolestuttavista piirteistä. Tietynlaisen kiepin tekevän haiman lisätiehyeen, ns. ansa pancreatican, esiintyminen oli yhteydessä laajemmin haimaparenkyymin kattaviin kystiin (OR 12.8). Johtopäätöksenämme on, että IPMN-potilailla on useammin kiemurteleva haiman päätiehyt.

1 INTRODUCTION

Intraductal papillary mucinous neoplasm (IPMN) of the pancreas is a cystic neoplasm that has the potential to develop into cancer. IPMN was first time described in 1982 [1]. Improving imaging technologies and the increased use of imaging have led to a situation in which an ever-growing number of IPMN patients are being detected and thus ending up into the surveillance program. A study by Kromrey et al. demonstrated that 49% of a healthy population has cysts in the pancreas [2]. These cysts are often diagnosed incidentally when the patient is imaged for other reasons. Only a minority of cysts cause symptoms [2,3]. Considering that only a minority of the IPMN patients develop pancreatic cancer during their lifetimes, and the numbers of IPMN patients under surveillance is growing, the burden on healthcare systems from IPMN surveillance is remarkable. Thus, we need to find new solutions to overcome this patient load.

Surveillance of the IPMN is performed both with serum biomarkers and imaging, but the recommendations for the optimal surveillance schedule have been changing. They are also quite variable according to local routines. European guidelines recommend lifelong surveillance that can be ceased when the patient is no longer fit for surgery [4]. On the other hand, the American Gastroenterological Association (AGA) recommends stopping the surveillance after 5 years if no changes have occurred and the patient does not have any of the specified risk factors [5].

In addition, there are no specific recommendations on how to perform imaging for patients under surveillance. Using a contrast agent in magnetic resonance imaging (MRI) is under debate, and whether to use computed tomography (CT) or MRI is also controversial. In Helsinki University Hospital (HUH), the primary diagnosis is performed with a long MRI protocol that includes both contrast agent and diffusion imaging series, while the MRI protocol used for surveillance is either long or a modified shorter one according to the specific type of the disease and other risk factors.

In this thesis we evaluated the natural course of IPMN patients under the surveillance. And we analyzed whether we could find features of the disease that could justify an even shorter, so-called ultrashort, imaging protocol in order to ease the healthcare system's burden of surveillance. We also studied whether there is any association between IPMN disease and the anatomical duct variants.

2 REVIEW OF THE LITERATURE

2.1 THE PANCREAS - OVERVIEW

The pancreas is located in the upper abdomen in the anterior pararenal space of the retroperitoneum [6,7]. It is a long and narrow organ, 15–20 cm long [8,9], 1–3 cm wide, and 3–5 cm high [10]. It is surrounded by the small intestine (duodenum), stomach, liver, and spleen [7]. The pancreas is anatomically divided into the uncinate process, head, neck, body, and tail. The uncinate process and the head lie in the center of the upper abdomen and the tail next to the spleen at the left upper abdomen [10].

The pancreas is supplied by several arteries that arise from the branches of the celiac trunk and the superior mesenteric artery, such as the superior and inferior pancreatoduodenal arteries, which supply the head of the pancreas. The branches from the splenic artery form the dorsal pancreatic artery and the greater pancreatic artery that supply the body and the tail. The superior and inferior pancreaticoduodenal veins drain from the head of the pancreas into the superior mesenteric vein and the portal vein. The veins from the body and the tail of the pancreas drain via the splenic vein into the portal vein. [10]

2.1.1 FUNCTIONS OF THE PANCREAS

The pancreas is both an exocrine and an endocrine organ, which plays a key role in the control of the body's metabolism and energy consumption. Its exocrine tissue comprises acinar cells that produce pancreatic enzymes, which allow digestion. These enzymes include proteases such as trypsin, chymotrypsin, and elastase, which digests proteins, and amylase, which digests carbohydrates. The pancreas also produces several lipases; the best-known is pancreatic triglyceride lipase, which digests fat. These exocrine enzymes are delivered via the duct system, which is crucial in terms of IPMN disease. [11–13]

Endocrine cells of the pancreas, the five major types of islet cells (Langerhans cells), produce five hormones: insulin, glucagon, somatostatin, ghrelin, and pancreatic polypeptide [11,12]. For example, insulin regulates blood glucose levels by letting cells to take in glucose and use it for energy. In contrast, glucagon raises blood glucose levels by stimulating the liver to break down glycogen and release it as glucose [14].

2.2 THE DEVELOPMENT OF THE PANCREAS

During gestation, the ventral and dorsal pancreatic buds first develop separately from both sides of the distal foregut endoderm [9,12]. By the end of the sixth or during the seventh weeks of gestation, the ventral and dorsal pancreatic buds, along with their corresponding ducts, fuse; this follows clockwise rotation of the ventral bud around the foregut's caudal part [9,15]. The dorsal duct system upstream from the point of fusion is called the main pancreatic duct (MPD) [9]. The remaining dorsal portion draining to the minor papilla is called duct of Santorini (also known as the accessory pancreatic duct). The ventral duct draining from the fusion point into the major papilla is the duct of Wirsung. The duct of Wirsung drains mainly the MPD, and together they are referred to as MPD in this thesis (**Figure 1**). The ventral bud forms the uncinate process and the inferior part of the head of the pancreas while the dorsal bud forms the upper portion of the head of the pancreas, the body, and the tail of the pancreas. There are numerous tiny branch ducts that unite with the MPD and together they form the pancreatic drainage system for pancreatic juice. [15]

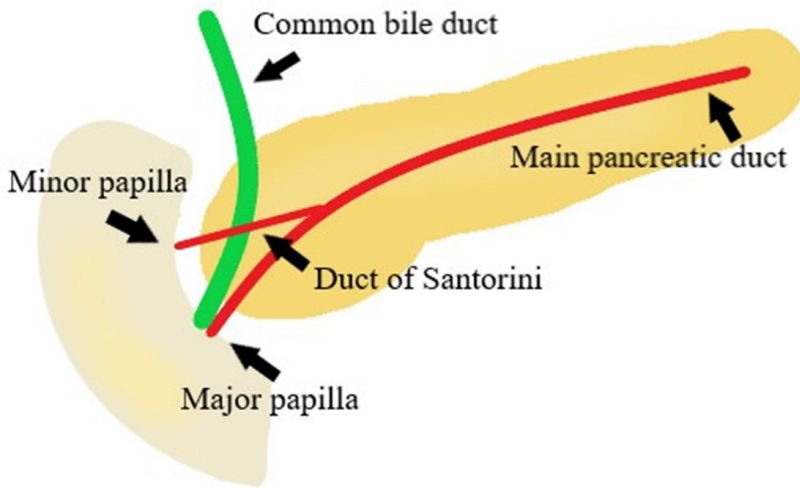

Figure 1 Pancreas and its ducts. At the fusion point the duct of Santorini attaches to the main pancreatic duct (MPD). The duct of Santorini drains to the minor papilla and the MPD to the major papilla together with the common bile duct.

2.2.1 ANATOMICAL VARIATIONS

The development process can face several failures, leading to anatomical variations that can be divided into three groups. The first group contains migration anomalies such as annular pancreas and ectopic pancreas [16]. The second group includes fusion anomalies such as pancreas divisum, whereas the third group contains ductal variations such as ansa pancreatica and duplication of the MPD [16,17].

Annular pancreas is a rare condition in which the head of the pancreas partially or completely surrounds the second portion of the duodenum [18,19]. It forms due to a rotation failure during gestation. Pancreas divisum has been reported in 30–38% of patients with annular pancreas [15,20].

Even though the pancreas is an uniform organ in upper abdomen in rare cases pancreatic tissue can be found as an ectopic pancreatic tissue almost everywhere in the abdomen [16]. However, most commonly ectopic pancreas tissue is small, usually 0.5–2.0 cm in size; most commonly, it is located in the stomach and duodenum, but sometimes also in the jejunum, in a Meckel's diverticulum, or elsewhere in the ileum [9]. It is most commonly asymptomatic, but may cause symptoms dependent on the location—for example, stenosis or bowel intussusception when located in the small bowel, and sometimes also symptoms from tissue activity [21].

Hypoplasia of the pancreas, in other words partial agenesis, results when the ventral or dorsal bud is absent. Absence of the dorsal bud leads to a short or truncated pancreas [9,15,21]. Hypoplasia can be classified into three types: total agenesis of the dorsal pancreas, hypogenesis of body and tail, and hypogenesis of the tail [8]. The hypoplasia of the uncinate process results when the ventral bud is absent [22]. Due to reduced tissue volume, hypoplasia is associated with diabetes [8,9] but can also be asymptomatic. Total agenesis is a very rare and potentially fatal condition. It is associated with other anomalies, such as polysplenia [21], and gallbladder aplasia [9].

Furthermore, the morphology of the pancreas can vary in more subtle ways which are not commonly considered true anatomical variations. For example, the lobulation of either the head or the tail of the pancreas can mimic a mass without being either pathology or anatomical variant. Uneven pancreatic lipomatosis can also be seen, and it is not a true anatomical variant. In the presence of situs inversus the pancreatic and biliary ducts can be inverted like the other organs. [9,18]

2.3 PANCREATIC DUCT VARIATIONS

The MPD diameter is typically approximately 3.5 mm in the head of the pancreas, 2.5 mm in the body and approximately 1.5 mm in the tail [9]. At the fusion point of the ventral and dorsal ducts the duct can be narrowed which is normal and is not a true stricture if the duct is not dilated upstream [9,23].

As mentioned before, the developmental variations can affect the pancreatic ducts as well. MPD can be duplicated, meaning that there are two separate ducts side by side in some part of the pancreas, usually in the body or tail [24]. This is called pancreas bifidum, which can lead to so-called fishtail variation, in which there are two separate tails of the pancreas [16]. However, most patients with pancreas bifidum are asymptomatic [24].

2.3.1 THE DUCT OF SANTORINI AND ANSA PANCREATICA

As mentioned before, the bifid configuration of the duct of Santorini and MPD is the most common form of duct system in the head of the pancreas and is seen in approximately 43–60% of the population [9,23,25,26]. The duct of Santorini can also lose its connection to the minor papilla, which is seen in approximately 30–32% of individuals [9,23] (**Figure 2**). In that case it persists only as a branch of the MPD or can alternatively be rudimentary or even invisible. On the other hand, the duct of Santorini can also be prominent, meaning that it equals the diameter of the MPD, which is seen in approximately 1% of the population [9].

Ansa pancreatica occurs when the duct of Santorini is obliterated at its junction with the ventral duct and replaced with a curved communicating duct between the ventral and dorsal ducts at the head of the pancreas [23,27,28] (**Figure 2**). Ansa pancreatica drains from the ventral fusion point first to the medial side and then turns towards back and directs to the minor papilla. It then drains either into the minor papilla or ends near it as a blind end without a true opening to the minor papilla [23]. Ansa pancreatica was identified for the first time in 1961 by Dawson and Langman and was present in 17% of the patients in their autopsy study population [23]. This variation has clinical significance with its association with idiopathic acute pancreatitis [27,29]. A study by Hayashi et al. found that in a Japanese community group, ansa pancreatica was present in 0.85% of the population, but in a recurrent acute pancreatitis group, it had a significantly higher frequency (11.1%) [27]. On the other hand, the researchers raised the idea that a relatively low proportion of ansa pancreatica in the community group could be either due to race or due to thinner ducts which maybe not even be visible in the magnetic resonance cholangiopancreatography (MRCP) images. In the study by Ishii and colleagues ansa pancreatica was considered one of the fusion variations that

was detected in 41% of their patient population and was also possibly related to congenital cystic dilatation of the common bile duct (CBD) [28].

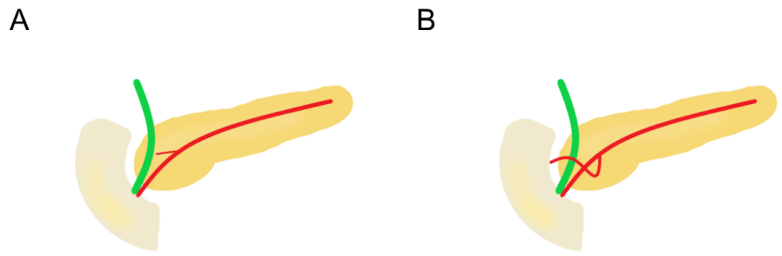

Figure 2 The duct of Santorini and ansa pancreatica. A) The rudiment duct of Santorini that does not connect into the minor papilla. B) Ansa pancreatica.

2.3.2 PANCREAS DIVISUM

Pancreas divisum is a congenital variant where there is a failure of fusion of the dorsal and ventral ducts and the dominant drainage occurs through the dorsal duct system into the minor papilla, which is seen in 4–14 % of population [9,15,30]. However, in Asian countries the rate is lower than in western countries [20,31]. Pancreas divisum usually causes no symptoms but can associate with abdominal pain and idiopathic pancreatitis [9,15,20,30,32].

In literature there are some variations of the recognized forms and classifications of pancreas divisum. Altogether there are four variants of pancreas divisum: complete (classic form), incomplete, reverse and absent ventral duct. At complete form, the dorsal and the ventral ducts drain separately without any uniting ducts between them. It is the most common form of pancreas divisum (70%). [20,33,34]

Pancreas divisum is called incomplete when there is a small duct uniting the dorsal duct and the smaller ventral duct. Its prevalence of all pancreas divisum cases is approximately 15%, but in Asian population its prevalence is higher [20,35].

In the reverse pancreas divisum there is a normal MPD that drains to the major papilla, but the duct of Santorini does not unite with the MPD and Santorini drains into the minor papilla [36]. A recent study by Renzulli et al. (2020) demonstrated the same with the name of pancreas divisum inversus. In their study this isolated duct of Santorini was longer, and it coursed to a more caudal direction than the ventral duct [37]. In other studies this inverted Santorini is described to be shorter in size [20,38]. In the autopsy study by Dawson and Langman, 4/120 cases (3 %) showed an accessory pancreatic duct that has lost its connection to the MPD, but the duct opened into the

duodenum. They did not name the finding, but it is consistent with the reverse pancreas divisum [23].

In the absent ventral duct type of pancreas divisum, only the MPD drains to the minor papilla but no ventral duct can be seen [35]. In a study by Bernard et al. the ventral duct was considered to be atrophic in 8% of patients with the pancreas divisum [32].

2.3.3 THE PAPILLA

2.3.3.1 The minor papilla

The function of the minor papilla has been under discussion. During embryological development, the minor papilla is the drainage route of the dorsal bud, but during development process the major papilla becomes the main drainage route for the pancreatic fluids. The patent minor papilla may serve as a second drainage system to secure the adequate drainage of fluids and to reduce the pressure in the MPD [26]. In a study by Kamisawa et al. (1998) made with endoscopic retrograde cholangiopancreatography (ERCP) observed that the number of permeable minor papilla was lower in the patient group with acute pancreatitis than in the healthy patient group (6% vs 41%) [39,40]. The same authors reported in their other study (1997) that the minor papilla was impervious in 79% of the ansa pancreatica patients [41]. Dawson and Langman noticed that almost 67% of their autopsy population's ansa pancreatica cases had impervious minor papilla [23]. This unfunctional minor papilla can be the disposing factor to pancreatitis with abnormal duct variations such as ansa pancreatica due to poor drainage of the pancreatic zones that are dependent on ansa pancreatica [26,40]. Also, the unphysiological course of the ansa pancreatica can be an issue that prevents good flow of the pancreatic fluids and predisposes the gland to a stenotic atmosphere [40].

2.3.3.2 Santorinicele

Santorinicele is a condition in which there is a cystic dilatation at the end of the duct of Santorini just before drainage into the minor papilla [20]. The accuracy of MRCP in detecting santorinicele could be improved by using intravenous secretin administration [42–44]. Santorinicele is more often seen with pancreas divisum, but it can also be seen with a normal duct arrangement or with other duct anomalies [45,46]. It was first described by Eisen et al. in 1994 and was speculated to be a result of prevented pancreatic fluid flow [47]. A study by Boninsegna and colleagues of secretin stimulation MRCP

discovered that 33% of their population with pancreas divisum had also santorinicele [42]. They also demonstrated that the dorsal duct was significantly larger in the head of the pancreas compared to that in patients with pancreas divisum that did not have santorinicele. In a study by Manfredi et al., 50% of their pancreas divisum patients had santorinicele [43].

Sphincterotomy can be used to enlarge the minor papilla to allow better flow of the pancreatic juice. In a study by Boninsegna and colleagues, the size of the santorinicele was reduced by 33% and the dorsal duct was reduced by 17% after sphincterotomy [42]. In a retrospective study by Crinò et al., sphincterotomy was performed on 31 patients who suffered from recurrent acute pancreatitis and had the complete type of pancreas divisum with santorinicele; 80% of patients got a complete response for treatment [44].

2.3.3.3 The major papilla and the pancreaticobiliary junction

In most cases (80–90%) the common bile duct and the MPD unite within a muscular sphincter, which is the part of both the MPD and the common bile duct that enters the major papilla into the duodenum [9]. This is called the common channel (sphincter of Oddi), and it can vary in length. It can be long (Y-type) or short (V type). A high junction above the sphincter may allow reflux of pancreatic secretions into the CBD, which in turn is often associated with choledochal cysts [9]. This reflux can also predispose pancreatitis, stone formation, and malignant transformation of the biliary epithelium [48,49]. When the common channel is over 15 mm, it is regarded as anomalous [9,18]. The major papilla is presented in **Figure 3**.

There can also be other pancreaticobiliary junction anomalies, such as the pancreatic duct entering the CBD more upstream from the sphincter or the CBD entering the pancreatic duct [18]. Also more complex junctions have been seen, for example, as accessory communication between the CBD and the pancreatic duct along with the normal junction [18,50,51].

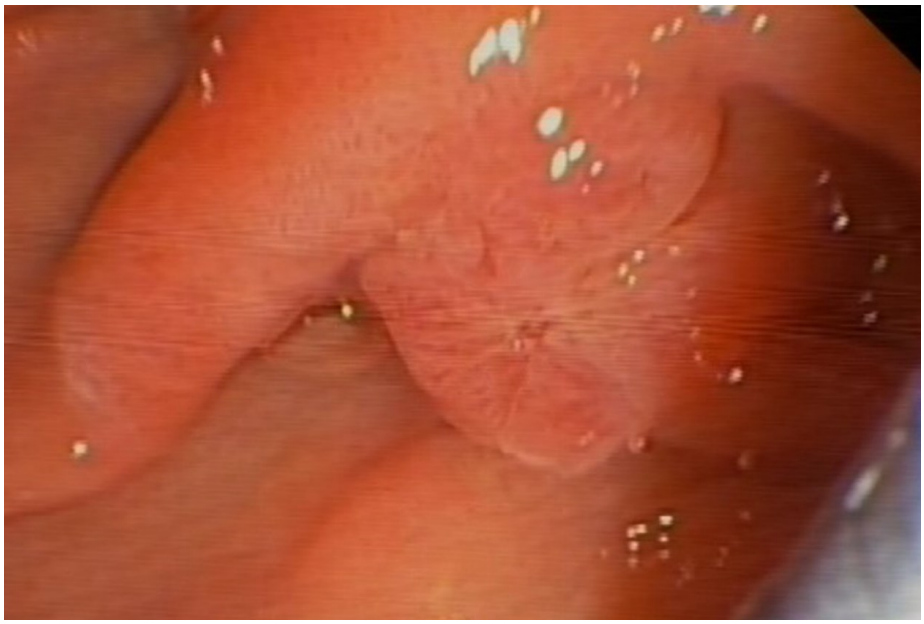

Figure 3 The major papilla. Image from HUH endoscopy unit.

2.4 COURSE OF THE MAIN PANCREATIC DUCT (MPD) AND THE MEANDERING MAIN PANCREATIC DUCT (MMPD)

The course of the MPD in the head of the pancreas has also been researched. Typically, the MPD has a so-called descending course where it smoothly descends from the level of the neck of the pancreas to the major papilla. It is most common and occurs in 50% of individuals [52]. The sigmoid course means that the MPD does a sigmoid curve en route from the neck of the pancreas to the major papilla [25]. The vertical course goes straight down in the caudal direction from the neck of the pancreas to the major papilla [52] (**Figure 4**). The course of the MPD can only be analyzed when the MPD is anatomically normal, not with pancreas divisum patients. At the fusion point of the duct of Santorini and MPD, the main pancreatic duct can demonstrate a loop configuration [15].

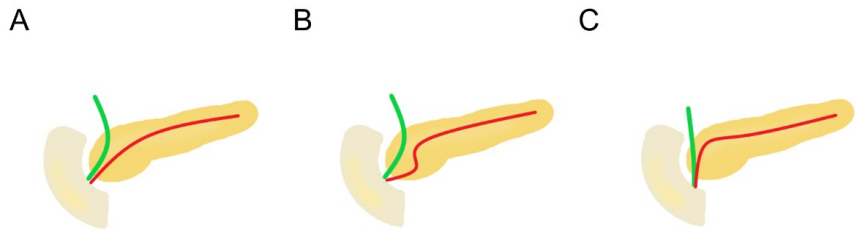

Figure 4 Different courses of the main pancreatic duct. A) Descending course. B) Sigmoid course. C) Vertical course. Modified from Figure 3 in **III**. The article is licensed under a creative commons license: http://creativecommons.org/licenses/by/4.0/. Some images were left out.

2.4.1 MEANDERING MAIN PANCREATIC DUCT

Meandering main pancreatic duct (MMPD) means that at the head of the pancreas, the MPD forms a loop or a so-called reverse-Z type form. The reverse-Z type configuration exists when the MPD forms tight turns in the same plane. These MMPD forms are not widely researched, but some studies have been made of the possible relation of MMPD and pancreatitis (**Figure 5**). A study by Gonoi et al. suggested that MMPD is a common anatomical variant and might be a precursor of idiopathic recurrent acute pancreatitis. In the normal Asian population MMPDs were detected in 2.2–4% of cases, which included both loop and reverse-Z type configurations. The loop configuration was present alone at 1% of cases. [53,54]

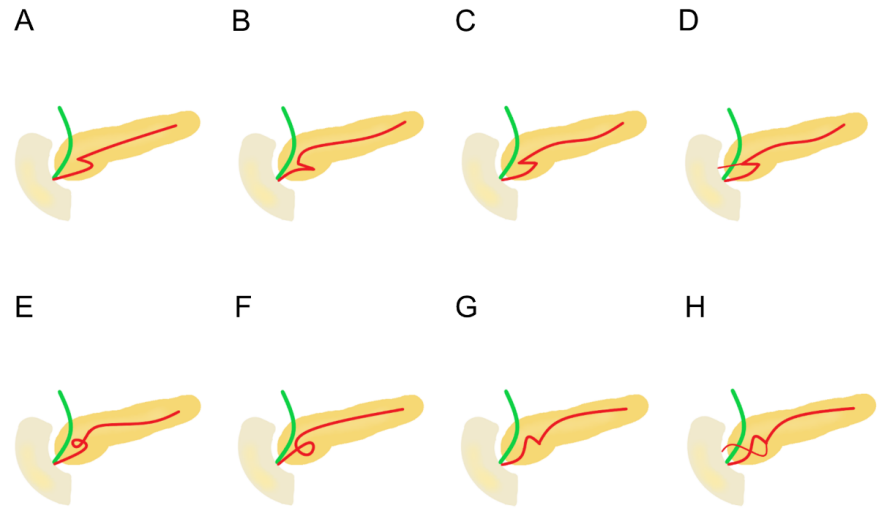

Figure 5 Meandering main pancreatic duct. A) Reverse-Z subtype C1 where the more upstream turn is <90° and the second turn is >90°. B) Reverse-Z subtype C2 where the more upstream turn is >90° and the second turn is <90°. C) In the reverse-Z subtype C3 there are two <90° turns in the horizontal direction along the same plane. D) Reverse-Z subtype C3 with the duct of Santorini which attaches to the right tight turn and then drains into the minor papilla. E) Loop-up configuration. F) Loop-down configuration. G) In the N-shape the duct forms a deep notch. H) N-shape accompanied with ansa pancreatica attaches to the deep notch and then drains into the minor papilla. From figure 2 in **III**. The article is licensed under a creative commons license: http://creativecommons.org/licenses/by/4.0/.

2.5 INTRADUCTAL PAPILLARY MUCINOUS NEOPLASM (IPMN)

Pancreatic intraductal papillary mucinous neoplasm (IPMN) is a cystic tumor which origin at the pancreatic ductal epithelium forming intraductal papillary masses. When normal ductal epithelium is replaced by cells forming papillary structures and producing mucus, the IPMN lesions start to develop. Mucus produced by these abnormal cells plugs the side branches, causing pressure, dilatation, and detectable cysts into side branches. Mucus production also causes ductal dilatation by obstruction. [55,56]

IPMNs' origin is under debate. Heterogeneous mutations are found among IPMNs. A study by Fischer et al. found that early-stage IPMNs contain multiple clones with distinct mutations, indicating that IPMNs' origin is polyclonal. In their study, mutations in proto-oncogenes KRAS and GNAS were more prevalent in the low-grade dysplasia stage than in the high-grade dysplasia stage of IPMN. The activation of KRAS and deletion of other tumor-

suppressor genes, such as Tff2, cause the hyperproliferation of papillary ductal gland cells, leading to the formation of IPMN. [55,57]

2.5.1 PREVALENCE

IPMNs are increasingly detected because of the increasing availability of higher resolution abdominal imaging [4,58]. Most IPMN patients are asymptomatic. In a study by Girometti and colleagues, the prevalence of incidental pancreatic cysts in asymptomatic patients at MRCP was 44.7%. In their study IPMN prevalence was 31.7% [59]. A study by Kromrey et al. demonstrated that the weighted prevalence of cysts in the pancreas is 49.1% in the healthy population [2]. Also, their study and a study by Lee and colleagues demonstrated that cysts' size and number increase with age [2,60]. A study by Zhang et al. came to the same conclusion about the fact that prevalence of pancreatic cysts increases with age [61].

2.5.2 CLASSIFICATION

IPMNs are divided into three categories: main-duct IPMN (MD-IPMN), branch-duct IPMN (BD-IPMN) and mixed type of IPMN (MX-IPMN) (**Figure 6**) [62]. MD-IPMN is the form of disease in which the MPD widens ≥ 5 mm without other causes of dilatation [62], and there are no dilated communicating cysts to the MPD. In the BD-IPMN type of disease, the branch ducts that communicate with the MPD dilatate and form cysts larger than 5 mm in size [58]. In the IPMN classification, cysts that are over 5 mm are considered IPMN cysts [62]. In MX-IPMN there are both ≥ 5 mm dilatation of the MPD and ≥ 5 mm cysts that communicate with the MPD [58].

IPMN is classified as one of the pancreatic cystic neoplasms (PCNs), which are discussed in the next chapter.

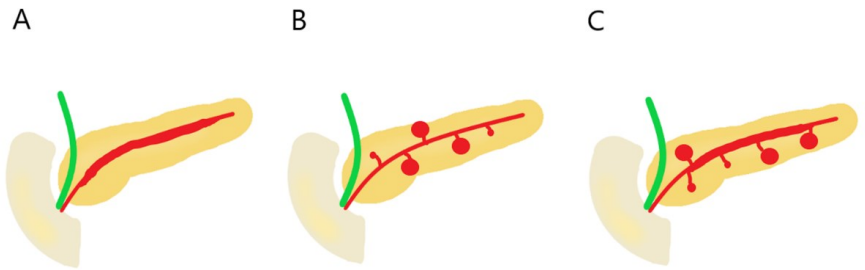

Figure 6 IPMN categories. A) Main-duct IPMN. B) Branch-duct IPMN. C) Mixed-type IPMN.

2.5.3 DIFFERENTIAL DIAGNOSTICS

Differential diagnosis includes other PCNs—for example, serous cystic neoplasm (SCN) and mucinous cystic neoplasm (MCN)—and other cysts such as cystic neuroendocrine tumor and solid pseudopapillary neoplasm (SPN) along with chronic pancreatitis, which affects the MPD and can form pseudocysts. Cystic acinar cell adenoma and serous cystadenocarcinoma are rare differential diagnoses. The SCNs and pancreatic pseudocysts are benign, while MCN, pancreatic endocrine neoplasm, and SPN may be premalignant [63].

Serous cystic neoplasms are often diagnosed at the ages of 50–70 and approximately 70% of patients are women. SCNs are mostly located in the body or tail of the pancreas. Typically, they are round lesions with multiple small cysts forming a so-called honeycomb pattern, but rarer oligocystic or macrocystic variants may also occur. Sometimes a central scar is seen inside the lesion. There is no connection between the MPD and the cyst that serves a critical feature in differential diagnosis between BD-IPMN and SCN. Furthermore, SCNs do not contain mucus and are considered basically benign (0.2% malignancy rate). When the size increases, and if the patient is symptomatic, the operation can be considered. [63–65]

Mucinous cystic neoplasm is unilocular or macrocystic and may have nodular calcification. It is usually located in the body or tail of the pancreas. Due to its relation to female hormones and having histology to ovarian stroma, they are basically found in women (95%) who are, most often, ages 40–60. Size of > 4 cm or mural nodules can indicate a more aggressive nature of the disease. The associated risk of malignancy is 10–15%, thus MCNs are recommended to be operated on, but they usually do not require surveillance after that. [63,64,66]

Solid pseudopapillary neoplasm is less common and more often diagnosed in younger patients (20–30 years), especially young women. SPN has a remarkable risk of malignancy. 10-15% of cases have malignant invasion or distant metastases. It is often seen in the distal pancreas as a well-circumscribed, heterogenous mass with cystic and solid components. [63,64,67]

Cystic neuroendocrine tumors have no gender, age or location preference but are more often seen in MEN-1 patients. Although they mainly consist of solid components, 18% have a cystic appearance. It may be differentiated from other cystic tumors by its hypervascular rim, thick septations and solid components. [68,69]

Choledochocele of the CBD is classified as a Todani type III choledochal cyst. Because it is located at the terminal portion of the CBD, it is important in differential diagnosis even though it is extremely rare. A duodenal diverticulum often arises in the periampullary region, but it is easy to differentiate because of its gas and fluid content. In rare cases CBD can drain into the diverticulum. [9,19]

2.5.3.1 Congenital and genetic differential diagnostics

Congenital true pancreatic cysts are very rare [30]. They are mostly seen in small children [70]. Congenital true pancreatic cysts are typically asymptomatic, but some patients may have abdominal pain or palpable mass [21]. Cysts can be single or multiple, and they are often located in the body or tail of the pancreas [9,21].

Multiple congenital cysts can be found in association with von Hippel-Lindau disease or autosomal polycystic kidney disease [21,70]. In von Hippel-Lindau disease, the pancreatic cyst involvement can vary from a single cyst to entire gland in which no visible normal pancreatic gland can be seen [9,21]. Peripheral calcifications can also be seen [9,24]. In autosomal polycystic kidney disease, pancreatic cysts are seen in 10% of patients [21].

Also, alimentary tract duplication cysts [19] or enterogenous cysts can involve the pancreas. They can communicate with the pancreatic duct within the bowel wall or they may lie inside the pancreas gland [21,70]. Also an accessory lobe of pancreatic tissue can be seen containing an aberrant duct that communicates with the enteric duplication cyst [18].

2.5.3.2 Pancreatic cancer

Pancreatic cancer is a lethal malignant disease that has a poor prognosis because it is difficult to treat, and most patients are diagnosed at an advanced stage of the disease [71]. The most common type of pancreas cancer is pancreatic ductal adenocarcinoma (PDAC). In 2018 pancreas cancer was the third leading cancer of death in women (18.7% of all cancers) and fourth in men (24.4% of all cancers) in Finland [72]. The 5-year survival was only 6% in Finland in the years 2016–2018 [72].

Three precursor lesions that may develop into PDAC have been identified: IPMN, MCN, and pancreatic intraepithelial neoplasia (PanIN) [55]. Some mouse studies indicate that PanIN may originate from the acinar cells of the pancreas [55]. PanINs are microscopic in size, under 0.5 cm [57], and therefore they are usually invisible in modern imaging and only detected in resected specimens [71]. PanIN lesions are most strongly associated with PDAC [55] and form the majority of pancreatic cancers [73]. All three precursors are curable if detected in the early stage and treated before progression into invasive PDAC [57]. In IPMN there is a risk of concomitant PDAC elsewhere in the pancreas [58], which occurred in 4% of cases with a surgical resection in a study by Yamaguchi and colleagues [74]. In general, patients with pancreatic cyst have higher risk for pancreatic cancer than patients without cysts. In study a by Munigala et al., the estimated overall risk for pancreatic cancer was 19.6 times greater in the pancreatic cyst group [75]. Generally, IPMN lesions may develop to tubular, colloid or oncocytic

adenocarcinoma, and the oncocytic type is diagnosed as cystadenocarcinoma [76].

2.5.4 THE RISK OF MALIGNANCY

As mentioned before IPMN can progress to pancreatic cancer [4,62]. But based on the high prevalence of IPMN changes and, on the other hand, the low incidence of pancreatic cancer, only a minority of IPMN changes progress to invasive carcinoma [77,78]. MD-IPMN and MX-IPMN are at a higher risk of malignant transformation compared to BD-IPMN. The risk of malignant transformation appears to be equal in MD-IPMN and MX-IPMN [4], 38–68% according to previous studies [58,79].

Many studies have shown that BD-IPMN without worrisome features has a quite stable course [58] and the risk of malignant transformation is only 3–15 % during surveillance [80–82]. A study by Oyama and colleagues (2020) demonstrated that the incidence of malignant transformations of BD-IPMN was 3.3% five years after diagnosis while it rose up to 15% at 15 years [80].

2.5.4.1 Worrisome features (WF) and high-risk stigmata (HRS)

There are certain radiological and clinical characteristics that are considered to be predictors of possible malignant transformation [4]. They are called worrisome features (WF) and high-risk stigmata (HRS) and were first defined in 2012 by the International Consensus Guidelines, the so-called Fukuoka guidelines [62].

Radiological WFs include cysts of ≥ 30 mm, a main pancreatic duct (MPD) size of 5–9 mm, an enhancing mural nodule < 5 mm, abrupt change in the MPD caliber with atrophy of the distal part of the pancreas, thickened enhanced cyst walls, and lymphadenopathy. Also, rapid rate of cyst growth (> 5 mm/ 2 years) is considered a WF as are elevated serum levels of CA 19-9 at the laboratory test [58]. **Figure 7** demonstrates the size of the cyst and MPD.

In HRS characteristics include an MPD ≥ 10 mm, an enhancing mural nodule ≥ 5 mm, and obstructive jaundice in a patient that has a cystic lesion in the head of the pancreas [58].

A study by Seo et al. demonstrated that the presence of a mural nodule is the most important predictor of malignancy in both BD-IPMN and MD-IPMN diseases. In that study both the size of the mural nodule and lymphadenopathy were significant predictors of malignancy in MD-IPMN. [83]

Several studies have shown that the diameter of the MPD is one of the most significant predictive factors of malignant transformation. The MPD sizes of 5–9.9 mm have been reported to indicate a 37–91% risk of high-grade dysplasia or cancer [4,83]. In a prospective study by Petrone and colleagues of

BD-IPMN patients with no WF/HRS at the beginning, the MPD dilatation was the strongest independent risk factor for malignant transformation (odds ratio, OR 24.5) [84]. According to the study by Buscail et al., MPD size ≥ 10 mm was significantly associated with malignancy (OR 7.52) [85].

Patients who have larger cysts have a higher progression risk of WF/HRS [86]. But there are debates as to whether the size alone correlates with invasive malignancy. Fukuoka guidelines recommend to use a 3 cm cutoff [58], but some think that a specific 3 cm size cutoff should not be recommended [63]. Several studies suggest that even cysts smaller than 3 cm are at risk of malignancy [63,87].

Kwong et al. demonstrated that BD-IPMN patients' cyst growth rate of ≥ 5 mm/year had a 19.5-fold higher risk of malignant progression [88]. In the study by Ciprani and colleagues (2020), the size increase of ≥ 2.5 mm/year represented the strongest predictor of malignancy compared to other worrisome features in BD-IPMN patients who had a small (< 15 mm) cyst without WF/HRS in the beginning of the study [89].

Buscail et al. demonstrated that jaundice is a strong predictor of malignancy (OR 11.85 in multivariate analysis) [85]. Acute pancreatitis and new onset of diabetes are also considered worrisome features [4,90,91].

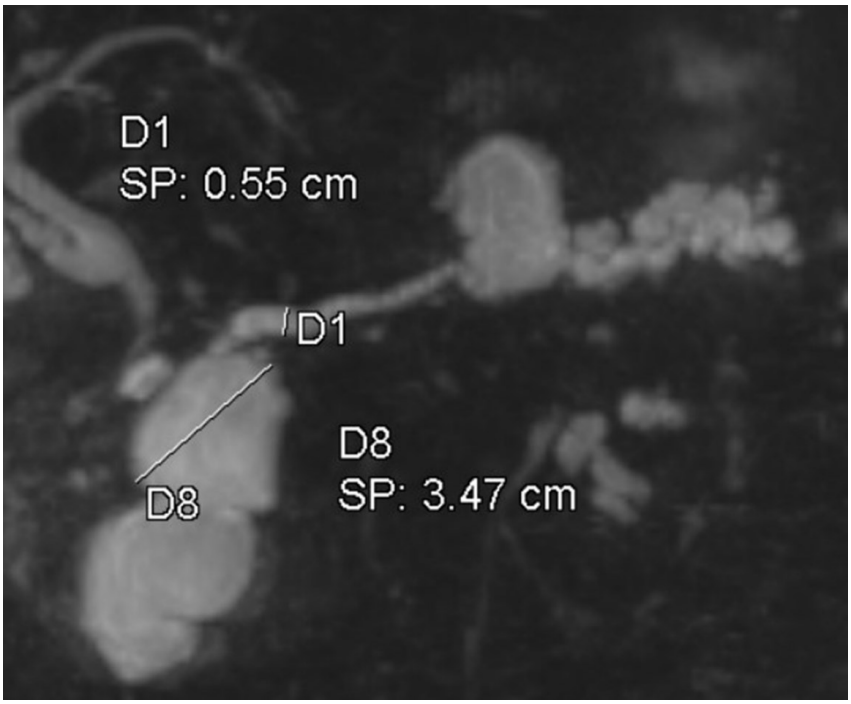

Figure 7 Mixed-type IPMN disease with a 35 mm cyst and 6 mm main pancreatic duct, which both are worrisome features. Image from HUH.

2.5.4.2 Indicators of the lower risk of malignancy

There have also been studies about the factors that indicate lower risk for malignant transformation, which have focused, e.g., on the size of the cyst and its growth rate. A recent study by Ciprani et al. (2020) demonstrated that cysts < 15 mm without WF/HRS at the time of diagnosis had a very low risk of malignancy. They also stated that the risk even decreases over time in such patients [89]. In their study 55% of patients had no increase in cyst size. A study by Han and colleagues also presented that smaller cysts grew less than larger cysts. In their study the smaller cysts that were under 10 mm grew 0.7 mm annually (median) and cysts < 20 mm grew 0.8 mm, when the bigger cysts 20–30 mm in size grew 1.1 mm annually and cysts over 30 mm grew 1.2 mm [92]. A study by Nakhaei et al. in 2021 demonstrated that asymptomatic incidental pancreatic cysts have similar long-term risk for pancreatic malignancy compared to those without cysts (0.9 cases per 1000 patient-years and 1.8 cases, respectively) [93]. A recent study by Tamburrino et al. in 2022 suggests that conservative management of BD-IPMN patients at low risk is safe [91].

2.6 IMAGING OF THE IPMN DISEASE

As mentioned before, most of the IPMN cysts are incidental findings and the patients do not have any symptoms [2,3]. The wide use of MRI and CT has led to increased prevalence of IPMN cysts. Cysts and MPD dilatation can also be detected with ultrasound (US) in the context of an upper abdomen examination. US is based on sound waves, not on radiation, which makes it a safe and widely used diagnostic method. However, ultrasound has its limitations with pancreatic imaging. The contents of stomach and intestines limit visibility to the pancreas. Frequently, the visualization is suboptimal, and only the head and part of the body can be seen, leaving the rest of the pancreas unseen. This is also dependent on the patient's body shape. [94]

Ultrasound is widely used in diagnostics, and pancreatic cysts and widening of the MPD are usually incidental findings. The resolution achieved with US does not allow detection of small cysts, especially evaluation of their possible connection to MPD. The proper evaluation and the differential diagnostics of the cysts should be done with MRI or CT. US can detect calcification within MPD if the calcification is big enough. The size of the structures is so small that US does not have the capacity for surveillance of the IPMN disease. Also, the bigger cysts and the wide MPD are risk characteristics that should be surveilled with MRI or CT imaging [4]. The sensitivity of the CT to detect the communication between the cysts and the MPD is lower than with

MRI; therefore, both the diagnostics and the surveillance of IPMN lesions rely primary on MRI [4].

2.6.1 MRI AND MRCP

Magnetic resonance imaging allows high-resolution imaging of the pancreas, and the MRCP sequences excellent visualization of the pancreatic ducts. MRI and MRCP have higher contrast resolution compared to CT [4,95]. Compared to CT, MRI has increased sensitivity in identifying communication between a cyst and the MPD, and the presence of internal septation inside a cyst or a mural nodule [4,96]. MRI is also more sensitive in detecting the amount and extent of the cysts [4,97]. MRI machines in clinical use are 1.5 Tesla (1.5 T) or 3 Tesla (3 T). The main advantage of using 3 T is the higher signal-to-noise ratio (SNR). Otherwise, 3 T does not offer remarkable improvement compared to 1.5 T [98], even though more recent studies have pointed that 3 T has superior image quality [99].

The set of MRI sequences, MRI protocols, used for pancreatic imaging may vary between countries and hospitals. T1-weighted (T1WI) sequences with fat saturation (fs) show high T1 signal intensity in normal pancreas tissue due to its high protein content in the acini [100]. Pancreatitis and pancreatic adenocarcinoma appear the opposite, as hypointense, in these sequences [101]. T2-weighted (T2WI) images show at low to intermediate signal in the normal pancreas while cysts and fluid collections show increased signal intensity [99], which is further strengthened by using fat saturation techniques allowing cysts and other fluid-containing structures to be highlighted. MRI technique is not based on radiation, which is a main advantage in terms of frequent need for imaging in surveillance.

MRCP should be performed as three-dimensional (3D) for better evaluation of pancreatic side branches and their connection to the main duct, their anatomy, and also visualization of the possible ductal stones. The post-processing of these images creates maximum intensity projection (MIP) sequences that are 3D. [99,102]

Contrast agent (gadolinium, gadoterate meglumine) is for detecting a possible pathological vascularity and thus enhancing structures in pancreatic tissue or within the lumen, such as solid tumors, mural nodules or septa. When scanning with contrast agent, the sequence that is normally used is 3D fat-suppressed spoiled gradient-echo, such as volumetric interpolated breath-hold (VIBE). In order to differentiate between natural high intensity in T1WI and true enhancement, precontrast (unenhanced) images in the axial plane are taken, followed by gadolinium-enhanced series with arterial, venous, and delayed phase. [98]

Administration of the secretin during MRCP increases visibility of the MPD and its side branches, which helps to detect anatomical duct variants such as pancreas divisum [30] or anomalous pancreaticobiliary junction. It can also

help to differentiate IPMN from other PCNs. In practice, secretin can be used after trauma to evaluate possible damage to the ductal system or after pancreatic operation to evaluate the patency of the pancreatico-enteric anastomosis. [103,104]

Proper patient preparation before MRI scanning of the pancreas and its ducts is crucial. Patients fast for 4 hours before the MRI or MRCP examination so that the gallbladder is distended and thus properly visible in images. To reduce the signal from overlying stomach and duodenum, pineapple juice is orally ingested. It serves as a negative oral contrast because the manganese in pineapple juice shortens the T2 relaxation time and reduces the T2 hypersignality from the stomach fluid. [98]

As in general use of the MRI examinations, the adverse effects should be considered. Gadolinium is well tolerated, but it can cause nausea, headache, and dizziness. Severe allergic reactions are rare. An inquiry about foreign objects such as pacemaker or metal prosthesis in the patient's body must be made because the MRI machine carries a magnetic field which can break, heat up or move metallic objects. This can be life-threatening for a patient. The proper patient positioning before scanning is also crucial to avoid adverse effects of the magnet such as burns. An MRI machine is noisy, and hearing protection for the patient must be provided with headphones and earplugs. [105,106]

2.6.2 COMPUTED TOMOGRAPHY (CT)

Even if the MRI is the primary imaging modality, CT is another option. CT can be used if MRI is contraindicated for some reason. Furthermore, CT should be used if there is a suspicion of calcifications, which are difficult to identify in MRI [107]. MRI does not show calcification; it shows only a defect at the site of a calcification. CT is based on ionizing radiation. The scan can be performed as non-contrast or with an iodine contrast agent (iohexol). CT is also a faster scanning technique, and as such, an alternative method for claustrophobic patients or those who cannot stay still during longer MRI scanning (for example, older patients). CT is also a more economical modality compared to MRI, although it is not suitable for performing a longer follow-up because of the radiation [108].

CT is a good imaging modality for tumor staging, and therefore it should be used when there is strong suspicion of a malignant IPMN or concomitant pancreatic cancer. In that case, CT is recommended to be performed as multiphase imaging, including an arterial phase, pancreatic phase, and venous phase [109]. Preoperative tumor involvement and its vascular invasion can be evaluated more precisely with CT compared to MRI. To evaluate possible metastases, venous phase imaging should include whole body from the jugular notch to underneath the pubic bone in order to evaluate possible non-

abdominal metastases that are not visible in MRI, which is generally limited to the upper abdomen. [110]

Possible postoperative complications, such as pancreatic fistula, abscess, postoperative hemorrhage, postoperative pancreatitis, anastomotic stricture, delayed gastric emptying, portal vein and superior mesenteric vein thrombosis, hepatic infarction, and leak from the gastrojejunostomy or from the biliary-enteric anastomosis, can be detected with CT [111]. CT is recommended to be performed in multiple phases: first, performing a non-contrast scan to detect surgical material, followed by arterial phase images if active bleeding is suspected and/or with venous phase.

Also, whole body CT with an intravenous contrast agent is recommended for follow-up with these patients in order to evaluate possible local recurrence of the pancreatic cancer as well as the metastatic spread of the disease to the lymph nodes and other organs. [110]

2.7 MANAGEMENT OF THE IPMN DISEASE

2.7.1 SURVEILLANCE

Due to the potential risk for malignant transformation, patients with IPMN are under surveillance. There is a huge alternation among three different consensus guidelines according on the length and way of doing IPMN surveillance (**Table 1**).

In year 2006 the international consensus guidelines at Sendai recommended that surveillance should be performed according to the size of the cyst [112]. In 2012 the new international guidelines recommended surveillance for a short interval (3–6 months) to show that the disease is stable [62]. Their revised guidelines in 2017 recommend that BD-IPMN patients without WF/HRS should undergo surveillance based on the cyst size: cysts < 1 cm, follow-up CT/MRI in 6 months and then every other year if no change [58]. In cysts 1–2 cm in size, CT/MRI twice in one year and then yearly for 2 years and then every other year if no changes. For cysts that are 2–3 cm in size, they recommend doing endoscopic ultrasound (EUS) in 3–6 months and then once a year MRI/EUS. According to their recommendation, cysts > 3 cm should be scanned every 3–6 months with MRI or EUS. [58]

European guidelines (2018) recommend lifelong surveillance of IPMN patients as they are fit for surgery. They recommend surveilling once a year, but twice the first year regardless of cyst size. They prefer MRI over CT. They also recommend measuring serum CA 19-9 yearly and doing clinical evaluations. [4]

The American Gastroenterological Association (AGA) guidelines from 2015 recommend scanning incidental BD-IPMN patients with MRI 1 year after

diagnosis and then every 2 years for 5 years. If the disease is stable and the patient does not have any WF or HRS after 5 years, they recommend stopping surveillance. If the patient has two high-risk features, they recommend EUS and fine needle aspiration (FNA). If there are no concerning findings, the same surveillance program can be proceed. [5]

The presence of WF or HRS requires evaluation of the imaging findings, laboratory results, patient's symptoms and general condition, which together form an entirety that should be carefully discussed, e.g., at a multidisciplinary team meeting (MDT) [113] to consider the next step—whether to do an EUS, an endoscopic retrograde cholangiopancreatography (ERCP) or even a surgery. [4,58]

Table 1. Three different consensus guidelines for IPMN surveillance

International guidelines based on cyst size:	**European guidelines** lifelong surveillance:	**AGA guidelines** surveillance for 5 years:
< 1 cm cyst: follow-up in 6 months, then every other year	Twice first year. Then yearly if no change.	First follow-up after 1 year. Then every other year for 5 years. Then stopping follow-up if no change.
1–2 cm: twice first year, then yearly for 2 years, and then every other year		If two risk-risk factors: first EUS and FNA. If no concerning findings, the same surveillance program can be proceed.
2–3 cm: EUS after 3–6 months, then once a year MRI/EUS		
> 3 cm: MRI/EUS every 3–6 months		

AGA = American Gastroenterological Association, EUS = endoscopic ultrasound, FNA = fine needle aspiration.

2.7.1.1 Imaging

MRI is the preferred method for IPMN surveillance [4,108]. However, there are no preferred specific MRI protocols recommended for IPMN surveillance according to European guidelines [4]. Also, the use of contrast material for MRI follow-up is controversial [109,114]. A study by Pozzi-Mucelli et al. (2016) demonstrated that a shorter protocol (SP) without contrast enhancement and diffusion sequences provided information comparable to the longer protocol with contrast enhancement [115]. Macari et al. (2009) presented that contrast enhancement has minimal impact in assessment of the PCN [114].

In Helsinki University Hospital (HUH) the longer protocol (LP) is used for primary diagnosis of IPMN patients. The LP includes the following sequences: T2-weighted (T2WI) half-Fourier single-shot turbo spin-echo (HASTE) axial plane, T2WI HASTE fs axial, T1WI fast low angle shot (FLASH) fs axial, T2WI HASTE fs thick coronal, T1WI 2D in/opposed phase in axial plane, T2WI 3D MRCP sampling perfection with application-optimized contrasts using different flip angle evolution (SPACE) in coronal plane and maximum intensity projection (MIP), T2WI HASTE fs thin coronal, diffusion-weighted imaging (DWI) and apparent diffusion coefficient maps (ADC) in axial plane, and T1-weighted fs VIBE before and after the administration of the contrast agent in axial and coronal plane. (**Table 2**)

For IPMN surveillance, patients with WF/HRS are scanned with LP in HUH, while patients who do not have WF/HRS are scanned with the shorter protocol (SP). The shorter protocol includes: T2WI HASTE axial plane, T2WI HASTE fs thick slice coronal, T1W FLASH fs axial plane, T2WI 3D SPACE MRCP coronal and MIP, and T2WI HASTE fs thin slice coronal (**Table 2**).

Table 2. MRI protocols used in Helsinki University Hospital for IPMN surveillance. Modified from Table 1 in **II**. The article is licensed under a creative commons license: http://creativecommons.org/licenses/by/4.0/. Data was left out.

Sequence, imaging plane	LP	SP	Slice thickness (mm)	TE (ms)	TR (ms)	Breathing technique
T2 HASTE axial	X	X	6.0	93	1400	BH
T2 HASTE fs thick slice [a] coronal	X	X	50.0	741	4500	BH
T2 HASTE fs axial	X		6.0	93	1400	BH
T1 FLASH fs axial	X	X	5.0	2.38	178	BH
T1 2D in/opposed phase axial	X		5.0	2.38/4.76	150	BH
T2 3D SPACE MRCP [b] coronal	X	X	1.0	700	2500	RT
T2 HASTE fs thin slice coronal	X	X	4.0	79	1200	BH
T1 VIBE pre-contrast axial	X		3.0	1.86	3.99	BH
T1 VIBE post-contrast [c] axial and coronal	X		3.0 1.7	1.86 1.07	3.99 2.92	BH
DWI [d] + ADC axial	X		6.0	63	4600	FB

ADC = apparent diffusion coefficient maps, BH = breath-hold, DWI = diffusion-weighted imaging, FB = free-breathing, fs = fat saturation, FLASH = fast low angle shot, HASTE = half-Fourier single-shot turbo spin-echo, LP = long protocol, MIP = maximum intensity projection, MRCP = magnetic resonance cholangiopancreatography, RT = respiratory trigger, SP = short protocol, SPACE = sampling perfection with application-optimized contrasts using different flip angle evolution, TE = echo time, TR = repetition time, VIBE = volumetric interpolated breath-hold.

[a] In six dimensions.

[b] Including MIP.

[c] 0.1 mmol/kg body weight of gadoterate meglumine. Post-contrast phases: arterial phase axial, venous phase axial, venous phase coronal, and late venous phase axial.

[d] DWI b-values are 50, 400, and 800 s/mm².

2.7.1.2 Laboratory tests, CA 19-9

At the moment there are no usable RNA, DNA or protein serum biomarkers for clinical use to identify IPMN disease or risk for its malignant transformation [4]. On the other hand, antigens CA 19-9 and CEA (carcinoembryonic antigen) are used in IPMN-related cancer detection [4]. A study by Mimura et al. demonstrated that elevated serum CA 19-9 level (> 37 U/mL) was an independent component predicting invasive IPMN disease [116]. It is good to note that 10% of White population does not produce CA 19-9 and when there are unmeasurable levels of CA 19-9, this laboratory test cannot be used in cancer detection [117]. Furthermore, CA 19-9 can also be elevated in pancreatitis. In addition, AFOS (serum alkaline phosphatase) may indicate malignant progression of the MX-IPMN disease during surveillance [118].

2.7.1.3 EUS, FNA, ERCP

The endoscopic ultrasound (EUS) is recommended to be performed if radiological or clinical features are causing concern, e.g., worrisome features such as elevated CA 19-9, a mural nodule or MPD 5–9 mm. EUS is recommended only if it is expected to alter the clinical management due to the risk for complications (up to approximately 4% of patients develop a harmful event). The fine needle aspiration (FNA) can been taken during EUS to analyze the cyst fluid in order to differentiate between mucinous and non-mucinous PCNs [71]. Also, the cytology as well as the levels of CEA and amylase in the cyst fluid can be analyzed for cyst differentiation. The amylase is usually elevated in pseudocysts while the CEA is elevated in mucinous cysts. The cytology can help to differentiate benign cysts from ones with dysplasia: low-grade and high-grade dysplasia. The contrast-enhanced harmonic EUS is used to evaluate whether there is vascularity in a mural nodule or within cyst septation. FNA should also be taken when there is visible hyperenhancement in the pancreatic parenchyma. [4,58,119–121]

A cytologic sample of pancreatic juice can be obtained also via ERCP. ERCP can help to distinguish the chronic pancreatitis from an MD-IPMN disease. A dilated papilla with mucin secretion or a mural nodule inside the duct confirms the MD-IPMN diagnosis. On the other hand, ERCP should not be used as a routine for differentiating PCNs due to its risk for adverse effects such as post-ERCP pancreatitis (incidence risk 3.5–9.7%). [4,58,122]

2.7.1.4 Histology, histopathology, and prognosis

IPMN is classified histologically by WHO classification into two categories: intraductal papillary mucinous neoplasm, which is divided into low-grade and high-grade dysplasia, and intraductal papillary mucinous carcinoma, which can be noninvasive or invasive [123]. Formerly, there was also an intermediate-grade (moderate grade) dysplasia category, which is now integrated into the low-grade category [124].

Histopathology also shows the epithelial subtype of IPMN. It is classified into four types: gastric, intestinal, pancreatobiliary, and oncocytic. The gastric subtype is the most common subtype, and pancreatobiliary and oncocytic subtypes are the least common. Gastric subtypes are typically located in BD-IPMN and have the lowest risk of malignant transformation, invasion rate being 9–14%, but they can develop into tubular adenocarcinomas. These are associated with poor overall survival rate, which does not significantly differentiate from pancreatic ductal adenocarcinoma. Intestinal subtypes are usually located in the main duct. They can develop into colloid carcinomas, which have a better survival rate (62–87%) when compared to tubular adenocarcinomas, which have a survival rate of 19–55%. The prognosis of the pancreaticobiliary subtype is the worst of all four subtypes and has the greatest risk of invasion (58–63%) and transformation to tubular adenocarcinoma (81.8%). The oncocytic subtype is rare, and it is typically located in the main duct. It can evolve into oncocytic carcinoma, which has a better survival rate than tubular carcinoma, but tubular carcinoma may also occur. An IPMN can contain multiple epithelial subtypes simultaneously. [56,76,121,125–127]

2.7.2 SURGICAL MANAGEMENT

As mentioned before, different IPMN types have different risk rates of malignancy. The prognosis of IPMN after surgery is favorable if the operation is done before the IPMN has progressed to invasive cancer [128]. On the other hand, the unnecessary operation in a benign state of IPMN is unfavorable because of the complication risks. Furthermore, the three international guidelines of IPMN management differ. Careful evaluation of the clinical, radiological, and possible EUS findings at the MDT is needed for every patient preoperatively. Pancreatic operations carry risk for major complications in as many as 24–30% of cases [129], such as harmful postoperative pancreatic fistula [130,131], a delayed gastric emptying (DGE) [132], infections, hemorrhages and hematomas [133], and even death [134]. The mortality rate after the pancreaticoduodenectomy varies from 1–4% within a month [85,135] up to 16.5% for the first year after operation [136]. It has been noticed that the mortality rate is higher for benign IPMNs [85]. For these reasons, the benefit of each procedure must be considered carefully and individually. A study by Marchegiani et al. in 2022 proposed that in preoperative evaluation, high age,

overweight and diabetes are factors that should direct treatment of these patients towards less aggressive management [129].

The majority of BD-IPMN patients can be managed conservatively with no need for surgery. But MD-IPMN and mixed-type IPMN patients carry a significantly higher risk for malignant transformation, and, e.g., surgery is universally approved for patients with MD-IPMN [4,83,116]. The presence of features of high-risk stigmata, such as size of the MPD ≥ 10 mm, an enhancing mural nodule ≥ 5 mm, or obstructive jaundice in a patient with a cystic lesion of the pancreatic head, are indications for surgery. Surgery has to be considered if EUS detects a ≥ 5 mm mural nodule, if there is a suspicion of malignant involvement inside the MPD, or if the cytology of the FNA is positive or suspicious for malignancy [58].

The European guidelines (2018) recommends that absolute indications for surgery are positive cytology for malignancy or high-grade dysplasia (HGD), a solid pancreatic mass, tumor-related jaundice, enhancing ≥ 5 mm mural nodule, and MPD ≥ 10 mm [4]. The relative indications for surgery are growth rate ≥ 5 mm/year, MPD dilatation between 5–9.9 mm, enhancing mural nodule that is < 5 mm, cyst size ≥ 40 mm, increased level of serum CA 19-9 ≥ 37 U/mL without jaundice, new onset of diabetes, and acute pancreatitis that is caused by IPMN [4]. A study by Buscail and colleagues noticed that the relative criteria of cyst size ≥ 4 cm and MPD 5–9.9 mm were more significantly associated with malignancy than the others that were recommended in the European guidelines [85].

According to the recommendation of the International Association of Pancreatology (2017), the absolute indications for surgery are jaundice, enhancing mural nodule > 5 mm, and/or MPD > 10 mm. The relative indications are growth rate > 5 mm/2 years, increased level of serum CA 19-9, MPD dilatation (5–9 mm), cyst size > 30 mm, pancreatitis, enhancing mural nodule < 5 mm, and abrupt change in caliber of MPD with distal pancreatic atrophy or lymphadenopathy [58].

The AGA guidelines (2015) recommendation for absolute surgery indications for asymptomatic IPMNs are MPD ≥ 5 mm, a solid component in the pancreas, and/or the cytology being positive for malignancy [5].

2.7.2.1 Operation techniques

Pancreatic operation techniques include pancreatoduodenectomy (Whipple procedure), total pancreatectomy and partial distal resection [135,137]. A study by Scholten et al. demonstrated that there was a clinically relevant lack of consensus in the operative treatment strategy in MD-IPMN and MX-IPMN disease about whether to operate or continue surveillance and whether to do a total pancreatectomy or pancreatoduodenectomy [138].

In the partial resection, usually the resection line runs at the tail or the body of the pancreas. The partial resection enables the endocrine and exocrine

function of the pancreas [128,138]. After partial resection, surveillance is needed for potential malignant recurrence [4,128].

The Whipple procedure is commonly performed for tumors in the head of the pancreas [135]. The European guidelines recommend using the Whipple procedure when the MPD is dilatated. The body and the tail of the pancreas are preserved after surgery, which requires lifelong surveillance, but on the other hand enables the pancreas to function [4].

Total pancreatectomy is associated with severe complications, which are mainly associated with unstable diabetes [137]. The European guidelines (2018) suggest that total pancreatectomy can be considered when there is a dilatation of the entire MPD and a mural nodule within the duct [4]. They also recommend considering total pancreatectomy for patients who have increased risk for malignancy if the entire MPD is dilated [4]. The International Association of Pancreatology (2017) recommends total pancreatectomy selectively for younger patients and that it also be considered in patients with a strong family history of PDAC [58].

During the operation, the frozen section analysis of the pancreatic resection margin should be done in case of resection [4,68]. If this analysis indicates that HGD or cancer is present at the surgical resection margin, a further resection is needed, even a total pancreatectomy if necessary. The frozen section analysis may also detect skip lesions of malignancy in areas of the pancreas other than the actual tumor, which occurs in 6–42% patients [4].

2.7.2.2 Surveillance after operation

Recommendations about the postoperative surveillance vary. IPMN recurrence rate in low-grade dysplasia is 5–10%, but in high-grade dysplasia it is over 50% [4,64]. The recurrence usually develops within 5 years, but it may also develop a long time after surgery [128]. European guidelines (2018) recommend that patients who are still fit for surgery should be under lifelong surveillance after their operation [4]. International consensus guidelines also recommend surveillance after surgery because of the possible recurrence of IPMN disease or a concomitant pancreatic ductal adenocarcinoma. They suggest that if a patient has a positive family history of PDAC or if there is a positive surgical margin for high-grade dysplasia in the operation, it is good to follow up with these patients twice a year. Otherwise, they think that every 6–12 months would be sufficient interval for surveillance [58].

Contrary to the above, the AGA guidelines (2015) recommend that patients with resected invasive cancer or dysplasia should be surveilled with MRI every 2 years. If there is no HGD or invasive carcinoma detected in the surgical tumor resecate AGA guidelines recommend no further surveillance. But mixed-type IPMN and a strong family history of pancreatic cancer are exceptions, and these patients should still be monitored after the surgery. [5]

3 AIMS OF THE STUDY

This thesis is based on the following studies, which are referred by their Roman numerals.

I To explore, which side-branch IPMN patients could be imaged less frequently at future IPMN surveillance.

II To evaluate whether even shorter MRI protocol, an ultrashort protocol, provides equivalent information compared to longer protocols that are used in HUH.

III To evaluate if variations in ductal anatomy and its course have any association with IPMN disease.

4 PATIENT COHORTS AND METHODS

4.1 PATIENTS

4.1.1 STUDY I

We conducted a retrospective search using clinical archives of HUH and collected 521 patients that were at the first time treated for pancreatic cystic lesions at the department of gastrointestinal surgery at HUH between years 2014–2016 (**Table 3**). Only patients with working-diagnosis of BD-IPMN made by study observer according to the radiological diagnostic criteria were included in the study. Also at least 6 months of surveillance was demanded. Exclusion criteria were: no MRI or CT images performed after initial diagnosis, a previous pancreatic carcinoma or pancreatic operation. Total of 144 patients were excluded. The final study population was 377. Mean age of patients was 65.3 years (range 31.1–87.0).

Table 3. Study populations in Studies **I**, **II** and **III**

<table>
<tr><td colspan="3">Patients surveilled for IPMN
January 2014 – December 2016
(n = 521)</td><td rowspan="2">Patients monitored for gallstone suspicion
April 2020 – January 2021
(n = 366)</td></tr>
<tr><td colspan="2">April 2015 – December 2016
(n = 183)</td></tr>
<tr><td>Excluded: 144</td><td>Excluded: 71</td><td>Excluded: 75</td><td>Excluded: 260</td></tr>
<tr><td>Study I

(n = 377)</td><td>Study II

(n = 112)</td><td>Study III
study population
(n = 108)</td><td>Study III
control population
(n = 106)</td></tr>
</table>

4.1.2 STUDY II

Study **II** is based on the same patient population as study **I** from which we included 183 patients that were treated between April 2015 and December 2016 (**Table 3**). Exclusion criteria were: non-IPMN disease, study of undiagnostic quality and images performed with other than 1.5 T Avanto

Systems. Total of 71 patients were excluded. The final study population was 112 patients (70 female and 42 male). Median age was 70 years (range 46–83). 99 patients (88.4%) had BD-IPMN, 3 (2.7%) MD-IPMN and 10 (8.9%) MX-IPMN.

4.1.3 STUDY III

We collected 183 IPMN patients from study **II** and excluded the ones who did not have an adequate image quality to visualize the ducts at the head of the pancreas (**Table 3**). The final IPMN population was 108. Mean age was 69 years (range 46–83). 68 was female (62.9%) and 40 male (37.1%). 96 patients did have BD-IPMN (88.9%), 1 had MD-IPMN (0.9%) and 11 had MX-IPMN (10.2%).

For gathering of the control population, we conducted a retrospective search using the radiological image archive of HUH and collected 366 abdominal MRI examinations performed at Meilahti HUH between April 2020 and January 2021 (**Table 3**). We included only adult patients without diagnosed pancreatic pathology or illness. The final control population was 106 patients. Mean age was 50 years (range 23–94). 62 was female (58.5%) and 44 male (41.5%).

4.2 ETHICAL CONSIDERATIONS

This retrospective protocol for Studies **I-III** was approved by the Surgical Research Committee of Helsinki University Central Hospital.

The retrospective study protocol for study **III** control patients was approved by the Radiological Research Committee of Helsinki University Central Hospital.

4.3 METHODS

4.3.1 STUDY I

4.3.1.1 Imaging protocols

We collected information from MRI and CT images as well as from ultrasound reports. MRI images were scanned with 1.5 T and 3.0 T MR scanners mainly in HUH or at other hospitals in Hospital District of Helsinki and Uusimaa (HUS). The MRI/MRCP protocol was either long (long protocol, LP) including volumetric interpolated breath-hold (VIBE) sequences before and after gadoterate meglumine (Dotarem, Guerbet, Roissy, France) contrast agent and diffusion (DWI) sequences or short (short protocol, SP) without enhancement nor diffusion sequences (**Table 2**).

CT images were mainly scanned in HUH. CT protocols varied from pancreatic tumor protocol to whole body CT. CT images were enhanced with non-ionic contrast medium (Omnipaque 350 mg of iodine/ml, Amersham Health, UK) or unenhanced.

Only reports from US examinations were collected, and the reports were used when the pancreatic abnormality was discovered for the first-time. US reports were not included in the further surveillance.

4.3.1.2 Radiological parameters and timelines

Radiological parameters were collected from the following timelines: 1) study observer retrospectively searched the first imaging where the pancreatic abnormality was seen, 2) first imaging when an overall assessment was made by a gastrointestinal surgeon at the operating unit at HUH, 3) the last imaging done during surveillance or last other CT or MRI scan. If the patient was operated on during surveillance, the preoperative MRI or CT was also analyzed.

The following parameters were evaluated from the datasets: number of cysts in accuracy of no cysts, solitary cyst or multifocal. Localization of cysts: the uncinate process, head, neck, body and/or tail of the pancreas. During surveillance we analyzed whether there were new cysts compared to older examinations (reported as no/yes). Largest cysts or multicystic lesions maximum diameter was measured (mm) and cyst appearance was evaluated (one cyst or multiple cysts). Largest cysts localization (uncinate process, head, neck, body, tail). Possible mural nodule was observed in accuracy of no, yes or unsure. Size of the mural nodule was measured (mm) and its possible enhancement with contrast agent was evaluated and documented as no, yes,

or suspect if there was contrast agent used. Thickening of the major cysts walls was evaluated (no, yes, unsure) and possible enhancement observed (no, yes, unsure). Major cysts possible restricted diffusion was observed and categorized as no, yes or unsure. Communication between cyst and the MPD was observed and cysts possible internal septation was evaluated (no, yes, unsure). Other cysts possible mural nodules were evaluated (no, yes) and measured (mm). Also, other cysts possible growth between images was observed. MPD was measured at the broadest point and its possible dilatation and its cause (MX-IPMN, MD-IPMN or unclear reason) were evaluated. Also, the location of the broadest point was collected. Change of the caliber and abrupt change of the caliber were evaluated (no, yes). Possible parenchymal atrophy upstream was evaluated. Possible mural nodule in the MPD was observed, and its enhancement was evaluated if there were contrast agents used (no, yes). Enhancement of the MPD walls was evaluated whether there were enhancement pictures taken. Type of IPMN disease was analyzed (BD-IPMN, MD-IPMN, MX-IPMN or unspecific). The pancreatic parenchyma was observed for abnormalities (for example, possible fatty replacement). Possible solid pancreatic tumor was observed (no, yes, unsure). Lymph node enlargement was collected (no, yes), and possible vascular invasion or growth outside pancreas was evaluated. Also, possible metastatic disease was evaluated.

The MRI images were analyzed with PACS system 3D reformation program when more accurate analysis were needed—for example, to analyze the communication between MPD and the pancreatic cyst and appearance of the cystic mural nodules by utilizing MRCP sampling perfection with application-optimized contrasts using different flip angle evolution (SPACE) sequences.

4.3.1.3 Clinical data collection

Patient demographics such as age and gender, and comorbidities were collected. Clinical presentations such as the symptoms (jaundice, pancreatitis, stomach pain, new diabetes, weight loss) or no symptoms at the beginning of surveillance and during surveillance were collected. Possible pancreatic operation date, procedure technique and information of histopathology were collected. Endoscopic ultrasound (EUS) and cyst fluid cytology or pathological-anatomical diagnosis (PAD) was collected when available. Possible US guided biopsy or aspiration and PAD or cytology was collected when performed. Information of SpyGlass procedure were collected when available, and possible ERCP information was collected. Reason for ending of surveillance was registered. Serum carbohydrate antigen 19-9 (CA 19-9) levels at the beginning of surveillance and at the highest point during surveillance were collected.

4.3.1.4 Statistical analysis

Categorical variables were reported as frequencies and percentages. Continuous variables were reported as mean and 95% confidence intervals (CIs) or as medians and 25^{th} – 75^{th} interquartile ranges (IQRs) when skewed. Comparisons of categorical variables were conducted using the Chi-square or Fisher's exact tests, as appropriate. Continuous variables were conducted by Mann-Whitney U test or using the Student's T test. All tests were two-sided and $p < 0.05$ was considered statistically significant. There were no statistically significant differences between patients whose surveillance had started before or after 1.1.2014, and therefore the whole population could be analyzed as a whole. Patients whose serum CA 19-9 levels were unmeasurable during whole surveillance time were considered to be Lewis antigen negative and handled as missing information in analyses involving CA 19-9. This included 9.3% of patients, which was in line with the previous study by Goonetilleke and Siriwardena [117]. The cystic or ductal mural nodules that were considered unsure by study observers were categorized as «not mural nodule« in statistical analyses.

4.3.2 STUDY II

4.3.2.1 Imaging protocols

We collected information from MRI images. MRI images were scanned with same 1.5 T Siemens Avanto MR equipment in HUH. The MRI/MRCP protocol was either long (LP) including VIBE sequences before and after contrast agent (Dotarem, Guerbet, Roissy, France) and with diffusion (DWI) sequences or short (SP) without enhancement sequences nor diffusion sequences. In the study we analyzed retrospectively these longer protocols (LP or SP). These longer protocols are together called by S-LP in this book. We also analyzed same images with a new shorter protocol, so-called ultrashort protocol (USP), which included only T2WI HASTE and 3D MRCP SPACE sequences (**Table 4**).

Table 4. MRI imaging sequences that were analyzed in the study **II**. Modified from Table 1 in **II**. The article is licensed under a creative commons license: http://creativecommons.org/licenses/by/4.0/.

Sequence, imaging plane	LP	SP	USP
T2 HASTE axial	X	X	X
T2 HASTE fs thick slice [a] coronal	X	X	
T2 HASTE fs axial	X		
T1 FLASH fs axial	X	X	
T1 2D in/opposed phase axial	X		
T2 3D SPACE MRCP [b] coronal	X	X	X
T2 HASTE fs thin slice coronal	X	X	
T1 VIBE pre-contrast axial	X		
T1 VIBE post-contrast [c] axial and coronal	X		
DWI [d] + ADC axial	X		

[a] In six dimensions.

[b] Including MIP in LP and SP.

[c] 0.1 mmol/kg body weight of gadoterate meglumine. Post-contrast phases: arterial phase axial, venous phase axial, venous phase coronal, and late venous phase axial.

[d] DWI b-values are 50, 400, and 800 s/mm².

4.3.2.2 Radiological parameters

Radiological parameters were collected from the S-LP and USP datasets (**Table 5**).

Table 5. The following parameters were collected from the datasets. Modified from Supplementary Table 1 in **II**. The article is licensed under a creative commons license: http://creativecommons.org/licenses/by/4.0/.

Parameter		
Cysts	amount	no cysts, solitary, multifocal
	localization	uncinate process, head, neck, body, tail
Largest cyst or multicystic lesion	maximum diameter	mm
	appearance	one cyst, multiple
	localization	uncinate process, head, neck, body, tail
	mural nodule	no, yes, inconclusive
	size of the mural nodule	mm
	thickening of the cyst wall	no, yes, inconclusive
	communication to MPD	no, yes, inconclusive
	internal septation	no, yes, inconclusive
WF in the other cysts		no, yes
	mural nodule size	mm
MPD	dilatation	no, yes
	cause of the dilatation	MX-IPMN, MD-IPMN, inconclusive
	width at the broadest point	mm
	location of the broadest point	uncinate process, head, neck, body, tail
	change of caliber	no, yes
	abrupt change of caliber	no, yes
	distal parenchymal atrophy	no, yes
	mural nodule	no, yes, inconclusive
Type of IPMN disease		MD-IPMN, BD-IPMN, MX-IPMN, unspecified
Pancreatic parenchyma		normal, no (definition by text)
Solid tumor in the pancreas		no, yes, inconclusive
Dilatation of the bile duct		no, yes, (diameter, mm)
Lymph node enlargement		no, yes
Invasion		no, metastasis, blood vessel invasion, growth beyond the pancreas

BD-IPMN = branch-duct IPMN, IPMN = intraductal papillary neoplasia of the pancreas, MD-IPMN = main-duct IPMN, MPD = main pancreatic duct, MX-IPMN = mixed-type IPMN, WF = worrisome features.

4.3.2.3 Cost calculations

We calculated the cost reduction from substituting longer protocols with USP. The cost analysis was based on the year 2018 invoice policy of HUH. At the calculation following factors were considered: use of contrast agent, patient preparation done by the radiology nurses, duration of the MRI-room occupation and duration of the case reading done by radiologist. In only LP contrast agent is used, which is more costly and also increases the time of patient preparation.

The patient preparation for LP was 10 min because of the venous cannulation for contrast agent usage, and for SP it was 5 min. For USP patient preparation time would also be 5 min. The sequence-based examination time for SP and LP was calculated from the details of the MRI machines control panel, and the MRI occupation times were collected from MR machines patient lists. All the sequences included in LP could theoretically performed in 23 min, but because of breath-holds and possible other pauses during scanning and patient preparation the MRI suite was reserved for 45 min for each patient. For SP the total sequence-based scanning time was 13 min, but MRI suite was reserved for each patient for 20 min. We calculated the case reading times from the beginning of the reporting to approval. These times were calculated from three experienced radiologists reading IPMN control studies during daily clinical workflow in 2020, and the times were reported as averages considering the variation of the patient material.

4.3.2.4 Statistical analysis

The pairwise concordances between readers were calculated by use of the Cohen's Kappa [139]. For the Cohen's Kappa agreement values were interpreted according to the following scale: 0–0.20 none, 0.21–0.39 minimal, 0.40–0.59 weak, 0.60–0.79 moderate, 0.80–0.90 strong, above 0.90 almost perfect [139]. We used bootstrapping (1000 samples) to obtain robust bias corrected accelerated 95% CI for diameter measures from image analysis. The exact Clopper-Pearson 95% CI were calculated for proportions. We used McNemar's test to assess differences in paired contingency tables. The Bland-Altman plot was used to assess non-inferiority [140] of the two methods in continuous measurements [141]. In order to assess non-inferiority for Boolean data the differences in proportion of detecting a condition with exact 95% CI were calculated. Non-inferiority limits for the cyst diameter was set from – 10 to + 10 mm according to previous studies where this was used to define the growth of the cyst [142,143]. Study by Dunn et al. used also 50% cutoff for difference between measurements but in our study there were not over 50% difference between any measurements [142]. For MPD non-inferiority limits was set to from – 2 to + 2 mm according to our studys measurement accuracy,

which was 1 mm. Our measurement accuracy led to rounding from 1.4 mm to 1 mm and from 2.5 mm to 3 mm, which meant that 1.1 mm difference led to 2 mm difference. For statistical analysis all inconclusive cystic mural nodules were analyzed as yes.

4.3.3 STUDY III

4.3.3.1 Imaging protocols

We collected information from MR images, which were scanned with 1.5 T Siemens Avanto MR equipment in HUH. Control populations MRI images were scanned with 1.5 or 3.0 T MR equipments in HUH.

4.3.3.2 Radiological parameters

We evaluated following parameters from both groups: Presence or absence of the duct of Santorini or the ansa pancreatica. And in cases of existing ducts of Santorini or ansa pancreatica if the duct ends into the small bowel or does not end, and possible prominence of the duct. Presence or absence of the pancreas divisum was evaluated, and when present its variations were categorized: complete, incomplete, reverse, or absent ventral duct. Presence or absence of the santorinicele was examined and measured if necessary. Possible meandering of the MPD (MMPD) at the head of the pancreas were evaluated and categorized to N-shape, loop configuration or reverse-Z, which includes subtypes C1, C2 or C3. Other patients that did not have MMPD nor pancreas divisum were categorized by the course of the MPD into descending, vertical or sigmoid course. The largest diameter of the MPD was measured.

The following parameters were evaluated from IPMN patients to estimate the extent of the cystic disease and to classify if a patient had WF or HRS: number of cysts in accuracy of no cysts, solitary cyst or multifocal. Localization of cysts: the uncinate process, head, corpus and/or tail of the pancreas. Largest cysts or multicystic lesions maximum diameter was measured (mm). Possible mural nodule was observed in accuracy of no or yes. Size of the mural nodule was measured (mm). Thickening and possible enhancing of the major cysts walls was evaluated (no, yes). Other cysts possible mural nodules were evaluated (no, yes) and measured (mm). MPD was measured at the broadest point. Abrupt change of the caliber was evaluated (no, yes). Possible parenchymal atrophy upstream was evaluated. Possible mural nodule in the MPD was observed (no, yes). Type of the IPMN disease was analyzed (BD-IPMN, MD-IPMN, MX-IPMN). Lymph node enlargement was collected (no, yes).

4.3.3.3 Statistical analysis

The Shapiro-Wilk's test was used when there were deviations from normal distribution in continuous variables. The Mann-Whitney test was used to evaluate differences between groups in the continuous variables. The Fisher's exact test or the Fisher-Freeman-Halton test was used in categorical variables, respectively. Logistic regression was used to obtain 95% CIs, odds ratios (ORs), and p-values to examine the associations between the outcome variable and the independent variables. Also, the Firth's penalized logistic regression was used to obtain the same outcome.

5 RESULTS

5.1 BD-IPMN PATIENTS WITH STABLE SMALL CYSTS AND WITH NO WORRISOME FEATURES REQUIRE LESS FREQUENTLY SURVEILLANCE (I)

Study **I** was a cross-sectional study of IPMN patients under surveillance at HUH. Of total 521 patients we included in the study 377 BD-IPMN patients. Of these 61.3% were female and 38.7% men.

During surveillance 2 patients emerged pancreatic carcinoma (0.5%). They both emerged a new WF/HRS during surveillance, and their CA 19-9 levels were high (67 500 kU/L and 9300 kU/L). Among study patients no carcinomas or high-grade dysplasias were detected with normal CA 19-9 levels ($p = 0.014$). 12% of patients (41/342) had an elevated CA 19-9 at some time point during surveillance. Among those who had an elevated CA 19-9 level during surveillance, 70.7% had a WF/HRS at the time of diagnosis compared to those 22.3% that did not have elevated CA 19-9 ($p = 0.0001$). Total of 12.2% of patients (5/41) with elevated CA 19-9 underwent surgery during surveillance compared to 1.7% of those that did not have elevated levels ($p < 0.003$). CA 19-9 screening may replace some imaging surveillance in branch-duct IPMN patients without any WF/HRS in the future.

During our study 232 patients did not have WF/HRS (61.5%). Of these patients 133 (57%) had a cyst < 15 mm at diagnosis and 116 (50%) had < 15 mm cyst still at the end of the surveillance. 74 patients (19.6% of total population) had a small < 15 mm cyst at the diagnosis, which did not grow at all during surveillance. Of all population those cysts that were under 15 mm at diagnosis and grew during surveillance developed more often new WF/HRS compared to those that did not grow (16.2% vs 5.3%, $p = 0.043$).

5.2 THE ULTRASHORT PROTOCOL IS COMPARABLE TO LONG PROTOCOL IN IPMN SURVEILLANCE (II)

Study **II** evaluated if USP could be used with BD-IPMN patients who have no WF nor HRS in the future IPMN surveillance. The same parameters from the same MRI datasets were collected by two study observers from 112 patients. The datasets included either 5-16 imaging sequences (S-LP) or 2 sequences (USP).

The Bland–Altman plots for the mean value of the largest cyst and main pancreatic duct revealed no significant bias in the difference between USP and

S-LP methods nor a visual trend as the size increased was detected. The mean size of the largest cyst was 19.7 mm according to the S-LP and 19.5 mm based on the USP. The McNemar's test was utilized to assess the differences between measurements, and the 0.19-mm difference between cyst size was not statistically significant. The mean MPD value was 3.33 mm using S-LP and 3.24 mm using USP, and a 0.08 mm difference between them was not statistically significant.

The Cohen's Kappa was used for intra- and interobserver agreement. The intra-observer agreement between USP and S-LP was 0.85 for the cystic mural nodules and 0.92 for WF/HRS for reader 1, and 0.77 and 0.75 respectively for reader 2. The inter-observer agreement using USP was 0.82 for WF/HRS and 0.76 for the cystic mural nodules between readers. The inter-observer agreement using S-LP was 0.76 for WF/HRS and 0.79 for the cystic mural nodules.

We analyzed how accurately the cystic mural nodules could be identified using S-LP and USP. All true cystic mural nodule cases were identified using USP and S-LP. Thus, the sensitivity reached 100%. The difference in specificity using the CIs were calculated to demonstrate how accurately the difference was defined, and for reader 1 it was -2.1 and for reader 2 1.1, respectively.

Agreement for overall cystic mural nodules between the S-LP and the USP was 94.9%, and for main pancreatic duct mural nodules agreement it was 99.1%. Agreement for WF/HRS between S-LP and USP was 92.4%, and for solid pancreatic tumor it was 99.1%, of all cases. We also calculated the difference in the proportion of detected cases between USP and S-LP with 95% CIs for both readers separately with cross-tabulation to assess the noninferiority between methods and did not identify significant systematic bias between these methods and found no difference at all between the confidence limits. The noninferiority limits exceeding the CI can be considered noninferior.

For USP the calculated scanning time for sequences was 7 min and we estimated that 15 min would be the time for needed MRI suite occupation for the patient visit. The case reading took approximately 15 min 30 s using LP and 12 min 30 s min with SP. We calculated that for USP case reading would take approximately 10 min.

We calculated that the USP cost was 39% of the LP cost and 77% of the SP-cost. The contrast-enhanced LP cost was €514 and the SP cost €261, and the calculator approximate of USP cost was €201.

5.2.1 ADDITIONAL (UNPUBLISHED) OBSERVATIONS

In this thesis we present a calculation of the cumulative total number of follow-up MRI/MRCP during the span of the lifetime of a hypothetical 45-year-old male IPMN patient, given that the hypothetical patient would not develop any imaging risk factors requiring operation [4]. The patient age of 79 years was

set as the upper limit for suitability for surgery based on the estimation of life expectancy of males at birth in Finland [144], and thus the end of the IPMN surveillance. The formula for calculating the cost reduction in the case of the hypothetical patient is in **Table 6**. For this hypothetical patient, the total number of examinations during surveillance is 34 when follow-up is performed annually, and therefore, the total cost reduction of using USP in the case of the hypothetical patient would be €2,040 compared to SP and €10,642 compared to LP.

Table 6. The cost reduction (CR) in the case of the hypothetical patient was calculated by the following formula, where LP is long protocol, SP short protocol, USP ultrashort protocol, CR_1 is cost reduction between LP and SP, CR_2 is cost reduction between LP and USP, CR_3 is cost reduction between SP and USP, MRI_{total} is the cumulative total number of examinations for the hypothetical patient during lifetime.

$CR_1 = (\text{cost LP} - \text{cost SP}) \times MRI_{total}$
$CR_2 = (\text{cost LP} - \text{cost USP}) \times MRI_{total}$
$CR_3 = (\text{cost SP} - \text{cost USP}) \times MRI_{total}$

5.3 MEANDERING MAIN PANCREATIC DUCT ASSOCIATES WITH IPMN DISEASE (III)

Study **III** evaluated if IPMN disease has association with developmental ductal variations of the pancreas. The final study population was 214 patients from the tertiary care unit, among whom 108 were IPMN patients and 106 were control patients.

The IPMN group manifested more MMPD cases, total 18.4% of IPMN patients had an MMPD versus 3.0% in the control group, respectively ($p < 0.001$). During this study we noticed a new specific MMPD type, which was named as an N-shape. The N-shape was present in 6 IPMN patients and in 2 control patients. In patients with N-shape the accessory duct, either ansa pancreatica or duct of Santorini, attached to a deep notch that was seen in the head of the pancreas. In IPMN group 8 had reverse-Z type ductal configuration and one patient in control group. In IPMN group 4 cases of loop-type configuration were seen but none in control group. Pancreas divisum was seen in 9.3% of IPMN patients and 5.7% of control group.

When comparing MMPD patients to non-MMPD patients, the OR was 6.4 experiencing an IPMN when case of MMPD ($p < 0.001$). Loop configuration

had OR 12.4 (p = 0.028) likelihood and the reverse-Z configuration OR 7.8 (p = 0.008) experiencing an IPMN when comparing to the descending course. The other courses did not have statistically significant association with IPMN. The association between IPMN and duct of Santorini was also seen (OR 3.9, p < 0.001) and for ansa pancreatica (OR 3.2, p = 0.013) compared with the absence of these accessory ducts, respectively. The N-shape had a higher likelihood to have a cystic mural nodule among at-risk IPMN patients (OR 5.9, p = 0.048). The other configurations had no statistically significant association with at-risk IPMN patients.

In IPMN group 53.7% had multiple IPMN cysts extending to ¾ of the pancreas or across the entire gland. The accessory duct ansa pancreatica belonged more likely to this subgroup with multiple IPMN cysts (OR 12.8, p = 0.001) when comparing with absence of these accessory ducts.

6 DISCUSSION

6.1 GENERAL REMARKS

During recent decades, growing numbers of IPMN patients are being detected. This ever-growing patient population, which is under surveillance because of the risk for malignant transformation, puts pressure on the healthcare systems. The aim of this thesis was to evaluate whether there are ways to lower this burden so that the surveillance of the IPMN disease would be both reasonable for healthcare systems and safe for the patients. In study **I** we evaluated the IPMN patient population under surveillance in Helsinki University Hospital (HUH) to explore the natural course of the disease, and furthermore, to see if we could find some features of the disease that would allow less frequent surveillance without compromising timely diagnosis of malignant transformation. In study **II** we delved into the most important part of IPMN surveillance, which is MRI imaging. Our goal was to evaluate whether an abbreviated so-called ultrashort MRI protocol with fewer sequences would be comparable with longer protocols that are in use at HUH at the moment. The shorter the protocol, the faster the imaging and the briefer the involvement of image rooms and personnel. Furthermore, it shortens time spent for image reading, enabling faster workflows and saving money. In study **III** we focused on investigating the unclear role of anatomical pancreatic variants and duct variations with IPMN disease and examining whether those different variations have any association with the progression or origin of the disease. This study was the first to analyze the possible connection between IPMN disease and MMPD.

6.2 WHICH PATIENTS SHOULD WE FOLLOW MORE INTENSIVELY AND WHO NOT?

In study **I** we found that there is a remarkable group (nearly 40%) of BD-IPMN patients with small cysts (under 15mm) that didn't grow at all during surveillance. The appearance in these cysts seemed to be stable, having worrisome features or high-risk stigmata less frequently. According to this study, these BD-IPMN patients with small cysts could be scanned less frequently in the future as long as no worrisome features or high-risk stigmata are seen. We assume that the possible growth of the cyst would be detected during the first two years of surveillance, and from then on the follow-up

imaging could possibly be every other year. For example, the American Gastroenterological Association guidelines recommends stopping the surveillance after 5 years if no change in character or in size is seen [5].

In study **I** no carcinomas or high-grade dysplasias were seen with normal serum CA 19-9 levels. We found no previous studies that would have discovered the same result. We suspect that other studies did not take into account that 10% of the White population does not produce CA 19-9 at all [117]. This patient group cannot be followed up with this laboratory exam. Our study included two patients with carcinomas, and they both did have highly elevated CA 19-9 levels. This result warrants further studies about this point of view with bigger patient population.

In study **II** we demonstrated that ultrashort protocol MRI is comparable with longer protocols. It should be considered as an alternative imaging protocol when a patient does not have WF/HRS. Thus, BD-IPMN patients without WF/HRS would be ideal to be surveilled with USP in follow-up.

We think that BD-IPMN patients with small cysts and no WF/HRS and who have measurable normal levels of CA 19-9 could be monitored once in a while with only laboratory tests, and MRI imaging could be performed less frequently. Perhaps this new approach to surveillance would be reasonable to start with those patients who have the least risk of cancer [89], such as the above-mentioned BD-IPMN patients who have an under-15 mm cyst that does not grow, have no WF/HRS, and have measurable and thus normal levels of CA 19-9. If such a patient remains stable for 2 years in MRI follow-up, the next control could be at 4 years from diagnosis and made by just CA 19-9 measurement. The next control could be at 5 years from diagnosis and both MRI and CA 19-9 could be performed then. However, this warrants further study [145].

In study **I** both carcinoma patients had a small cyst with no WF/HRS at the beginning of the surveillance. Their cysts grew during surveillance, and they developed a new WF/HRS. One exhibited highly elevated CA 19-9 levels during surveillance and a rapid cyst growth. The other exhibited highly elevated CA 19-9 levels after 1.5 years of surveillance. Thus, patients who have worrisome features or high-risk stigmata should be monitored as the European guidelines recommend [4] and imaged with longer protocols for surveillance, not with USP. However, study **II** demonstrated that patients with WF/HRS were similarly detected with USP compared to longer protocols, and measurements of cysts and MPD were equal, so this abbreviated protocol is also valid in detecting changes during surveillance.

In study **III** we noticed that MMPD and especially an N-shape configuration had positive association with cystic mural nodules, thus performing a possible risk factor for malignant transformation. Thus the patients having this pancreatic duct configuration could demand more precise follow-up. Also, the fact that a healthy patient has MMPD could serve as a risk signal for developing IPMN disease in the future.

6.3 CAN ULTRASHORT PROTOCOL BE USED IN THE FUTURE?

Study **II** evaluated whether an ultrashort protocol could be used for future IPMN surveillance. Our study demonstrated that USP is similar to longer protocols and can be used in BD-IPMN surveillance in the future. There are only a few studies about different MRI protocols in IPMN surveillance [146]. A study by Macari et al. (2009) demonstrated that the use of gadolinium contrast agent had only minimal impact in the follow-up of PCN [114]. The study by Nougaret and colleagues (2014) also came to the conclusion, that gadolinium had no additional value in surveillance [147]. A study by Pozzi-Mucelli et al. (2016) did evaluate the use of abbreviated MRI sequences in PCN imaging, and they found that so-called short-protocol (SP) MRI provided equivalent information to the longer protocol and could be used in IPMN surveillance. Their SP contained three sequences: T2WI HASTE axial, T2WI HASTE coronal, and T1WI 3D VIBE FS before contrast agent [115]. We chose just two sequences, T2WI HASTE axial and 3D MRCP SPACE, for the so-called ultrashort protocol. T2WI HASTE axial was chosen for proper parenchymal visualization, and MRCP SPACE for detailed MPD and cyst observation.

Our designed protocol was comparable for detecting worrisome features or high-risk stigmata. This is crucial because the MRI surveillance leans on finding these features. Both observers found all the patients who had a cystic mural nodule, which is the most important predictor of malignancy [83], with the ultrashort protocol. There were no significant difference between protocols, either between the MPD or cyst diameters. The results were convergent between protocols, even more precisely than in the study by Dunn et al., in which they had measurement variability of 4.0 mm for each cyst [142]. By contrast, our mean difference between all cysts was just 0.19 mm. In our study there was not over 50% difference between the cysts, but in their study, there were such cases. This result underlines that measurements are also similar between USP and longer protocols.

Adding USP to the IPMN surveillance program would save money and time. From 2016 on, IPMN patients at HUH are being scanned either with LP that includes contrast agent or with SP that does not include contrast agent or DWI. This has slightly shortened scanning times and costs, but still, the case reading takes time, and the number of patients in the surveillance is increasing in general. The elimination of the contrast agent is not enough, and we need a more time-saving protocol, such as USP. We calculated that USP would take 15 min of MRI room occupation, contrary to LP, which takes 45 min, while SP takes 20 min. Therefore, in 3 h, 12 patients could be scanned using USP, 9 using SP, and 4 using LP. Thus, this time savings is significant and allows more patients scanned each day. The case reading would also be faster with fewer sequences. Additionally, in this thesis we calculated the savings that would come from the use of USP instead of LP in the hypothetical patient's lifetime.

Savings from using USP instead of LP would be €10,640, and instead of SP savings would be €2,040. These savings are remarkable, considering the number of patients who have incidental cysts in the pancreas [2]. Finally, the fact that most IPMN patients have an indolent course of the disease, which won't transform to malignancy during the patient's lifetime, argues for more economical alternatives in patient surveillance [77,89].

6.4 WHAT ARE THE LIMITATIONS OF MAGNETIC RESONANCE IMAGING TECHNIQUES AT SMALL STRUCTURES AT PRESENT AND IN THE FUTURE?

The pancreas is a small organ in a location where there is movement caused by breathing and bowel movements. This situation demands sequences that can be scanned with one breath-hold to guarantee a good image quality. The pancreas is a fat-containing organ, and better fat suppression techniques allow improved contrast resolution [98]. Regardless of these improvements in imaging, the problem of movement artifacts was a big problem in the patient selection for proper image quality for studies **II** and **III**. In study **II** almost 29% of patients were excluded due to insufficient image quality. Many of the IPMN patients that are under surveillance are elderly [108]. Elderly patients may have difficulties to staying still during long MRI scanning times, and long breath-holds are more difficult to maintain. MR imaging takes a long time, and this also argues for shorter scanning times. We argue that especially with older patients, it would be relevant to have a shorter imaging protocol, such as USP, to maintain a proper image quality.

When considering the size of the normal MPD, which varies from 1.5 mm to 3.5 mm [9], we are talking about objects that need very good resolution to differentiate them from a blurry background. Many of the pancreatic cysts are also tiny, and the communication between the cyst and the MPD can be hard to visualize. Also, one has to understand the difficulties of measuring these structures freehand. To measure these objects, the radiologist has to first zoom into the target, which makes images blurrier when the pixel size gets bigger and more visible to the eye. Then the boundary between the structure and the other organ parenchyma is not sharp anymore, and the radiologist has to decide at which point to start and stop the measuring. The measurement tool gives result to tenth accuracy, but in the normal work, the result is rounded to the nearest even number. The size of the structure does not affect so much with this blurry boundary problem, but it is easier to measure bigger objects when you do not have to zoom so much.

Also the evaluation of the possible enhancement of the small structures is not easy. Mural nodules particularly are often tiny, and differentiation of the shades and tones of the image can be hard for the human eye. Artificial

intelligence (AI) could be a helpful tool for this task to differentiate the possible enhancement.

6.5 INTRA- AND INTEROBSERVER VARIATION

When thinking of the threshold levels for cyst size and MPD size to cross the level of worrisome features or high-risk stigmata, which are 30 mm and 5 mm, respectively [58], there can be variations in measurements from one imaging to the next imaging. This is not such a problem in normal everyday imaging, when there are usually previous images for comparison, but in study **II** this was a problem when all measurements were measured blindly. There were some cases where both study observers had these kinds of measurements, which were placed around the threshold levels for certain WF/HRS criteria. This naturally lowers the intra- and interobserver variability results. Despite this, we decided to approach our hypotheses with an even more complex classification of WF and/or HRS features where there are many different objects that had to be analyzed. For a possible future usage of ultrashort protocol, this aspect was also mandatory to investigate.

Interobserver reliability is used in the case of multiple data collectors, when the intra-observer reliability is of a single data collector [139]. Intra- and interobserver variability and agreement can be calculated in different ways ; the simplest way is to show the agreement with crosstabulation where the answer is in percentages.

Study **II** showed compatible results with ultrashort and longer protocols. First, we demonstrated agreement with crosstabulation. Agreement over presence or absence of mural nodules in the cysts was 94.9% and in the MPD it was 99.1%. These were also previously examined by Pozzi-Mucelli and colleagues [115], and their results were 93% and 98%, respectively, so our study demonstrated slightly better results for interobserver variability. Our intra-observer agreement for cystic mural nodule was 96.4% for reader 1 and 93.5% for reader 2. In the Pozzi-Mucellis study it varied between 90–97% over 3 observers, so our study results were in line with their study [115].

Then in study **II** we analyzed interobserver agreement for presence or absence of cystic mural nodules calculated with Cohen's Kappa. It was 0.76 for the ultrashort protocol and 0.79 for longer protocols, which are in line with each other and represent a moderate agreement. For WF/HRS it was 0.82 and 0.76, respectively, where the USP is better and indicates strong agreement but for the longer protocols there was only moderate agreement. Other studies had analyzed slightly different things. Interobserver variability over a number of PCN lesions was examined by Pozzi-Mucelli et al. [115] and calculated with intraclass correlation (ICC) [148]. Their agreement over the longer protocol was 0.89, and for the shorter protocol it was 0.86, which both stand for good

agreement [115]. In a study by Dunn et al. [142], the overall interobserver agreement calculated with Cohen's Kappa about radiological decision-making was first 0.59, which indicates weak agreement. After teaching the designated measurements standards to the study observers, the Cohen's Kappa improved to 0.65, which is moderate agreement [142]. For comparison, from other studies of interobservation variability, the interobserver variability in the prostate MRI for lesion detection was substantial in one study [149], and for lesion detection in breast MRI it was moderate [150]. These results indicate that there is significant interobserver variability that varies along the target of interest and the teaching status of the radiologist.

Lastly, intra-observer variability was also evaluated in study **II**. For reader 1 the intra-observer agreement between USP and S-LP was 0.85 for the cystic mural nodules, which is strong agreement, and 0.92 for WF/HRS, which indicates almost perfect agreement. And for reader 2 they were 0.77 and 0.75, respectively, which indicates moderate agreement. In a study by Kim et al. (2017), the intra-observer variation for measurements of the size of the brain aneurysm calculated with ICC was 0.71, 0.96 and 0.81 for different readers, which indicates moderate, excellent and good reliability [151]. These results highlights that intra-observer variation also exists, as interobserver variation does.

6.6 THE SIGNIFICANCE OF THE STRUCTURE VARIATIONS IN THE PANCREATIC DUCTS

In study **III** we demonstrated that IPMN patients more often have meandering main pancreatic duct (MMPD) compared to our control population with a healthy pancreas. Also three control patients had MMPD, indicating that MMPD is a developmental variant. We assume that the more twisted form of the main pancreatic duct (MPD) at the caput of the pancreas affects the drainage of the pancreatic fluids and more often causes obstruction in flow that may affect formation of IPMN disease. Also the previous findings of MMPD association with pancreatitis reaches the same conclusion of poorer fluid drainage [53,54].

The duct of Santorini and ansa pancreatica associated with IPMN disease so patients with these ducts are more likely to have IPMN. However, IPMN patients had wider ducts that were more easily seen, and this may affect the result. As compared to MMPD findings, we assume that presence of the duct of Santorini and ansa pancreatica may lead to a disturbance with fluid drainage when the pancreatic fluid branches to these accessory ducts. Patients with ansa pancreatica had a more extent form of the cysts that may indicate that ansa pancreatica causes more trouble in fluid drainage.

IPMN patients also had wider MPD than our control population. This finding suggests that IPMN disease affects the entire duct system; the division into three IPMN categories is rather outdated. Widening of the MPD over 5 mm is a worrisome feature and by itself a reason for more precise follow-up.

6.7 STUDY LIMITATIONS

The retrospective nature of studies **I-III** was a limitation in several ways. First, the working diagnosis of IPMN in studies **I-III** was based on the imaging where there was a requirement of communication of the cyst with the MPD, and the histopathological diagnosis was not available for the majority of patients. In study **II** only 14% of the study population underwent sample taking, but 30% of patients had WF/HRS. The reason for this difference may originate from the advanced age of patients that may have led to their more conservative treatment. Furthermore, in study **I** we chose to evaluate the first image that the surgical unit evaluated and the last image that was performed. This led to different lengths of follow-up between patients. Because some images were unenhanced, we analyzed all data in statistics without mural nodule enhancement. Also, some patients had only CT images, which does not feature such a high-contrast resolution and high sensitivity as MRI [4,95,96]. In addition, the possible modality variations between MRI and CT in one patient's surveillance may also have had some effect on measurements in study **I**, because of the considerable variation in estimates of pancreatic cyst size by different imaging modalities that was demonstrated in a study by Maimone et. al [143]. Lastly, for study **II,** a new prospective study with selected patients, such as BD-IPMN patients who do not have WF or HRS, would be justified to perform to clarify the prospective aspect of the new USP follow-up method.

As mentioned before, motion artifacts lowered the image quality, especially in the crucial MRCP sequences leading to the exclusion of patients in studies **II-III**. In study **II** almost one-third of patients were excluded due to this. In clinical practice, movement and breathing artifacts are an everyday problem in MRCP imaging and should be evaluated in every case reading; possible renewal of the imaging or changing to CT must be considered.

In studies **I-III** the major cyst was measured from one unilocular cyst or from the entire size of the multicystic cluster if such was seen. In studies **I** and **III** this may have led to some variation among patients who are near the criteria of the worrisome features. In study **II** this affected intra- and interobserver results when the observer was blinded from which cyst or multicystic cluster to take measurements and in which plane. This measurement variation is well known among radiological measurements [142,143].

In studies **I-III** the cystic mural nodule was first analyzed as no, yes, and unsure. The unsure was used when the cyst was considered to contain some material other than true mural nodule, such as moving sediment or a hemorrhage. In study **I** the unsure and the no categories were united before statistics work because the follow-up images often revealed the true nature of the suspected nodule. However, in study **II** and **III** the unsure category was united with yes because there were no other images for comparison. The reason to do so was to ensure that the radiological analysis would be as precise as possible. Because of the retrospective study design, we did not have a histopathological diagnosis for every mural nodule.

In study **I** we detected only two carcinoma patients during surveillance. Also, the follow-up time was only 5.6 years. Because we aimed to discover an IPMN population that would be at the lowest risk of malignancy, this warrants a further study reaching over 10 years of follow-up. The accuracy of CA 19-9 in the detection of cancer warrants a validation study regarding CA 19-9 among a larger population to clarify our finding.

In study **II** the noninferiority limit for MPD was set to ±2 mm by our own rationalization about the fact that the measurement accuracy led to a 2-mm difference when rounding was present. There were no other studies made about this aspect before. For study **II**, the aim of the study was focused on investigating whether both readers could report equivalent information for clinical decision-making using USP and S-LP for the same patient under surveillance. We did not assess the specificity and sensitivity of these two protocols. For study **II**, the calculated reductions of costs from substituting S-LP with USP were based on the costs of SP and LP at HUH, and variations in prices can exist between countries.

In study **III** the collection of control patients was difficult because of the high exclusion rate of patients (109/366) with an existing cyst in the pancreas (approximately 30% of patients). This finding resembles the findings from previous studies of the high incidence of pancreatic cysts in an aging population [2,59]. This led to the situation that our control population was 20 years younger than the IPMN patient population. However, pancreatic developmental variations remain stable during one's lifetime, and thus, the results of configuration may be considered comparable.

6.8 DEVELOPMENT AND FUTURE RESEARCH DIRECTIONS

Currently artificial intelligence (AI) is receiving the biggest interest in radiology. When thinking of the small structures of the pancreatic ducts and the various sizes and shapes of the cysts and their content, it is may be too early to think that AI will be soon be helping us detect patients who have WF

or HRS. At least, it cannot replace humans in this task at present. Perhaps it could help with the visualization of the main pancreatic duct, which would be easier to detect by computer and measure. However, dilated branch ducts may cause errors, and remarkable narrowing or stenosis of the duct by tumor could be troublesome to detect by AI. Perhaps AI could detect an abrupt change of the caliber by calculating and comparing an image with earlier images from the same patient. Also, the estimation of the mural nodule enhancement might be possible to execute with AI, and we assume that AI will be part of our everyday work one day in IPMN follow-up.

As mentioned before, a new prospective study with selected patients—that is to say, BD-IPMN patients who do not have WF/HRS—would be justified to perform to clarify the possible use of the new USP method presented in study **II**. USP would be faster to perform and faster to read by radiologists because of the lower number of sequences. This leads to a cheaper price, which would be remarkable for the healthcare systems. The faster scanning time is also more pleasant for patients.

Study **III** sets up a totally new hypothesis of the origin or development of IPMN disease. Our result of IPMN patients exhibiting MMPD more often than the control population with a healthy pancreas is interesting and demands further research on these patients with follow-up. Do MMPD patients have more severe disease? How many MMPD patients in the population develop IPMN disease? Our study result of IPMN patients with ansa pancreatica that associated with multiple cysts would need further follow-up to see if they are at greater risk for developing WF or HRS.

Also study **I** did create a new research question that would be interesting and important to solve. In our study no high-grade dysplasias or carcinomas exhibited with normal CA 19-9 levels. However, our study had only two carcinoma patients, and thus, to clarify the role of the CA 19-9 in the surveillance of IPMN patients warrants further studies with a bigger patient population. CA 19-9 could possible replace some of the MR imaging in the follow-up, which should be a significant step towards easier, faster, and cheaper surveillance of IPMN patients.

7 CONCLUSIONS

The conclusions provided by this work are:

I. BD-IPMN patients with no WF/HRS and don't have growing cysts could possibly require less frequent imaging in the future. No carcinomas or high-grade dysplasia were seen in BD-IPMN patients with normal serum CA 19-9 levels.

II. An ultrashort MRI protocol including only T2-weighted HASTE axial and 3D MRCP SPACE sequences, provides nearly similar information compared to the more time-consuming and costly long protocol. It can be used in future IPMN surveillance with BD-IPMN patients that does not have WF or HRS.

III. IPMN patients exhibit an MMPD more often than control patients with healthy pancreas. An N-shape configuration associates with cystic mural nodules, and may require more precise follow-up in IPMN patients.

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